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THE

UNIVERSITY OF CALIFORNIA

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to

THE STATE BOARD

Second Report

Fiscal Year 1968

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University of California Medical School
San Francisco, California

Robert Gordon Sproul, President
University of California
Berkeley, California

Dear President Sproul:

There is herewith transmitted to you the second annual report on the University of California program in cancer research.

The report is based on progress reports submitted by recipients of grants made from the annual State of California appropriation for cancer research and from the endowed funds for cancer research. Summaries of progress and results of investigations in cancer research supported by other sources were also available in many instances.

The report has been read and approved by Drs. A. W. Bellamy, acting chairman of the Cancer Research Coordinating Committee, D. M. Greenberg, chairman of the Cancer Research Committee, Northern Section, and R. S. Stone, chairman of the Cancer Board of the University of California Medical School, San Francisco.

Respectfully submitted,

Michael B. Shimkin

Michael B. Shimkin, M. D.
Secretary, Cancer Research
Coordinating Committee

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The University of California Program in Cancer Research

(Second Report, January 1963)

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INTRODUCTION

The first report of the cancer research program of the University was published in February 1948. It recorded the organization of a [illegible] approach to the problem of cancer that was initiated in June 1947. The administrative steps so far taken have got [illegible] the expressed need for a coordination of [illegible] based upon the spirit of free inquiry which is [illegible] scientific endeavor. The scope of the program [illegible] of the scientific personnel of the University to investigations on cancer.

The Cancer Research Committees appointed by the President to advise him on the policies and financing of the cancer research program have held three series of meetings, in September 1947, in December 1947 and in May 1948. It is gratifying that all major decisions of the Committees were wholeheartedly endorsed by the President and the Regents. This confidence and unity of purpose have resulted in continued and increasing support by the State legislature and by the National governmental and voluntary agencies dealing in the field of cancer.

In their deliberations, the Committees have realized that the status of cancer research makes it impossible to foresee the crucial facts that are essential for the solution of the problem. As stated by Inge (Scientific Method, Oxford, 1931), "the primary factor in bringing about scientific discovery is not necessity, or individual genius, but the relentless pressure of accumulating knowledge."

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The definition of cancer research was made as broad as possible, and complete freedom was left to the individual investigator in his scientific pursuits. The ability of the investigator to carry out his research was considered to be a more important criterion than a specific project outlined in a request for funds. Cancer, an abnormality of growth, is as little a biologic problem as growth itself. It must be attacked by the methods of basic science. And progress in basic science is best achieved by the minimum of direction and organization (see Taliaferro, Science, 100: 145, 1940).

The pursuit of science, however, needs facilities, equipment, and financial continuity that enable the investigators to plan and to complete long-range endeavors. Coordination is essential in planning a broad program, especially when it involves the development of large new areas, and this was considered to be one of the major tasks of the Committee.

ADMINISTRATIVE

Among the achievements in which the University can take pride during the past year are the following:

(1) Assurance of a long-term, long-range program in cancer research expressed by a regular State appropriation of $250,000 for cancer research at the University.

(2) The State appropriation of $160,000 for the construction of the Cancer Research Genetics Laboratory at the Berkeley campus.

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(3) The pledge of $1,000,000 by the United States Public Health Service for construction of a cancer research wing at the Medical Center in San Francisco.

(4) The organization of the Cancer Research Institute of the Medical School in San Francisco, which includes a section of the National Cancer Institute.

(5) The position and accelerated plans for development of similar activities on the Los Angeles campus.

Table I indicates the major sources of financial support of the cancer research program of the University during 1948, and should be compared with a similar table in the original report. It shows that the funds available during 1948 totalled $818,000, or an increment of $198,000 over 1947, due to larger donations and grants. This sum does not include items for new construction, nor the two cancer teaching grants extended to the Medical and Dental Schools in San Francisco. In total, cancer research and closely allied activities in the University were supported by a sum of over one million dollars.

The first year of operation of this wide program was to a great extent preparatory in nature. This is well represented by the allocation of the State funds. Of the $350,000 available, over $190,000 was designated for Equipment and Expense, and went toward the procurement of essential scientific instruments, rehabilitation or expansion of laboratory areas, and similar purposes. It should be remembered that the money became available in November 1947, and with the present delays in purchases and labor, many items of equipment had not been procured and installed as late as July 1948.

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Table 2

Funds Available for Cancer Research
1948-1949

1. California State appropriation 1/	$250,000.00	
2. University funds and gifts		
a. Income on endowed funds 2/	40,000.00	
b. Donations and gifts 3/	100,530.51	
3. Grants from other agencies and foundations		
a. U. S. Public Health Service 4/	221,349.85	
b. Laboratory of Experimental Oncology 5/	107,050.00	
c. American Cancer Society 6/	90,778.00	
d. Other foundations 7/	18,145.84	
TOTAL		$818,053.20
4. New grants		
a. Cancer Research Genetics Laboratory, California State appropriation	160,000.00	
b. Construction grant, U. S. Public Health Service (Total grant $1,000,000)	50,000.00	
c. Teaching grants, U. S. Public Health Service 8/	29,958.00	
TOTAL		239,958.00
GRAND TOTAL		$ 1,058,021.20

1/ Addendum I.

2/ See first report.

3/ The Jewish Foundation Donation for Zoology Research; W. H. Crocker Trust Donation; Ayerst, McKenna and Harrison; California Institute for Cancer Research, Lederle Laboratories Division of American Cyanamid Company; Cedars of Lebanon Hospital; and miscellaneous gifts.

4/ Addendum II, including grant through California Department of Public Health.

5/ Direct allocation from National Cancer Institute, National Institutes of Health, U. S. Public Health Service.

6/ Addendum III.

7/ Donner Foundation, Rockefeller Foundation, and Jane Coffin Childs Memorial Fund for Medical Research.

8/ Not including pledges of additional funds, research fellowships and traineeships.

9/ Medical ($25,000) and dental ($4,958) Schools, San Francisco.

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In contrast with the previous year, in 1960 over $175,000 was allocated toward necessary [illegible] for the equipment and facilities made possible by the last yearly appropriation. This represents an addition of 48 full-time [illegible] to the cancer program, of these, [illegible] are doctoral scientists, 17 are technicians, and 7 are administrative personnel. This total does not include at least 20 part-time assistants and student helpers.

During 1961, the state appropriation and the endowed funds of the University available for cancer research supported 61 projects, of which several could be divided into four or five separate research problems. The projects are listed in Attachment I. None of the projects should be considered as separate entities sharply departmentalized, and few of them are supported entirely by one specific financial source. Rather, the great majority represent cooperative projects in which many disciplines and departments are intimately involved. This collaboration results in an important increase in force due to amalgamation of effort and exchange of information, as well as avoids unnecessary duplication of effort.

The separate projects in cancer research in the University supported by grants from the National Cancer Institute and from the American Cancer Society are listed in Attachments II and III. Reports on the progress of each of these grants are submitted through channels other than those of the Cancer Research Committees, although in most instances the pertinent information is available to the

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Committee. The proposals put together the work covered by the State appropriation, although, as stated above, no sharp demarcation is possible or desirable.

RESEARCH PROGRAM

The investigative approaches to the cancer problem may be divided into five main categories:

I. The study of carcinogenesis, or the cause and the formation of neoplastic growth. It is through the understanding of carcinogenesis that the basis of prevention and control of cancer can well be expected.

II. The study of the nature of the cancer cell, its chemical and physical characteristics, including the dynamic phase of metabolism, and how such characteristics differ from those of normal cells. Increasing information in this broad field may yield the clue to a rational approach to cancer therapy.

III. The study of cancer-host relationships, or the effects of cancer growth on the organism. This approach involves the investigation of the natural history of the disease in animals and in man, the metabolism and other physiological reactions of cancer-bearing organisms as compared with normal organisms. A better understanding of this field may reveal the basis for diagnostic tests for the presence of cancer, as well as improve the management and treatment of patients with cancer.

IV. The study of the diagnosis of cancer, which may be divided into the improvement of existent methods, such as by roentgen

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examination and [illegible] cytology, and the introduction of new methods, depending on the clinical trial of information based on the study of the cancer cell and host-tumor relationships.

V. The study of the therapy of cancer, which also may be divided into the improvement of existing methods of surgery and radiation, and the laboratory and clinical trial of new chemical and physical agents. A thorough understanding of the natural course of the disease, and continued observation and follow-up of patients are implied in these investigations.

No attempt has been made to divide the approaches into clinical and laboratory studies. The clinical studies are more difficult because of the greater cost, [illegible] control over the material, and the additional responsibilities inherent whenever human beings are involved, basically, no real difference exists. Nor has attempt been made to divide the studies into the so-called fundamental and applied approaches, although the study of diagnosis and therapy of cancer, at least by existent methods, would fall into the latter group. It is realized that the categories are somewhat arbitrary, and the implications of any problem or the results therefrom may extend beyond the confines under which it is described.

