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S. L. Warren

Laboratory of Experimental Oncology
Laguna Honda Home
San Francisco 16, California

9 July 1951

MEMORANDUM:

To: Members of the Cancer Board, Cancer Research Coordinating and Northern Committees.

From: Michael B. Shimkin, M.D.

Attached is the Annual Report of the Laboratory of Experimental Oncology, transmitted to you for your information. It is requested that the use of the report be restricted to administrative, intramural purposes.

Attached: Annual Report

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LABORATORY OF EXPERIMENTAL ONCOLOGY

ANNUAL REPORT 1950-1951

TABLE OF CONTENTS

INTRODUCTION..... 2

RESEARCH PROGRAM..... 4
1. Physiologic dynamics of leukocytes in vivo in man.... 5
2. Blood supply of tumors in man..... 10
3. Experimental therapy of neoplastic disease in man.... 12
4. Biochemical effects of experimental therapy..... 16
5. Immunochemical studies of tissue proteins..... 18
6. Nucleic acids and nucleoproteins..... 20
7. Radio-iodated antibodies and other proteins..... 23
8. Other activities..... 25

ADDENDA
1. Professional staffs..... 28
2. Clinical work of the research ward..... 30
3. Publications..... 31

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INTRODUCTION

The Laboratory of Experimental Oncology is a Section of the National Cancer Institute and a Laboratory of the University of California School of Medicine. It was detailed from the National Cancer Institute to the University of California in January 1947, for cooperative clinical and laboratory investigations on neoplastic diseases. The main financial support is derived directly from the National Cancer Institute, and supplemented by funds from the University of California, which also furnishes the essential professional consultations and collaboration by various members of the Faculty of the School of Medicine. The Laboratory is housed in the Laguna Honda Home, by arrangement between the University of California and the Department of Public Health of San Francisco. In 1953, it is scheduled to move to its new quarters at the Moffitt Hospital, now under construction at the Medical Center of the University of California.

The major objective of the Laboratory is clinical research in cancer. With the cancer patient as the focal point of investigation, the work is oriented along four broad approaches: (1) Experimental therapy, providing clinical material for other studies as well as permitting evaluation of such procedures on neoplastic diseases; (2) Physiology, particularly hematologic physiology of patients with

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neoplastic diseases; (3) Biochemistry, particularly specific biochemical reactions and radioactive tracer studies on cancer patients, and (4) The study of protein fractions of cancer and normal tissues of human and animal origin, utilizing physicochemical and immunochemical techniques.

Reference is made to the Annual Reports of the Laboratory of Experimental Oncology for 1947-48, 1948-49 and 1949-50, which present the administrative and research developments during the first three years of activity. The personnel, finances, physical facilities and equipment remain at approximately the same levels as in 1949-50. A major administrative modification is entailed in the transfer of the support of the research ward from National Cancer Institute Grant C-396 to a contract basis between the National Cancer Institute and the University of California, scheduled to become effective July 1, 1951.

The present staff of the Laboratory numbers 51. Of these, 13 are of professional rank and are listed in Addendum I. The list also includes the members of the active consulting and the collaborating staff from the Faculty of the University of California School of Medicine.

The clinical work in terms of patients seen and studied at the Laboratory since the opening of the research ward on July 6, 1948, is summarized in Addendum II.

The publications of the staff since the inception of the Laboratory are listed in Addendum III.

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RESEARCH PROGRAM

The primary research achievements of the Laboratory of Experimental Oncology during the past year include the following:

1. Discovery of the importance of the lung in the physiologic dynamics of leukocytes in man, and the demonstration of the importance of the leukocyte removal mechanisms in leukemia.

2. Demonstration by new arteriography methods of the increased vascular supply of tumors in man, and the application of the finding to diagnosis, treatment and physiologic studies.

3. Appraisal of several chemotherapeutic agents in cancer in man, with negative results, and the study of a patient with melanoma in whom the hypophysis was removed surgically.

4. Development of accurate quantitative methods for the preparation of stable radio-iodated proteins, and their use in laboratory and clinical studies.

5. Development of a new micro-spectrophotometric method for measuring the state of titration of the acidic and basic groups of nucleic acids.

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Physiologic dynamics of leukocytes in vivo in man.