I. Carcinogenesis.

There are now well over 400 chemicals which have been described to produce cancer in experimental animals. These chemicals are of many types, particularly polycyclic hydrocarbons, azo dyes and steroid hormones. Other agents which are known to be associated etiologically

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with the neoplastic state include x-rays, ultraviolet light, and protein entities falling into the biologic class of viruses. The latter are involved in the etiology of several mammalian tumors as well as sarcoma in fowl. Little is known regarding the process by which these agents act upon tissues to alter them from the normal to the neoplastic. The use of isotope-tagging technique has allowed approaches for studying the fate of such compounds in the animal body.

1. Dr. Cason of the Department of Chemistry (I,2)10/ has been most successful in synthesizing a number of carcinogenic hydrocarbons with radioactive C^{14}. The biological distribution and metabolism of such compounds in animals can be best studied by the use of resultant radioactively-tagged compounds. An important contribution to this fundamental field of the fate and effect of cancer-producing chemicals in the animal organism has been made by Heidelberger and Jones (Cancer, I: 252, 1948). This study concerned the use of 1,2,5,6-dibenzanthracene labeled in the 9 and 10 positions. A similar study using 20-methylcholanthrene, which is several times more potent than dibenzanthracene, has been carried out at the Division of Medical Physics (I,3). It has been shown that the findings are similar to those with dibenzanthracene. Dr. Cason is at present synthesizing 1',9-dimethyl-1,2-benzanthracene, another carcinogenic hydrocarbon. This work allows the use of an inestimably valuable material by workers in biological sciences.

10/ Figures in parenthesis refer to Addendum, and item number within the Addendum. This form is used throughout the report.

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2. Drs. Strait, Julian and DeOme (I,10), in their study of the effects of solvents on carcinogenesis with carcinogenic hydrocarbons, found that sesamine increases the carcinogenic activity of 3,4-benzpyrene.

3. Dr. DeOme and his associates have developed a substrain of inbred Strain A mice which has very few breast tumors. This strain carries the milk factor and develops the pre-tumorous lesions of the breast, but fails to develop mammary carcinoma. By appropriate crosses and foster-nursing experiments it has been shown that the factor suppressing tumors in this substrain is hereditary and is independent of the previously known factors influencing breast tumor formation in mice.

4. Dr. Evans and his associates (I,1) are continuing their studies on the relationship of growth hormone and other pituitary hormones and tumor incidence in rats. They are finding that a higher incidence and appearance of tumors at an earlier age occur in rats injected with growth hormone.

5. Dr. Bern (I,8) is studying the content of phosphatase in the male sex accessory organs of several animal species. There are wide divergences in the occurrence of alkaline phosphatase as found by histochemical techniques in different species. Eventually tumors will be induced in these tissues with carcinogenic hydrocarbons and the changes in phosphatase during the development of neoplastic process will be observed.

6. Drs. Krichesky and Geissman (I,30,b) are continuing the study of the lipids of cancerous liver. It was reported by previous

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workers that a methylcholanthrene-like fluorescent substance was extracted from such livers. This would be an important contribution to the possibility that carcinogenic hydrocarbon-like materials are elaborated endogenously by the body. So far, however, the present investigators have been able to isolate only one compound, cholestenone, from such livers. Extensive chromatographic fractionation led to the isolation of several other fractions which are still mixtures and do not yield identificable ultra-violet spectra.

A corollary to this study was the use of similar lipid fractions for the production of immune serum in animals. Such immune serum has been shown by Dr. Bellamy's group (I,28) to be ineffective against a rat fibrosarcoma. Similar preparations previously were claimed to have had some regressive effects upon the Brown-Pearce carcinoma in rabbits.

7. Drs. Rinehart and L. D. Greenberg (I,17,b) are continuing their work on the nutritional aspects of cancer by studying single vitamin deficiency states in monkeys. The investigations include metabolic and hematological determinations and detailed histopathological studies as well as bio-assays of tissues, in animals on protracted deficiency of single vitamins. Initial studies have included thiamin, folic acid and pyridoxine deficiencies. Concurrent studies are being made on patients with cancer, to include estimation of blood concentration of vitamin A, carotene, ascorbic acid, thiamin and pyridoxine as well as tissue assays for thiamin and pyridoxine.

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II. Nature of the cancer cell.

The key question in cancer research, an answer to which would most likely produce the necessary clue to its control, is, "In what essential ways does a cancer cell differ from a normal cell?" Much research has sought to find a qualitative difference, the presence of an unnatural chemical in cancer cells which never occurs in normal cells, or the absence of some chemical in cancer that is invariably a component of normal cells. To date all such searches have failed, and it is probable that the essential difference is much more subtle, involving quantitative alterations in growth patterns, differentiation and metabolism. It is obvious that for a full understanding of how a cancer cell differs from a normal cell it is necessary to know the characteristics and functions of normal cells.

Several methods are being particularly emphasized in present research on cellular physiology. One is the study of metabolism by use of isotope tracer compounds. Another is the qualitative and quantitative analyses of the cell by histochemical methods. A great segment of research is concerned with the fractionization of the cell into its various components by ultracentrifugal and other physico-chemical methods, and the analysis of such components by further analytical techniques. Cytologic research of today may well be likened to physics just prior to the age of nuclear fission. Within the unit of living matter, the cell, are locked the secrets of individual and race life, of which cancer represents but one aberration.

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1. For the further understanding of the factors involved in the alteration of normal cells into their neoplastic counterparts, one of the richer sources of information is from work on unicellular organisms. Results on this type of material furnish clues for eventual investigation on mammalian cells. Drs. Doudoroff and Stanier (I,5) are pursuing fundamental studies on the growth, adaptation and mutation in bacteria. The metabolic alterations in adaptive forms of bacteria have possible direct application to cancer since cancer cells can also be considered as adapted tissue cells and if they behave at all like bacteria their different adaptation to different substrates strengthens the likelihood of finding metabolic antagonists to their growth.

2. Dr. Greenberg and his associates (I,7) have found in the course of study of the mechanism of protein synthesis that cell-free homogenates of many tissues are capable of incorporating labeled amino acids (glycine, alanine) into their tissue protein by means of enzymatically mediated reactions. The process is endergonic and normally requires the presence of oxygen and an oxidizable compound in the incubation medium. Evidence that the incorporated labeled amino acids are truly an integral part of the protein is offered by the observation that they are not set free upon partial hydrolysis with proteolytic enzymes, but only upon complete hydrolysis of the protein. The great interest of this work is that it opens up the possibility of isolating the individual enzymes and cofactors concerned with the synthesis of proteins.

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Investigation of the subject of growth and regeneration is being carried out by means of the study with isotopically-labeled amino acids of the rate of protein synthesis in embryonic tissue, tumor tissue and regenerating liver. Rapidly growing tissues and regenerating tissues exhibit an accelerated uptake of amino acids. It is quite striking that this increased rate of incorporation is exhibited in vitro by the cell-free homogenates of the anabolically active tissues as well as by the intact organism. From the experimental work it has been concluded that tumor growth is caused preponderately by an acceleration of anabolic reactions rather than by a retardation in the rates of the catabolic reactions of the organism.

3. Dr. Allen (I,8) is continuing his studies on the structure of ribonucleic acid from yeast, and the products obtained from such nucleic acid after ribonuclease activity. The structure of ribonucleic acid from yeast is being compared to a similar compound from the pancreas. This work is essential before its extension is undertaken to different nucleic acids from normal and neoplastic tissue.

4. Dr. M. S. Dunn (I,31) is studying the possible differences and concentrations of various amino acids in normal and tumor tissue by microbiological assay methods which he has developed. These methods involve the use of specific bacteria which have the ability to utilize only specific amino acids. At present, microbiological assay for 13 amino acids have been completed on 8 types of tumor tissue and their normal counterparts, and the data are being summarized and correlated with the literature. Analagous work is in progress on blood proteins

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in normal and tumor-bearing animals. The studies so far have been limited to the so-called natural or L-forms of amino acids. The lack of analytical methods for determination of the D-forms of more than a few of the amino acids has made it necessary to develop adequate tests for the latter objective. These fundamental studies will go far toward elucidating the qualitative and quantitative aspects of the content of amino acids in tumor and normal tissue. If striking differences are elicited, possible implication of extension to the diagnosis and even therapy of cancer would be worthy of exploration.

5. Drs. Eiler and McEwen (I,12) are investigating aerobic phosphorylation in normal and malignant tissues. The first problem was to determine conditions whereby oxidation in tissues could be confined to a single reaction. This led to the finding that pentobarbitol effectively isolates the reaction wherein succinate is oxidized to fumarate. It is now possible to extend the work to the comparison of normal and tumor tissues. A finding incidental to the work suggests the possible effectiveness of succinate as an antidote in barbitol poisoning. This is a demonstration of how discoveries in cancer research may have significance in quite unrelated fields and emphasizes the reverse, that the most significant findings towards cancer research may well occur in investigations most tenuously related to the subject of cancer.

6. Drs. Sponsler and Bath (I,34) are carrying out basic investigations on the physical structural aspects of protoplasmic and other cellular constituents, particularly the nucleo-protein portion of the cytoplasm which consists of particles having the dimension

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between 50 and 200 Å. In this range of particles are to be found some of the most essential portions of the cell, the enzymes and genes, and is also the range for viruses and phages. The separation is pursued by centrifugation methods and the particles are then studied by x-ray diffraction, polarized ultra-violet absorption, fluorescence and electron microscopy. The electron microscope studies have utilized particularly the nucleo-histone fibers and chromosomes from the thymus and the nucleoprotamine fibers from sardine sperm heads. The dimensions, positions of nucleic acid and the protein changes by polarized ultra-violet are also being studied.

7. Drs. Biale and Geisaman (I,32) are exploring the mechanism of electron transfer by enzyme systems. This study first has to be undertaken on normal tissues before application to tumor material can be soundly started. It has been decided to use D-amino acid oxidase as their material. Methods are being worked out for the extraction and purification of both the apoenzyme and the coenzyme.

8. Dr. Chaikoff (I,4) is delineating the iodine compounds in thyroid tumors in an attempt to determine whether any qualitative or quantitative changes occur in this group of compounds as the tissues change from the normal to the malignant. The investigation is made feasible by development of suitable methods of separating minute amounts of thyroxine and di-iodotyrosine, particularly with radioactive iodine as an ancillary tool. Tumors are being produced experimentally in animals by use of propylthiouracil and acceleration of carcinogenesis is being attempted by simultaneous use of 2-aminofluorene and I^{131}.

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The metabolic aspects and the lipid composition of a guinea pig liposarcoma as compared with normal adipose tissue are also being followed. These studies are exploratory investigations with the aim of detecting possible significant differences between the behavior of normal and neoplastic tissues.

9. Dr Bierman and his associates (I,11) have devised sensitive electrometers to measure electric potentials of tissue. Before applying this to tumors, electric potential studies have been conducted on growing chick embryos. It is now possible to record the egg potentials continuously for the entire 21-22 day life-cycle of a chick embryo. Potentials develop markedly after the 10th day and generally have a positive polarity, reaching the extreme of 20 to 50 millivolts between the 14th to 18th day. During the differentiation period of the first 5 days there is no potential beyond ± 3 millivolts. It has been observed that temperature causes the potential to move toward the positive pole.

10. A study (I,11) of formed elements of the blood exposed to ultrasonics frequencies of 835,000 per second is in progress at the Laboratory of Experimental Oncology. The number of the white blood cells falls logarithmically with a range of 0.9 to 6.7 minutes for destruction of 50 percent of the cells. The lymphocytes are less resistant to ultrasonics vibrations than polymorphonuclears. Red cell destruction by the same method has shown a half-life of the red cells of approximately 4 minutes, with a range from 1 to 5.5 minutes. Preliminary studies on leukemic cells have shown them,

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to have a [illegible] than the ultraviolet [illegible] for half-lives of [illegible] times that of the normal [illegible].

11. [illegible] has applied immunological [illegible] towards different [illegible] proteins fractionated from normal and tumor tissues obtained from human sources. Several of these fractions have been used to induce antibody formation in guinea pigs and in rabbits. The lipid fractions extracted by benzene and ether from sarcoma material were capable of inducing only non-specific reactions when tested by in vitro anaphylaxis. A more promising fraction from sarcoma was a protein obtained by 20 percent methanol precipitation. It did not cross react by in vitro anaphylaxis with normal liver or spleen fractions. Further work is being done with this fraction to establish its antigenic specificity.

Rabbits were also immunized to fractions obtained from carcinoma of the cervix, as well as liver from the same patient. These animals were bled and their sera were tested by the precipitation reaction with homologous and heterologous antigens. There is some crossing between these two tissues in the fractions tested. Precipitin absorption experiments are under way to secure the antibody speicific for the tumor antigen.

Transplantable mammary carcinoma tissue of mice has been fractionated into various components and injected into rabbits to elicit antibodies. Gamma globulin fractions were extracted from the rabbit blood. These globulins will be radio-iodated and injected into mice with mammary tumors to observe whether any localization in the tumor will occur.

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[illegible] (1,9) [illegible] techniques to the [illegible] of model [illegible] antigens. The model [illegible] are [illegible] for [illegible] into animals for the production of antibodies. The [illegible] of [illegible] bodies to these [illegible] is then tested by agglutination, precipitation and hemolysin tests.

III. Cancer-host relationships.

Cancer, as manifested in man or in animals, involves an intimate relationship between the cancer tissue and the organ and upon which it grows. The work of [illegible] investigators during the past decade has emphasized that the presence of cancer may produce many subtle changes in the organism [illegible] to the actual neoplastic growth. Comparison of animals or patients with cancer in regard to biochemical and physiological differences they might exhibit from the normal is a basic approach that may well yield new diagnostic tests for cancer and improve the clinical management of patients with cancer through better understanding of the abnormalities that result from the presence of neoplastic disease.

1. The metabolism of a number of simple organic compounds labeled with radioactive carbon has been studied by Dr. Hardin Jones (1,3) in collaboration with Dr. Calvin's group (1,2) with a view to determining whether any significant differences in metabolic pathways exists between normal and tumor-bearing animals. Among the compounds studied are the following: formate, carboxy-labeled acetate, methyl-labeled acetate, carboxy-labeled glycine, methyl-labeled glycine,

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carboxy-labeled pyruvic acid, methyl-labeled pyruvic acid, carboxy-labeled propionic acid, methyl-labeled propionic acid [illegible]. A single dose of each of these substances was administered intravenously, and the rate of excretion of the last 1/2 [illegible] was used by its rate of appearance in the exhaled carbon dioxide. At least two rates of elimination occurred for each organic compound, indicating at least two different pathways of metabolism of the labeled carbon, and each compound undergoes an individual pattern of metabolism.

The rate at which it undergoes each phase of utilization is also different for each compound and the position in which the carbon is labeled. The metabolism of each compound is independent of the presence of radiation. Some compounds, including glycine, acetate and formate, have been studied in animals receiving large doses of liver irradiation. No differences were detected qualitatively or quantitatively in the metabolism of these substances in the irradiated animals.

The metabolism of several of the above compounds was studied in animals bearing neoplasms. Of the materials studied to date, two, methyl-labeled pyruvic acid and carboxy labeled propionic acid, show significant differences between normal and neoplasm-bearing animals. For methyl-labeled pyruvic acid there are three metabolic rates of oxidation of this carbon to carbon dioxide. The second rate component is increased quantitatively and slightly slowed, while the faster and slower rate components remain practically identical with the corresponding components in normal animals. Notably, the carboxy carbon of

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propionic acid [illegible] in normal as compared with tumor-bearing animals. In the case of methyl-labeled propionic acid the amount of the labeled carbon metabolized was in the case rapid by [illegible] of [illegible] in tumor-bearing animals as compared with normal animals, this increase being apparently at the expense of that labeled material which in the normal appears in the pigment pattern. In contrast to the case of methyl-labeled propionic acid, it is found that the methyl-labeled carbon of propionic acid is metabolized more rapidly in normal than neoplasm-bearing animals.

The differences observed between normal and neoplasm-bearing animals may well be due to shifts in enzyme-metabolite balances accompanying the neoplastic state. Whether or not these differences are derived from the whole body metabolism or are due to the neoplastic tissues alone is conjectural at this time. However, the great magnitude of the effect observed is suggestive of a whole body mechanism.

2. A series of investigations on animals as well as on man are being pursued by the group composed of Drs. Low-Beer, Scott and others (I,21 and I,22), on the deposition and excretion of radioactive isotopes in animals and patients with cancer. The deposition of carrier-free complexed and uncomplexed Cb^{95}, Zr^{95}, Zn^{65}, I^{131}, di-iodofluorescein, radiothyroglobulin, La^{140}, P^{32}, Ag^{105}, Y^{48}, and Y^{91} has been studied in rats with transplantable fibrosarcoma. Satisfactory localization of Zr^{95}, Zn^{65} and Cb^{95} has been achieved. This is a lead toward investigating the same phenomenon in patients as a possible aid in the diagnosis and treatment of cancer.

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3. Similar studies of localization of radioactive isotopes have been carried out by the group (I,II and I,20) on patients in the new facilities at the Laboratory of Experimental Oncology (I,11). Au^{198}, Au^{24}, hydroxyquinoline-diiodofluorescein tagged with I^{131} have been used. No significant results can be reported as yet on patients, although it appears that continuous metabolic studies will yield more information concerning biological activity of the tumor and the tumor-host relationship than single determinations. It is anticipated that Cb^{95}, Y^{90} and Zn^{65} will shortly be applied to human metabolic studies. At present, effort is being spent in obtaining these elements free from contamination with other radioactive constituents. At the same time, the group is studying the uptake of Zn^{65} and Cb^{95} in human breast tumors in vitro. Concentrations from 5 to 100 over Tyrode solution have been obtained on the 10 human tumors so far studied. It is too early to indicate the possible extension of this investigation.