A major research achievement has been made in a series of investigations by a team headed by Dr. H. R. Bierman, and including Drs. K. H. Kelly, N. L. Petrakis of the Laboratory and Drs. R. L. Byron, Jr. and R. Gilfillan of the Division of Surgery. The studies became possible through the successful development of several difficult, imaginative clinical techniques. These include the intra-arterial catheterization of various viscera in man, which has now been performed on over 110 patients; the artery-to-artery continuous cross transfusion of up to 150 liters of blood, achieved upon 12 occasions; and the cannulation and drainage of the thoracic duct in man, with subsequent closure, in three patients. The rapid transfusion of large amounts of leukemic and non-leukemic leukocytes, combined with simultaneous venous and arterial catheterization, has allowed the study of the fate of leukocytes in the circulation of the lung, spleen and liver, gastro-intestinal tract and the kidney. The findings on rapid samplings of blood under normal conditions and under conditions of physiologic and pharmacologic stress have cast new light on the physiologic and pathologic dynamics of white blood cells in man.

1. It has been established that a mechanism for removal of leukocytes from the circulation resides within the pulmonary circulation. Infusion of white blood cells of leukemic or normal

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origin into veins fails to raise the white blood count in the brachial artery although such cells can be recovered from the right ventricle. The fate of the leukocytes in the lungs is not known at present. White blood cells introduced into the femoral artery can be recovered in the femoral vein, indicating that this removal does not occur in capillary beds generally. In cross-transfusion studies, it was found that the lungs of non-leukemic patients can remove almost all the transfused leukocytes, whereas the lungs of leukemics who have elevated or normal peripheral counts are relatively ineffective in the removal of white cells. A patient with sub-leukemic leukemia, however, removed transfused leukocytes continuously for 26 hours at the highest rate observed.

It has been established, therefore, that one of the factors involved in the high peripheral blood counts of frankly leukemic patients is some unknown deficiency in, or the saturation of, the function of the pulmonary leukocyte removal mechanism. The finding has no established bearing at present upon the pathogenesis aspects of the disease, although postulations in that regard are possible and feasible of experimental approaches.

2. Four transfusions of myeloid leukemic blood into the celiac axis on non-leukemic patients have shown that most of such cells are recovered in the right ventricle, whereas practically no cells are found in the blood of the brachial artery. Thus, the spleen and liver, through which such cells circulated, were relatively

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less efficient than the lungs in removing the cells from the circulation. The observations cast serious question on the presumed important role of the spleen in releasing and in discharging white blood cells, and again emphasize the importance of the lungs in this dynamic equilibrium.

3. Approximately 70 per cent of the lymphocytes of the peripheral blood are said to enter the circulation through the thoracic duct. It was desired to ascertain whether this delivery site of lymphocytes was increased in leukemia. Thoracic duct lymph was collected within half-hour after death in five leukemic and five non-leukemic patients with neoplastic disease. Regardless of the peripheral lymphocyte or granulocyte count, the lymphocyte count in the thoracic duct lymph has been consistently within the normal range of 5,000 to 20,000 per cmm. The thoracic duct in two patients with lymphatic leukemia and one with multiple myeloma was surgically isolated and cannulated. The lymphocyte count of the lymph was normal, and the drainage of lymph fluid for up to 10 days did not alter significantly the lymphocyte count of the peripheral blood. The patients were of course maintained throughout with whole blood and plasma transfusions. This information indicates that lymphocytes in lymphatic leukemia do not gain access to the blood in increased numbers through the thoracid duct.

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4. Administration of histamine intravenously is associated with a prompt decrease in the circulating leukocytes. By catheterization of both right and left ventricles or aorta in non-leukemic patients this leukopenia was shown to be caused by removal of granulocytes cells within ten seconds, the removal being first manifested in the arterial blood which has passed through the pulmonary circulation. In leukemic patients, the rapid intravenous injection of histamine failed to decrease the white count, although this could be achieved by the constant drip of histamine over a three-hour period. These studies suggest that histamine may be involved in the pulmonary leukocyte removal mechanism.

5. The catheterization sampling technique of both right and left ventricles during the Valsalva maneuver (forced holding of breath at inspiration) has shown a consistent and significant decrease in the peripheral leukocyte level due to removal of cells within the pulmonary circulation. With release of the Valsalva there is a prompt increase of leukocytes from the lungs into the circulation well above the original level. Other respiratory movements influence the number of circulating leukocytes, indicating an ebb-and-flow of leukocytes into and from the pulmonary circulation.