4. Dr. Biorman (I,11) has devised a method for determining pulmonary circulation time by means of the orimeter. It is now possible to determine total pulmonary circulation time, right heart and left heart circulation times. There is direct, constant relationship between anoxia and left heart circulation time, so that with increasing grades of anoxia or decreasing arterial oxygen saturation there is a shortened circulation time. By correcting for body surface area an index of approximately 3 to 3.5 seconds left heart time is obtained for normal subjects. A preliminary impression is that patients with neoplastic diseases have considerably longer circulation

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times per square meter body surface area. The slope of the circulation time curve can be altered by heroplobin, red blood cell levels, and various vasoconstricting drugs. It is hoped to adapt this method for studying the vasoactive function of the pulmonary capillary bed of patients with vascular disorders, especially those with pulmonary carcinoma or pulmonary metastases.

5. Dr. Lamman (1,11) has been studying the effect of intravenously large numbers of white cells into compatible recipients and following the disappearance of these transfused white cells. Which indicates there is a prompt removal of white cells from the peripheral blood although large numbers of such cells have been given within a few minutes. Apparently the mechanism for controlling the level of white cells in the blood is rapid and most efficient. There is some indication that the lungs play an important role in this mechanism.

6. Dr. Krichesky (1,30,a) is pursuing studies on steroid hormones in relation to cancer. The estrogen and related steroid hormones are known to have an important role in the genesis of many types of tumors in animals. Methods for determination of excretion of estrogen and 17-ketosteroid in animals have been developed, including the microchemical method which will measure estrogen in a range of 10 micrograms and less. It has been found that damage of the liver with carbon tetrachloride produces a marked peak of estrogen excretion, up to 350 times the normal level, in approximately 50 days. Despite continuation of carbon tetrachloride, however, the estrogen excretion

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returns to slightly above normal level in approximately 100 days. This phenomenon occurs in rats as well as in animals with intermittently injected [illegible] pellets. The work suggests that the liver, which is thought to play a large role in the inactivation of steroid hormones, still preserves this function in the inactivation is taken over by some (?) organs or tissue. The next step in the work is obviously the extension of it to animals with hepatic and other tumors to show whether the metabolism and inactivation of steroids is different in tumor-bearing as in contrast with normal animals.

7. Dr. Thacker (I,11) has been measuring a new enzyme, polyphenoloxidase, in human blood serum. Polyphenoloxidase activity was demonstrated in the serum of one patient with myelogenous leukemia and one with carcinoma of the larynx. No carefully controlled study has as yet been carried out with normal blood. There are indications, however, based on two determinations with normal blood, that the polyphenoloxidase activity in normal blood is kept in check by an inhibitor, such that oxidation of catechol in the presence of normal serum is inhibited for considerable lengths of time.

8. Drs. Applewhite and Shavinski (I,33) are studying the changes in hemoglobin, porphyrins and cytochrome C in tumor bearing animals and following these changes during the growth of the tumor. These porphyrin-containing entities have been described as being altered in concentration during the formation of experimental tumors. It has been found that the hemoglobin-catalase ratio in the rat cell remains constant even in advanced stages of cancer.

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9. It has been demonstrated at the Laboratory of Experimental Cardiology (I,II) that blood histamine may be extremely elevated in patients with chronic myelogenous leukemia, to values over 100 times the upper limits of normal. Since blood histamine is carried chiefly by the granulocytes, these values are in rough correlation with the white blood cell count. Of more interest, therefore, is that in acute myelogenous leukemia, during exacerbations of the disease, the blood histamine is relatively low despite very high white cell counts. Blood histamine determinations may be of prognostic importance, as all patients with high white cell counts and low histamines expired soon afterwards. Upon injection of epinephrine intravenously, blood histamine in chronic myelogenous leukemia rises sharply, but in patients with acute forms of the disease, a drop in histamine occurs. It is possible that this may be a manifestation of lack of homeostatic balance between epinephrine and histamine in acute myelogenous leukemia.

10. The hemorrhagic diathesis which complicates many cases of leukemia, and which is often the direct cause of death, is only partly understood. Thrombocytopenia alone is not the feature responsible for the bleeding tendency in this disease. Extensive blood coagulation studies have been carried out on a total of 84 patients, with leukemia and lymphoma, and on 53 normal subjects. The studies have included two new techniques developed in the Division of Medical Physics (I,3): the use of electrical resistance measurements in the quantitative determination of clotting time and clot retraction, and a modified heparin tolerance test. Although the results are incomplete, it appears that

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the modified [illegible] in patients with [illegible] that might not have [illegible] techniques for [illegible] problem.

II. Diagnosis of cancer

The discovery of a simple, early clinical test for the presence of cancer would be a [illegible] only to the discovery of an effective chemotherapeutic agent for the disease. Present data appear to indicate that it may not be feasible to anticipate any single diagnostic procedure that would be applicable to all neoplastic diseases. Studies on the nature of the cancer cell and the effects of cancer on the host, such as alterations in enzyme systems or formation of abnormal excretory products, may well yield information that would be helpful toward the development of new diagnostic tests. Another approach to this problem is to search for agents that selectively localize in tumors.

1. Wide extension of the exfoliative cytological tests for cancers in various sites is being actively developed at the Medical School in San Francisco (11,12). There has been correlation of activities in this field by placing the responsibility in the Division of Pathology. There is no question but that this method is extremely valuable for the early detection of cancer in many sites of neoplastic growth in man. Its use in cervical and uterine carcinoma has now been well established but it is also proving its worth in carcinoma of the lung, bladder, nasopharynx and stomach. In direct clinical application this is probably the most significant advance in the early diagnosis of cancer achieved in the past several decades. The field now involves

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not only additional [illegible] but wide [illegible] in the training of technical personnel [illegible], the establishment criteria, and the wide application of the method to public health preventive medicine and to clinical practice. Until scientific technical selection tests for cancer are developed, and if the concept mind appears on the horizon, this major contribution in cancer diagnosis should be fully supported and extended.

2. Dr. Farber (Ryan) has been investigating the diagnosis of carcinoma of the lung by the exfoliative cytology method. Up to December 1948, 5,000 specimens from cases suspected of having carcinoma of the lung were examined. Malignant cells were found in 100 cases. Demonstration of the malignant cells in 71 percent of 100 proved lung cancer cases is indicative that this method compares favorably with results obtained with any other diagnostic procedure for cancer of the lung.

3. Study of the effect of glucose administration on gastric lactic acid production in patients with gastric carcinoma, and in controls without gastric carcinoma, have been continued at the Laboratory of Experimental Oncology [illegible]. The results indicate that there is generally a rise in gastric lactic acid following administration of glucose to patients with gastric carcinoma, whereas in non-carcinoma cases no significant change in gastric lactic acid is observed. In two cases of gastric ulcer where a rise in gastric lactic acid was observed following glucose, there was a marked and concomitant rise in gastric pH, indicating a probable regurgitation of intestinal contents.

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The conclusion of [illegible] the gastric lactic acid present in [illegible] is probably the product of bacterial fermentation. [illegible] due to the glycolytic activity of the [illegible]. [illegible] in the gastric [illegible] to patients with gastric [illegible], [illegible] and reliable [illegible] applied to the diagnosis of gastric cancer.

4. [illegible] group (1,24) are interested in the possible presence of abnormal substances in the urine and blood in cancer-bearing animals and human subjects. The detection of such substances is to be approached by the new method of filter-paper chromatography. The use of [illegible] and others [illegible] the presence of abnormal standards in [illegible] patients and a direct attack by a new method seem well justified. At present, this research has gone towards the procurement of some essential equipment, and facilities of space are still not available to pursue the investigation. It is already reported that it will be possible to work out a quantitative method for determination of [illegible], developed by this method, which may be an important aid in the detection and study of these important substances in man.

5. Some tumors are reported to contain a concentration of [illegible] several times higher than normal tissues. If this can be substantiated and if the concentration difference is of sufficient magnitude, it is planned to investigate the use of the radioactive Ln^{65} for in vivo diagnosis of tumors. This work of Drs. Reybeck and

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[illegible] (1,4) reported the determination of Zn^{65} in various normal tissues following injection of the possibility of enhancing concentration through prior treatment with radioactive zinc. The prior treatment of [illegible] was found to be a more rapid disappearance of intravenously injected Zn^{65} as a result and more rapid excretion from the animal. Prior feeding of zinc enhanced the concentration of the radioactive zinc only in the pancreas [illegible] other tissues, the concentration in the [illegible] was found in tissues of animals which had not received zinc. [illegible] with transplanted tumors is currently being studied.

6. A novel method of obtaining increased radiographic visualization of the body elements, formulated by Dr. Luis Alvarez, is being investigated in the Division of Medical Physics [1,5]. It makes use of the fact that for each element there is an abrupt five-fold increase in its x-ray absorption coefficient at a wavelength dependent on the element. This wavelength is called the K shell characteristic absorption wavelength. Radiograms would be made of the body using X-radiation of wavelength slightly greater and less than the K wavelength of the element to be studied. All other elements in the body would have [illegible] the same absorption at both wavelengths and therefore would cast equal shadows in both radiograms, whereas the element [illegible] would be accentuated. The two radiograms would be electronically [illegible] as to their densities and a map automatically constructed which would show each area of density difference, and thus the location of the element studied.

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[illegible]

[illegible]

[illegible] investigations toward finding new [illegible] and synthetic agents for the treatment of cancer in man are being actively pursued. Although the results of these studies are far negative, some of them contribute valuable data to biochemistry and pharmacology.

[illegible] Dr. [illegible] and his associates (1,7) are continuing studies in compounds which may exert an effect on the utilization or the synthesis of essential or limiting nutrients, possible agents for the therapy of cancer. In view of the more rapid growth of tumor tissue as compared with normal tissue, it seems plausible that it may be possible by means of appropriate antimetabolites to interfere with the growth of the malignant tissue to a greater degree than with normal tissue.

The effect of certain chemical analogs of essential amino acids and vitamins on the growth of transplantable tumors in mice maintained on diets which exhibit deficient diets is being tested. The synthetic program includes the synthesis of C^{14} labeled compounds of biological interest, in particular the amino acids, and other compounds potentially useful in the investigation of cancer.

Significant progress has been made in the development of an effective program of screening with the aim of detecting the compounds of greatest biological significance. This screening program consists of the following steps: (1) the effectiveness of the compounds as growth inhibitors of standard [illegible] bacteria used in microbiological assay

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is determined; (b) the inhibiting effect of the compounds on the transplantability of a leukemia, as shown by a standard direct homogenate preparation is determined; (c) the compound is tested for toxicity and then analyzed for their action on tumor growth. These phased tests are carried out in mice in order to insure established that the dosage is maintained for one week. The animals are then sacrificed and the tumors excised, weighed and examined. To date, approximately forty compounds have been synthesized, most being quite bulky analogs. The number of compounds subjected to preliminary screenings, including those secured from other laboratories, is now over fifty. No significant activity has as yet been observed in tumors. However, observations of several interesting biological data have been made with a number of compounds.

2. Dr. Rapoport (9,8) is pursuing further studies on the chemical structure of arginase, an inhibitor of mitosis which has been shown to have some effects on experimental tumors in animals. This work is of importance in cancer research as well as being a contribution to pure organic chemistry.

3. Dr. Shecter (9,11) is conducting studies on the possible chemotherapeutic effect in lymphoma bearing mice of C,4 D, a weed killer, and several of its esters. Strain A mice bearing transplanted lymphoma, receiving varying amounts of C,4 D daily, show slower growth of the tumor than do untreated mice. The pathological findings include more cellular destruction and the presence of more pyknotic cells in the tumors of mice receiving 4 mg. of C,4 D daily than in those receiving lesser amounts or in uninjected controls.

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From [illegible] on transplantable tumors [illegible] of [illegible], in addition to [illegible] and [illegible].

4. [illegible] Chang [illegible] interested in the effect of [illegible] particularly from the [illegible] species, upon growth of [illegible] tissue. This [illegible] of investigation is still in the preliminary stage of [illegible] the [illegible] equipment [illegible].

5. The extensive formation of melanin by melanoma led to the suggestion of [illegible] the localization of radioactivity in such tumors through the administration of a [illegible] prepared labeled with carbon-14. [illegible] and dopa were prepared with [illegible] methyl bridge, [illegible] and [illegible] (3,5) and were administered to mice bearing transplantable melanoma. While the accumulation of tyrosine in the tumor was substantially higher than that of the liver, intestine, adrenal, and thyroid. Radioactive tyrosine, therefore, itself offers promise as a therapeutic agent against melanoma. The situation was not as good for dopa. Although these compounds have not proved useful as agents for selective irradiation of melanoma, they have provided information on the metabolism of melanin precursors.

6. Drs. Tobias and Lawrence [1,2] have studied the properties of the deuteron and alpha particle beams of the 184" cyclotron in an attempt to produce new methods for depth dose therapy. The 190 Mev deuteron beam penetrates [illegible] 16 cm. in tissue and the ionization near the end of the range of the beam is approximately four times that at the high energy portion. Most of the ionization occurs in the last one-half inch of the range of the widening of the beam due to scattering

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[illegible] the end of the range of the [illegible]. Thus there is still it was possible to irradiate [illegible] [illegible] by [illegible] the beam was directed through the body of the [illegible] before it reached the tumor. This [illegible] percentage of cases complete regression was obtained without lethal effects to the [illegible] zone of [illegible] tissue was required for [illegible] while all the control patients were [illegible] to death. Further work is being continued in an effort to improve the localization of the depth dose and also to study the physiological and long range effects of the new type of irradiation produced by the cyclotron.

B. Clinical.

Inherent to the evaluation of any clinical diagnostic and therapeutic measure is the study of the natural history of the disease through constant careful follow-up observations of patients subjected to various diagnostic and therapeutic procedures. Progress in clinical investigations is impossible without periodic and continual collection and analysis of case data. The General Tumor Registry [1,10] serves this purpose for the Medical School in San Francisco. At present the Registry has [illegible] 1,000 cases of cancer seen at the University of California in 1947. These were analyzed according to sex, age, duration of symptoms, method of treatment, and survival. A new method of coding in conformity with the California State Department of Public Health forms has been established, making the data available to the Department of Public Health as well as to the staff of the hospital. Follow up secretaries are responsible for keeping track of cases.

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The Department Medical has a registry of 8,000 cases, of which 700 are alive and being followed. The Gynecology Division has 1,000 registered cases, of which 175 are alive and being followed. The Radiology Division has over 4,000 cases, of which 1,000 are alive and being followed and the Pathology Department has approximately 500 active cases in its followup. Some time in the scientific survey and evaluation are made of certain types or groups of tumors. The Division of Neurological Surgery (1,25) is at present reviewing and evaluating the diagnosis and therapy of all brain tumors seen at the University of California Hospital during the past 20 years. It is inevitable that careful reviews of this type will not only allow greater understanding of the biologic problems involved but will also serve to estimate the present and past modes of therapy, in order to improve diagnosis and therapy of clinical cancer.

1. Active work is proceeding in the Division of Surgery in the Medical School in San Francisco (1,19) on several phases of investigating improvements in sphincter procedures. It has been found that free peritoneal fascia grafts are quite effective in the repair of large gastric and intestinal defects in dogs.

2. A new technique of irradiation is being investigated by the staff of the Division of Medical Physics (1,6). The method consists in injection and irradiation of high intensity (about 50 kv) directly into the region of the tumor. The amount of radiation delivered would not be impeded by adipose of other parts of the body as are present methods for deep therapy. Preliminary measurements

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[illegible] radioactive [illegible] passed through copper tubes [illegible] to 1/2 inch in diameter and [illegible] inches long to deliver a therapeutic dose [illegible] to the tissues. The [illegible] radiation is [illegible] from the body and the [illegible] of the [illegible] of the tissues and.

B. A collaborative effort of the Division of Medical Physics (DMP) and the MD staff of Bikini is devoted to the evaluation of radioactive colloids of phosphorus (P^{32}) in malignant disease.

Conclusions can be drawn only after long-term follow-up, but certain facts appear well established: (a) The distribution of the radioactive colloids, as studied from post mortem material, is essentially similar in man to that in animals. (b) Excretion studies indicate that [illegible] percent of the injected dose of radioactive colloid is excreted following intravenous administration. This means that [illegible] can be counted upon to produce radiation effects. (c) In chronic myelogenous leukemia, chronic lymphatic leukemia, and polycythemia vera definite remissions, both hematological and clinical, have been obtained. The dose of radioactive colloid required to produce a remission is variable from patient to patient, just as it is with other forms of therapy. To date the responses obtained just as with P^{32}. (d) Patients who have had some other form of therapy in adequate amounts, such as X-ray or P^{32}, and who have become refractory to such therapy do not seem to be benefited by radioactive colloids. (e) Patients with acute leukemias or in the acute phase of chronic leukemias show the same

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[illegible] association [illegible] with [illegible] therapy as they do with other forms of therapy. (f) Patients with clinical leukemia are not protected from [illegible] the [illegible] of their disease by this therapy.

4. [illegible], in the development of studies on physical improvement of [illegible], nutrition and health protective [illegible] have been [illegible] to provide certain needed equipment. Now [illegible] in [illegible] distribution of space provided for setup and use. These studies are [illegible] and results until [illegible] physical facilities of [illegible] are developed.