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6. Four patients with subleukemic lymphatic leukemia were used as recipients to study the length of survival of white blood cells in the circulating blood. In two instances leukemic myelocytes showed a cell-survival of 96 hours. In the other two cases, non-leukemic granulocytes were found to have a cell-survival time of approximately 24 hours. The results indicate that leukemic myelocytes survive longer in the peripheral circulation than do normal granulocytes.

These investigations have already added fundamental knowledge and have revised many old and apparently well-established concepts in several aspects of the normal and abnormal physiology of leukocytes. Proper recognition by the National Institutes of Health of these important studies, now appearing in full in the literature, has been recommended.

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Blood supply of tumors in man.

The afferent artery to a tumor represents one point of attack upon the neoplastic growth. Techniques have been devised by Dr. H. R. Bierman, in collaboration with Drs. R. L. Byron, Jr. and K. H. Kelly, to enter arteries leading to specific viscera by introducing and passing special radiopaque catheters from the brachial and femoral arteries. The celiac axis, hepatic artery, splenic, renal or smaller branches can thus be entered and the blood supply of the organs visualized by means of artoriograms with the use of radiopaque substances.

The blood supply of primary and metastatic tumors in man has been found to be increased in most instances. The temperature of metastatic cutaneous lesions is increased over surrounding or comparable areas. In ten patients, there was arterialization of the venous blood from tumors, with the production of arterial-venous shunts. In cases exhibiting abnormal arteriograms found to be characteristic of neoplasms (tumor stains, increased vascular bed, distortion of larger vessels) nitrogen mustard in doses of up to 2.5 mg. per kg. body weight was administered through the catheter to the lesion. More recently trisethylene melamine and S. marcascens polysaccharide have been employed.

Over 100 patients with far-advanced neoplastic disease with visceral involvement have been so treated. Complications in the earlier cases, consisting of damage to arteries at point of entry,

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bleeding and hemiplegia, which occurred in 25 per cent of the patients, have been reduced to under 10 per cent by avoiding the use of the carotid arteries and patients over 60 years of age.

In approximately 25 per cent of the treated cases, definite objective effects of partial regression of tumor growth and temporary improvement in the patient's condition have been achieved. There is less effect upon the hematopoietic system when HN_2 is administered into visceral arteries than when comparable doses are given intravenously. In Hodgkin's disease with extensive involvement of the liver, jaundice and hyperpyrexia, HN_2 into the hepatic artery causes dramatic fall in temperature in patients demonstrated not to have responded to similar intravenous doses of HN_2. Unfortunately the beneficial effect is transient. In contrast, patients with metastatic carcinoma of the liver to whom HN_2 is administered into the hepatic artery often demonstrate a hyperpyrexia lasting several days.

The therapeutic implications of the procedures are of secondary importance in comparison to the contributions made to the general problem of the anatomy and physiology of the vascular supply of tumors. The techniques developed also allowed the study of white blood cell physiology recorded in a previous section, and can further be extended to biochemical studies of blood constituents leading to and away from an area involved by neoplastic growth. Full reports of the procedure and the results are now being recorded in the literature.

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Experimental therapy of neoplastic disease in man.

1. During the past year, surveys of clinical experience on the length of survival and effects of various therapy have been made for several neoplastic diseases of man, including myelogenous leukemia and acute leukemia in children. Such surveys, based upon clinical material made available at the University of California Hospital, establish more adequate baselines for the eventual comparison of results with newer therapeutic procedures.

Since January 1951, a review has been undertaken by Drs. M. B. Shimkin and E. Lucia of all cancers of the breast seen at the University Hospital from 1918 to 1945. The follow-up of the patients has been over 99 per cent due to the efforts of the Division of Surgery, and allows a comprehensive study of survival and effects of surgery and radiation in these cases.

2. The chemotherapy program of the Laboratory has been limited by the lack of regular sources from which compounds deemed worthy of clinical trial on the basis of observations on animal tumors. Recent collaboration with Drs. D. M. Greenberg and E. M. Gal of the Division of Biochemistry has furnished two malononitrile derivatives which showed partial inhibition of growth of transplantable mammary tumors in mice. Dr. Arthur Furst, of the University of San Francisco, has also furnished us with a number of ethylene imine compounds as well as p-hydroxypropiophenone and p-hydroxycinnamic acid, the latter

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a tryptophane inhibitor, but these have not been assayed in animals.

The major chemotherapeutic materials which have been tried at the Laboratory include:

a.	Nitrogen mustard (methyl-bis(beta chloroethyl) amine HCL)..... approximately	170 patients
b.	Triethylene melamine (triethylene imino-s-triazine).....	30 patients
c.	Cortisone and/or ACTH.....	22 patients
d.	Estrogens or androgens.....	15 patients
e.	Aminopterin or methopterin.....	9 patients
f.	Monobenzyl ether of hydroquinone.....	8 patients
g.	Guanazolo (amino-triazolo pyrimidine).....	10 patients
h.	Benzimidazole.....	5 patients
i.	Chymotrypsin.....	8 patients
j.	Malononitrile (5-nitro furanal malononitrile)	4 patients

The experiences with triethylene melamine have been prepared for publication, and the results indicate that this agent has a use in the management of some cases of Hodgkin's disease and lymphatic leukemia. It probably has no advantages over HN_2 other than greatly reduced emetic and nausea effects, but has a narrower chemotherapeutic index. The remissions are of short duration, and no evidence is available that it prolongs survival of the patients.

Cortisone and ACTH have been used in alternating courses of approximately 10 days each, with ten-day rest periods between the courses. Hematologic and clinical remissions of the disease have been observed in childhood leukemia and in one case of monocytic leukemia. Treatment of relapses following temporary remissions, however, have resulted in little or no responses, and the total length of survival has not been prolonged. The data are being prepared for publication.

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Benzimidazole has been tried on five patients without consistent effects. Guanazole was given orally to six and parenterally to four patients. All of the latter developed a generalized skin eruption which was not affected by nicotinic acid.

Eight patients with melanoma received orally up to 1,470 grams of monobenzyl ether of hydroquinone, an inhibitor of melanin formation. No definite effects were observed, except that one patient who excreted melanin in the urine before and after therapy failed to show melanin in the urine while on the drug.

The experience with 5-nitro-furenal malononitrile has been negative, other than to indicate that no toxic effects other than local pain develop following intramuscular injection of up to 800 mg of the agent in sesame oil per day. No definite effects on the tumor have been observed in four patients treated with this agent.

3. One of the serious problems in the management of leukemias and lymphomas is hemorrhagic diathesis. Toluidine blue has been used on 21 such patients, with inconstant and unimpressive effects on the hemorrhagic tendency. Recently continual intravenous drip of histamine, in doses of up to 1.5 mg. per day, has been tried on the basis of observations of low blood histamine in acute or terminal myelogenous leukemia and of increased coagulability of blood following intravenous histamine administration. Decreases in

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leukocyte count with transient cessation of bleeding have been suggestive, but the present data are insufficient. On the basis of information extended by Dr. E. Lorenz, a series has been started on the use of intravenous injection of normal bone marrow in hemorrhagic exacerbations of leukemia.

4. Study continues of the role of the pituitary on the growth of certain neoplasms in man. It was shown that the normal adult pituitary is resistant to X-radiation in doses up to 10,000 r delivered to the gland. On January 25, 1951, Dr. E. B. Boldrey successfully removed the pituitary gland in a 32-year-old male with metastatic melanoma. The patient survived for nine weeks, expiring from widely disseminated neoplasm. During this period, there was marked effect upon the basal metabolic rate, protein-bound serum iodine, 17-ketosteroid excretion in the urine and insulin sensitivity. Autopsy revealed that only a microscopic ridge of adenohypophyseal cells was left in the sella, the surgical removal being at least 99 per cent complete. No retardation in the growth of the melanoma was noted.

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Biochemical effects of experimental therapy.

Among the limiting factors in determining the effects of various experimental therapeutic procedures in human neoplastic disease are the high degree of subjective bias which may be introduced by the patient as well as the physician, and the lack of adequate objective measures by which to judge and to quantitate effects on the tumor and the general condition of the patient.

Two investigations, one on the general-effect level, and the other on the cellular level, are being pursued with the hope of establishing on animals additional procedures which may be applied to the evaluation of the clinical status of patients and of the neoplasm.

1. Dr. P. Shooter, working at the Naval Radiological Defense Laboratory, is continuing studies on the effect of radiation and other stimuli on the sulfhydryl content of plasma.

A delayed decrease in the sulfhydryl content of rat plasma occurs after total body X-irradiation, or following the administration of nitrogen mustard and triethylene melamine. Following surgery, on the other hand, the sulfhydryl content of plasma falls more rapidly. The decrease in plasma sulfhydryl levels appears to be related to tissue repair following injury.