5. The laboratory of Experimental Oncology and other divisions of the project [illegible] continuing trials on new chemotherapeutic agents being [illegible] for clinical use in neoplastic diseases.

a. Over [illegible] patients with Hodgkin's disease and cancer have now been treated with the nitrogen mustards (HN2) in this area. The standard procedure now employed is 0.8 mg. per kg. body weight in a single dose, with possible repetition of 4 to 6.0 mg. per kg. if the smaller dose produces no toxic effects and if the hematologic status of the patient allows the therapy some 4 to 6 weeks later. An alternate method of administration of intravenous procaine with nitrogen mustard [illegible] has been started, the evidence so far has been equivocal. A [illegible] for first 27 patients treated is now in press.

b. A series of patients treated with "dioptorin" or "hemipterin" has been [illegible] after 17 cases, 8 of whom received

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Hot in addition. In no case was there objective evidence of any effect on the progress of the malignant disease; occasional temporary feeling of well-being is reported by Bruber and Lehr, has been observed but may be attributed to psychologic factors.

c. Six patients with acute leukemia have been treated with 6-mercaptopurine (6-MP) (Purinethol). Four of these patients died within 2 weeks while still on therapy; 2 patients remain alive after approximately 2 weeks of treatment. There has been no startling improvement, although the progress of the disease apparently abated in 2 of these patients with regression of lymph nodes, spleen, and petechiae.

d. A preparation which has received considerable interest locally, cryptophine dipentyppine, is being tried in a series of patients with a variety of neoplastic diseases. To far, 10 patients have received or are receiving daily injections of 20 or 60 mgm. of the preparation, which is furnished by the Easter Laboratory of San Francisco. To date no there been any evidence of effect upon tumor growth or clinical condition, and 6 patients have died.

e. Three patients with melanoma received oral monobenzyl ether of hydroquinone, a chemical known to block melanin formation. In all three there was apparent increase in the rate of tumor growth after beginning of the medication for three 2 weeks. Histologic section of one tumor of two patients showed only increased vascularity of the tumors.

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5. A collaborative study of the Laboratory of Experimental Oncology with Drs. [illegible] of the Medical School has been undertaken to study the possible effect of virus infections in patients with [illegible]. Previously, the rat pancytopenia virus (a non-[illegible]) and [illegible] were chosen for the first studies. The choice was based on laboratory reports that viruses can selectively [illegible] tissue of mice, and at least one has been reported to have [illegible] properties on such tumor growth. A direct [illegible] was not deemed desirable, since the high species specificity of tissue [illegible] results of animal studies inapplicable to man.

CONCLUSIONS

The University of California program in cancer research is on a solid footing, and is developing further in an orderly, soundly scientific manner. It is a well-rounded program, but could be improved by the stronger inclusion of two fields of endeavor: animal genetics, experimental embryology, [illegible] (especially plant tumors), and tissue culture. The increased participation of at least two of these fields in cancer research at the University may be anticipated within the forthcoming years. It is [illegible] apparent that this million-dollar program would be facilitated by the release of a full-time administrator, one of whose functions would be to integrate more closely the projects supported by funds outside of University sources.

In an undertaking of the size of the University of California program in cancer research, at least a year is necessary for the

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[illegible] of [illegible] and [illegible] potential to pursue the work, and another [illegible] to checking technical methods, [illegible] of the most promising principles for experimentation, and [illegible] [illegible]. [illegible], most basic problems have [illegible] and [illegible] of [illegible] animals to human disease before the results can be applied to the control of the animals bearing cancer or with [illegible]. The majority of the research problems in [illegible] are [illegible] less than a year old, and [illegible] to the [illegible] and biological problems. It is therefore [illegible] that [illegible] of [illegible] or advances in most of the projects of this [illegible]. Before expansion of the program which was initiated [illegible] can expect definite findings, but significant contributions from the program cannot be expected to start before the [illegible] years have elapsed, and this is predicated on continued adequate financial support on a long-term basis. It should be a matter of satisfaction that [illegible] individual scientists indicate that approximately [illegible] directly related in their content to cancer have appeared in [illegible] to the technical literature (see Appendix [illegible]), and [illegible] equal number of investigations are being prepared for publication.

The greatest limitations to progress are due to the delayed construction of essential physical facilities for the medical schools in San Francisco and in Los Angeles. Neither equipment nor personnel are of use if no space exists to house them. The full development of the cancer program, therefore, cannot take place until the projected building program is

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ADDENDUM

Allocation of State Appropriation, 1947-48 and 1948-49
for Cancer Research Program, University of California

Central Stores	(Meeting Date)	(Amount)
1. Secretariat, Cancer Research Committee		
Guadalupe, Cal Branch Research	Sept 47	2,317
Guadalupe, Northern Section	May 48	4,000*
2. Secretariat, Cancer Research Committee,	Sept 47	4,350
Southern Section	May 48	5,130*
3. Research Stores:	Sept 47	2,000
1-Northern	May 48	1,500*
2-Southern	Sept 47	1,000
	May 48	1,000*
4. Administrative Charge	May 48	1,500*

($23,797)

Berkeley

Chief Investigator, and Title of Project

1. Evans, H. M., Institute of Experimental Biology		
Study of tumors resulting from chronic	Dec 47	5,000
administration of pure growth hormone	May 48	5,500
2. Division of Chemistry (Cohen, S., Dutton, R. C. and Rapoport, H.)		
a. Synthesis of carcinogenic hydrocarbons with C^{14}		
b. Study of chemical structure of colchicine		
c. Synthesis of high molecular weight fatty acids containing C^{14} and	Sept 47	4,000
Isolating of fatty acids from tumors	Dec 47	600
Heading equipment	May 48	8,400

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5. Division of Medical Physics (Lawrence, J. H., Hamilton, L. D., Cuttler, J. G., Lewis, H., Tobias, C. A., and Zelle, M. E.)			
Study of normal and malignant processes, in neoplastic tissues as of hospitals and MTA, and individual effects of radiation	Sept 47	21,210	
	Dec 47	9,410	(3,820*)
	May 48	16,000	
6. Sheriff, F. J., Division of Physiology			
Study of specific patterns of normal and neoplastic tissues using radioactive tracers	Sept 47	6,000	
	May 48	6,000	
7. Sponsoff, H. and Fanning, M. D., Division of Bacteriology			
Growth, virus-bacteriophage interaction	Sept 47	3,500	
	May 48	3,500	
8. Ross, M. A., Department of Zoology			
Study of phosphorus in relation to the metabolic processes	May 48	2,000	
9. Rheinberg, J. R., Division of Bacteriology	Sept 47	10,000	
Biochemical studies on the nature and reproduction of bacterial growth	Dec 47	2,750	(2,287*)
	May 48	10,000	
10. Allen, F. M., Division of Biochemistry			
Chemistry of nucleic acids	May 48	5,100	
11. Harris, M., Division of Zoology			
Establishment of tissue culture laboratory	Pending	5,880	
			($205,282)

San Francisco

12. Shmit, V. A., Spectrographic Laboratory			
Extension of existing spectrographic facilities to cancer research	Dec 47	5,500	
13. Shirkin, H. R., Intern, Lab. of Experimental Oncology			
a. Study of physiology and experimental chemotherapy of cancer patients	Sept 47	10,000	
	May 48	10,500	
b. Maintenance of laboratory of Experimental Oncology	May 48	4,500	

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12. Fitch, J. T. and Wallace, H. A., College of Pharmacy		
Study of synthetic and chemotherapeutic agents for cancer	Sept 47	4,010
class.	May 48	1,500*
13. Hood, S. R., College of Dentistry		
Study of the relationship of regional and migratory to resistance of cancer	Dec 47	8,500
14. Kuhlen, R. W., Division of Medicine		
Study of cystic adenomatoid malformation in carcinoma of the lung	Sept 47	5,000
	May 48	10,000
15. Neffelgren, R. A. and Andrews, E. D., Division of Neurological Surgery	Sept 47	3,150
Review of tumors of the nervous system	May 48	1,000 (050*)
16. Ohem, F. L., Division of Pathology		
Study of fibrinolytic function in cancer	May 48	1,500*
17. Rinehart, J. F., Division of Pathology		
a. Development of basic scientific equipment	Sept 47	25,000
	Dec 47	1,000
b. Study of constitutional factors influencing aging and their relationship to cancer (with Greenberg, L. D.)	Sept 47	5,000
	May 48	10,000
c. Pathology Unit, Laguna Honda Home (with Shimkin, M. B.)	Sept 47	10,000
	May 48	7,000
18. Stern, R. S., Cancer Research Institute	Dec 47	1,000
General Tumor Registry	May 48	7,540
19. Wahrhaftig, H. R., Division of Surgery		
Operative technique and radioactive iodine studies of thyroid tumors	Sept 47	1,910
	May 48	3,500
20. Stone, R. S., Division of Radiology		
Physical measurement of ionizing radiation and develop quantitative measures	Sept 47	7,000
	Dec 47	1,000*
	May 48	9,400
21. Law-Tsar, D. W. Y., Division of Radiology		
Continuous metabolic studies on human patients using radioactive isotopes (with Scott, R. C. and Shimkin, M. B.)	Dec 47	6,185*
	May 48	9,500

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[illegible]. [illegible], Division of Zoology
a. Study of the composition of medullated nerves in experimental animals (with [illegible], M. D., A.) — May 48 — 6,400
b. Study of the composition of medullated nerves in human tumors (with [illegible], M. D., A.) — May 48 — 7,110
(Pathology, [illegible]) — Pending — 800

[illegible], [illegible], Division of Zoology
Study of pathologic processes of thyroid gland — Pending — 1,130

($194,525)

Los Angeles

[illegible], [illegible], Medical School
Study for acetone in urine and blood of [illegible]-bearing animals and human subjects by the [illegible] paper chromatograph method — [illegible] 47 — 1,050; May 48 — 3,850

[illegible], [illegible], Medical School
Obtain basic equipment for a new cancer research laboratory in the Medical School, Los Angeles — Dec 47 — 14,050; Pending — 2,500

26. Dowdy, A. H., Medical School
Study of the effect of bacterial toxins upon cancer — May 48 — 13,050

27. Naylor, J., Division of Physics
Identification of lipoid fractions from cancerous livers — Sept 47 — 3,125

28. Hallery, A. M., Division of Zoology
Identification of lipoid fraction from liver and body fluids of cancer patients — Sept 47 — 4,525

29. Scherchman, A. N., Division of Zoology
Immunological and biochemical studies of constituents of normal and neoplastic tissues — Dec 47 — 1,000; May 48 — 5,375; Pending — 210

30. Krichesky, B., Division of Zoology — Sept 47 — 4,450
a. Study of steroid hormones and fractions in cancer — Dec 47 — 850*; May 48 — 6,020; Pending — 800

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[illegible]	[illegible] Study of [illegible] of [illegible] [illegible] (with [illegible], T. A.)	May 48	6,640
[illegible]	[illegible], B. [illegible], Division of Chemistry		
	Study of [illegible] and [illegible] in [illegible]	Dec 47	4,665
	[illegible] of [illegible] and [illegible]	May 48	6,275
[illegible]	[illegible], B. [illegible] and [illegible], T. A., College of Agriculture and Division of Chemistry		
	Study of the [illegible] of protein [illegible] electron	Sept 47	5,200
	[illegible] [illegible] in [illegible] enzymes	Dec 47	1,200*
		May 48	4,950
[illegible]	[illegible], T. [illegible], College of Agriculture		
	Study of [illegible] of [illegible]	Sept 47	4,500
	[illegible] [illegible] of [illegible] of	Dec 47	500*
	[illegible] and [illegible]	May 48	7,000
[illegible]	[illegible], [illegible], T. A., Division of Anatomy		
	Studies of structural aspects of protoplasm [illegible] and [illegible]	Dec 47	3,200
	[illegible]	May 48	3,150
			($111,235)
	TOTAL		$534,839

Allocated from [illegible] funds, as follows:

		Sept 47:	Dec 47:	May 48:
Albert C. Hooper Fund:				
Central Items:	4.			4,000
	5.			5,130
	6.			1,500
	8.			1,000
	9.			1,500
Berkeley:	7		2,950	
	9		2,287	
San Francisco:	15			1,500
	18			1,000
	20		1,000	
	21		6,485	
Los Angeles:	30		850	
	32		1,200	
	33		500	
TOTAL			$15,272	$15,630
Kate S. Schutz Cancer Research Fund:				
Berkeley	3		870	
San Francisco:	14			850
TOTAL			$870	$850

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Addendum I, continued:

Fund Available for Allocation	1947-48	1948-49	Total
Endowment Funds:			
Hooper	15,872	21,268.43	36,540.43
Debts	870	850	1,720
State appropriations	250,000	250,000	500,000
TOTAL	$266,742	$272,118.43	$538,260.43

Funds Allocated:

Endowment Funds:				
Debts	Berkeley	870		870
	San Francisco		850	850
		(870)	(850)	(1,720)
Hooper	General Items		13,130	13,130
	Berkeley	5,237		5,237
	San Francisco	7,485	2,500	9,985
	Los Angeles	2,550		2,550
		(15,272)	(15,630)	(30,902)
State appropriations:				
	General Items	10,667		10,667
	Berkeley	94,795	98,500	193,295
	San Francisco	93,870	37,890	131,760
	Los Angeles	49,165	56,010	105,175
		(248,497)	(242,400)	(490,897)
Pending allocation:				
	Berkeley		5,880	5,880
	San Francisco		1,930	1,930
	Los Angeles		3,510	3,510
			(11,320)	(11,320)
	TOTAL	$264,639	$270,300	$534,839

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[illegible]

APPENDIX [illegible]

Projects Approved on the [illegible] Public Health Service, [illegible]

Investigator	Initiated	Credit
1. [illegible], [illegible] Pathology Study [illegible] [illegible] gastric, differentiation and development of [illegible]	[illegible]	$16,608.00
2. [illegible], [illegible] and [illegible], [illegible], Biology Antagonism to [illegible] as influenced by physiological [illegible] of the [illegible] [illegible]	[illegible]	[illegible]
3. [illegible], S., Biochemistry Studies on transportation of blood amino acids [illegible] in [illegible]	[illegible]	4,000.00
4. Greenberg, [illegible] W., Pharmacology Isotopic tracer studies of tissue synthesis and the [illegible] of metabolic [illegible]	[illegible]	[illegible]
5. Chaikoff, I. L., Physiology Radioactive iodine and radioactive carbon as indicators of metabolism and thyroid function	8/46	8,532.00
6. Lawrence, [illegible] H., Medical Physics Pathological physiology of polycythemia	8/46	[illegible]
7. Evans, H. [illegible], Institute of Experimental Biology Biological [illegible] and physico-chemical properties of pure growth and adrenocorticotrophic hormones	[illegible]	21,240.00
8. Kirk, [illegible] L., Biochemistry Studies in [illegible] ophthalmological chemistry	10/48	1,620.00

(65,090.35)

San Francisco

9. **Eiler, J. J., College of Pharmacy** **Study of the efficiency of aerobic and anaerobic phosphorylation in surviving slices of normal and tumor-bearing tissues**	**8/48**	**5,724.00**

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Addendum II, continued.

30. Bortick, [illegible], Stanford Serial passage of [illegible] virus disease extracts in [illegible] chicken embryo	9/46	2,556.00
31. Grimsby, [illegible], Department of Experimental Pathology Evidence for [illegible] in patients [illegible] of patients of [illegible] and [illegible]	8,[illegible]/46	[illegible]
32. Moore, E. [illegible], Pathology Induction of [illegible]	1/46	2,091.00
33. Rippenart, [illegible], Medical School Laboratory [illegible] tests for [illegible]	7/46	40,550.00 **
		(133,755.50)

Los Angeles:

34. Zeisman, T. A. and [illegible], Chemistry and Agriculture Role of protein [illegible] transfer system in resp. [illegible]	5/46	5,000.00
35. Dunn, M. S., Chemistry Requirements of microorganisms for amino acids and other nutrients	8,11/46	7,790.00
36. White, A., Biochemistry Study of the [illegible] of endocrine secretions on the [illegible] and function of lymphoid tissue	10/46	9,720.00
		(22,510.00)
TOTAL		$221,348.85

*Accepted by Regents [illegible] month indicated.

**Through California [illegible] of Public Health.

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APPENDIX III

Projects Supported by the American Cancer Society

Committee on Growth

Berkeley:	Date:*	Rec'd:
1. Kirk, P. L., Biochemistry		
a. Quantitative chemical studies of cellular protein and metabolism in tissue culture	1-7/48	10,950.50
b. Study of attenuation of tissue culture virus	10/48	3,950.50
2. Tarver, H., Biochemistry. Studies on protein turnover and vitro protein synthesis with radioactive isotopes of sulfur	1-10/48	7,219.50
3. Greenberg, D. M., Biochemistry. Isotopic tracer studies on enzymes and mechanism of protein synthesis	1-10/48	7,555.01
4. Evans, H. M., Institute of Experimental Biology		
a. Nature and function of growth hormone	4-10/48	15,101.00
b. Research on the relation of the growth hormone to neoplasms	7-10/48	13,012.50
5. Chaikoff, I. L., Physiology		
a. Study of synthetic processes in the diabetic animal as studied with radioactive glucose and palmitic acid	8-10/48	4,725.00
b. Study of cerebrin synthesis in the animal body with radioactive isotopes	8-10/48	420.00
c. Studies on the use of radioactive iodine as indicator of thyroid function	2-8/48	1,475.00
6. Laboratory expenses for fellowship holders.		
a. Dr. W. D. Fraser (under Dr. Wendell M. Stanley)	10/48	500.00
b. Dr. C. M. Grisham (under Dr. D. M. Greenberg)	11/48	500.00
c. Dr. E. Farber (under Dr. D. M. Greenberg)	5-7-48	1,000.00
		(54,459.02)

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Los Angeles:

7.	Dunn, M. S., Chemistry Relation of [illegible] acids to growth	1-11/48	7,530.00
8.	White, A., Biochemistry Biophysics of the lymphocyte (Research project transferred from Yale University)	9-11-48	4,200.00
			(11,730.00)

American Cancer Society, California Division

San Francisco:

9.	Research in pathology	7/48	6,250.00
10.	Cancer research	10-11/48	2,659.31
11.	For research on the relation between cancer growth and its host, studied with radio-isotopes (From the Henry and Laura and Irene P. Dernham Fund)	11/48	15,680.00
			(24,589.31)

TOTAL: $90,778.33

*Accepted by Regents during month or months indicated.

University of California at Berkeley
Contract No. W-7405-Eng-48 with the United States Atomic Energy Commission
COPY

ADDENDUM IV

Publications

Bern, H. A., Urinary and Genital Tract Phosphatases of the Male Dutch Rabbit, Am. J. Physiol. (in press).

Bierman, E. S., A Device for Recording Pulse Physiologic Pressure Phenomena Using the Linded SR-4 Electrical Wire Resistance Strain Gage, Review Scient. Instruments, 19: 707-710, 1948.

Bierman, H. R., Newer Methods of Treatment of Leukemias and Lymphomas, Calif. Med., 69: 284-289, 1948.

Bierman, H. R., Shimkin, M. B., Dettler, G. R., Weaver, J., Berry, W. C. and Wiss, O. R., Metaphedis (beta-chloroethyl)amine in Large Doses in the Treatment of Neoplastic Diseases, J. Nat. Cancer Inst. (in press)

Bostick, W. L., The Serial Passage of Hodgkin's Disease Tissue Extract in Chicken Eggs, J. Immunol. 59: 189-193, 1948.

Dauben, W., Biology of Methylcholanthrene Labeled with C^{14}, Cancer (in press).

Davis, D. and Slater, C., Androgen 17-Ketosteroid Ratios in Normal Rabbit Urine (in press).

DeKoning, J., Krichesky, M. and Glass, S. J., Total 17-Ketosteroid Excretion in Normal and Ovariectomized Rabbits, Proc. Soc. Exper. Biol. & Med., 68: 320-322, 1948.

DeKoning, J., Krichesky, M. and Glass, S. J., Effect of Orally Administered Sodium Estrone Sulfate on Total 17-Ketosteroid Excretion in Female Rabbits, Proc. Soc. Exper. Biol. & Med., 68: 322-323, 1948.

DeOme, K. B., Julian, L. M. and Streit, L. A., Preliminary Note on the Effect of Sesamine on the Carcinogenic Potency of 3-4 Benzpyrene in Sesame Oil, presented for Symposium on Cancer held by Societe de Pathologie Comparee, October 1948 (manuscript in preparation)

Eiler, J. J. and McEwen, W. K., The Effect of Pentobarbitol on Aerobic Phosphorylation in Brain Homogenates, Arch. Biochem. (in press)

Farber, S. M., Benioff, M. A. and Tobias, G., Primary Carcinoma of the Lung: Diagnosis by Cytological Studies of Sputum and Bronchial Secretions, Calif. Med., 68: 95-99, 1948.

COPY

Barber, S. M., Benioff, A. [illegible], Frost, J. K., Rosenthal, M. and Tobias, G., Cytological Studies of Sputum and Bronchial Secretions in Primary Carcinoma of the Lung, J. Am. Coll. Chest Phys., 14: 633, Sept.-Oct., 1948.

Friedberg, F., Winnick, [illegible] Greenberg, D. M., Incorporation of Labeled Glycine into the Protein of Tissue Homogenates, J. Biol. Chem., 170: [illegible], 1947.

Friedberg, F., Schulman, [illegible] Greenberg, D. M., The Effect of Growth on the Incorporation of Glycine Labeled with Radioactive Carbon into the Proteins of Liver Homogenates, J. Biol. Chem., 178: 437-438, 1948.

Reiner, M., Brinkesky, [illegible], Effect of Induced Liver Cirrhosis on the Reproductive System of the Male Rat, Proc. Soc. Exper. Biol. & Med., [illegible]-239, 1947.

Gofman, J. W. and Jones, [illegible], Application of Radioactive Colloids in the Therapy of Neoplastic Disease, J. Clin. Investigation (in press)

Gofman, J. W., Elliott, [illegible] Lindgren, F., Ultracentrifugal Studies of the Lipoproteins of Human Serum, J. Phys. and Colloid Chem. (in press).

Greenberg, D. M. and Schulman, M. P., Application of "Metabolite Antagonism" to Cancer Research, Science, 106: 271-272, 1947.

Greenberg, D. M., and Rao Sanadi, D., The Effect of Amino Acid Deficiencies on the Incorporation of Radioactive Carbon-labeled Amino Acids into Animal Tissue Proteins, Proc. Soc. Exp. Biol. & Med. (in press)

Greenberg, D. M. and Winnick, T., The Transformation in the Rat of Carboxyl-labeled Acetate, Methyl-labeled Acetate, and Labeled Bicarbonate into Amino Acids, Arch. Biochem. (in press).

Greenberg, D. M., Friedberg, F., Schulman, M. P., and Winnick, T., Studies on the Mechanism of Protein Synthesis with Radioactive Carbon-labeled Compounds, Cold Spring Harbor Symposia on Quantitative Biology (in press).

Jones, H. B., Heidelberger, [illegible] and Calvin, M., Metabolism of Certain Simple Carbon Compounds with Special References to Differences between Normal and Neoplastic Animals, J. Biol. Chem. (in press).

COPY

Krichesky, B. and Glass, [illegible], Estrogenic Activity of Rabbit Whole Blood Determined by the Intravaginal Pellet Method, Endocrinol., 40: 192-198, 1947.

Krichesky, B. and Glass, [illegible], Vaginal Cornification in Spayed Rats by Intra-vaginal Application of Non-estrogenic Substances, Endocrinol., [illegible], 1947.

Lawrence, J. H., Falconer, [illegible] and Hofman, J. W., Experiences in the Clinical Application of Radioactive Colloids of Yttrium in the Therapy of Leukemia and Polycythemia Vera, J. Clin. Investigation (in press).

Mace, G. T. and Schechtman, [illegible], Development of Non-vitelloid Substances in the Blood of the Chick Embryo, J. Exper. Zool., 108: 217-234, 1948.

Metzeld, [illegible], Synthesis of Chlorogenic Acid and Glycine Labeled with Radioactive Carbon in the Carboxyl Group, J. Biol. Chem., 173: 207-209, 1948.

Mitchart, J. F. and Greenberg, [illegible], Arteriosclerotic Lesions in Pyridoxine Deficient Animals, Fed. Proc., 7: March 1948 (abstract)

Schechtman, A. M., Antigens in Early Developmental Stages of the Chick, J. Exper. Zool., 105: 329-348, 1947.

Schechtman, A. M., Organ Antigens in the Early Chick Embryo, Proc. Soc. Exper. Biol. & Med., 68: 263-266, 1948.

Schechtman, A. M., Detection of the Phospho-protein, Vitellin, in the Serum of the Fowl, Proc. Soc. Exper. Biol. & Med. (in press)

Schechtman, A. M., Vitellin Substances in the Serum of the Developing Chick, J. Exper. Zool. (in press)

Sponsler, O. L. and Bath, [illegible], An Alternative Method for the Culture of Sciara Larvae, Science (in press)

Sponsler, O. L. and Bath, [illegible], Molecular Basis for Protoplasmic Study, (abstract of book submitted to publisher; final revision of manuscript of book in process)

Stanier, R. Y., The Oxidation of Aromatic Compounds by Fluorescent Pseudomonads, J. Bacteriol., [illegible] 477-494, 1948.

COPY

Strait, L. A. and DeOme, K. B., Desoxycorticosterone Acetate, Mammary Gland Growth and Carcinogenesis in Mice, Cancer Research, 7: 310-311, 1947.

Strait, L. A., Hrenoff, A. W., and DeOme, K. B., The Influence of Solvents upon the Effectiveness of Carcinogenic Agents, Cancer Research, 8: [illegible], 1948.

Schacter, B. and Shimkin, M. B., Carbonic Anhydrase Content of Normal and Neoplastic Tissues, J. Nat. Cancer Inst. (in press)

Shimkin, M. B., Breast Cancer in Mice, Calif. Med., 68: 264-269, 1948.

Shimkin, M. B., Intracranial Metastasis of Primary Pulmonary Carcinoma, Calif. Med., 69: 224-[illegible], 1948.

Shimkin, M. B., Sapirstein, [illegible], Goetzl, F. R., Wheeler, P. M. and Berlin, N. I., Blood Histamine in Leukemia and Erythremia, J. Nat. Cancer Inst. (in press).

Shimkin, M. B. and Bierman, [illegible] R., Experimental Chemotherapy of Neoplastic Diseases, Radiology (in press).

Tobias, C. A., Anger, H., Weymouth, P. P., and Dobson, R. L., The Radiological Use of High Energy Deuteron Beams, AECD 2099-A.

Winnick, T., Friedberg, F. and Greenberg, D. M., The Utilization of Labeled Glycine in the Process of Amino Acid Incorporation by the Protein of Liver Homogenate, J. Biol. Chem., 175: 117-126, 1948.

Winnick, T., Moring-Claesson, I., and Greenberg, D. M., Distribution of Radioactive Carbon Among Certain Amino Acids of Liver Homogenate Protein, Following Uptake Experiments with Labeled Glycine, J. Biol. Chem., 175: 127-132, 1948.

Winnick, T., Friedberg, F. and Greenberg, D. M., Incorporation of C^{14}-labeled Glycine into Intestinal Tissue and its Inhibition of Azide, Arch. Biochem., 15: 160-161, 1947.

Winnick, T., Friedberg, F. and Greenberg, D. M., Studies in Protein Metabolism with Compounds Labeled with Radioactive Carbon. I. Metabolism of DL-tyrosine in the Normal and Tumor-Bearing Rat, J. Biol. Chem. 173: 189-197, 1948.