Preliminary experiments have indicated that a lesser fall in plasma sulfhydryl levels occurs after adrenalectomy of rats than

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following sham operation. Moreover, there are numerous indications in the literature [illegible] between sulfhydryl groups and adrenal cortical steroids. The investigation is therefore being extended to determine the effect of various adrenotropic materials, including ACTH, cortisone, desoxycorticosterone, and adrenal cortical extract on the sulfhydryl levels of normal, adrenalectomized and sham-operated rats.

2. Dr. N. L. Petrakis is conducting microphotometric histochemical studies on the mechanism of mitotic inhibition by various chemotherapeutic agents. Studies have been made with the Feulgen and methyl green stains on the desoxyribonucleic acid (DNA) content of strain A mouse lymphoma before and after treatment with nitrogen mustard and colchicine. It has been found that a thirty per cent decrease in methyl green staining resulted in 18 hours in tumors treated with LD_{50} doses of nitrogen mustard. No effect was found in Feulgen staining suggesting that the primary effect of nitrogen mustard is on the state of polymerization of DNA.

These findings are being applied to other agents in mice, as well as to bone marrow and tumor cells from patients with neoplastic disease.

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Immunochemical studies of tissue proteins.

One of the chief objectives of the Laboratory is to investigate protein constituents of normal and of neoplastic tissue, particularly of human origin, with the possibility that specific protein components unique for certain tumor tissues may be found. Emphasis has been placed upon immunochemical and physicochemical methods for characterizing and distinguishing such components.

Drs. L. R. Melcher and J. Shack have studied a number of tissue protein fractions by chemical and immunological methods. It was considered desirable to separate the tissues into soluble and particulate fractions and then to study each fraction.

The soluble cytoplasmic proteins of a number of normal and malignant tissues of human and animal origin were investigated first. Electrophoretic analysis yielded complex patterns in every case: no electrophoretic components unique to malignant tissue have thus far been detected. The patterns all showed considerable quantities of a protein electrophoretically indistinguishable from serum albumin. Determinations of hemoglobin indicate that most of this albumin component is not derived from contaminating blood but from either the extracellular fluid or the cell itself.

After antigenic analysis, it was found that the soluble cytoplasmic protein fraction was not suitable for immunologic comparison between various tissues. Cross reactions were noted when antibodies

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against this cell fraction was compared with serum and various tissues. This was found to be due partly to the presence of serum albumin in all tissue fractions so prepared. Albumin was detected by both electrophoretic and immunochemical means (using rabbit anti human albumin quantitatively) in all tissue "solubles" studied which included tumor and normal tissues.

With this experience it was then considered that another fraction of the cell should be investigated and this fraction should have reproducible physicochemical characteristics. Guinea pig liver cell mitochondria were prepared by the method of Hogeboom and Schneider. A soluble protein was obtained from these particulates. The resulting preparation has been made numerous times with electrophoretic patterns that are nearly identical. This material contained no discernible serum albumin. It induces antibody formation in rabbits. It is a heterogenous material both by electrophoretic and immunochemical criteria which reacts negligibly with guinea pig serum. However, this rabbit antibody when introduced intravenously into guinea pigs will not produce shock which is evidence for removal of the Forsoman antigen present in the intact mitochondria of guinea pig liver. The findings are being prepared for publication.

The immunologic and chemical properties of this fraction are being compared with analogous fractions derived from other tissues. This approach is also being extended to human neoplastic tissues.

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Nucleic acids and nucleoproteins.

This project has as its major objective the isolation and comparison of nucleic acids and nucleoproteins from normal and malignant tissues. Special emphasis has been placed on the use and development of physicochemical methods which offer promise of establishing distinctions among nucleic acids from different sources.

1. Dr. J. Shack, assisted by R. Jenkins and J. Thompsett, has compared different methods of isolating nucleohistones and nucleic acids from tissues. Large batches of desoxypentose nucleic acid and nucleohistone have been prepared from calf thymus to serve as standards. The content of ribo- and desoxyribonucleic acids of several generations of strain A mouse lymphoma, and of samples of human lymphosarcoma has been determined. A method was developed for quantitative isolation of the desoxyribonucleic acid of these tumors as the nucleohistone. From the nucleohistones were prepared highly polymerized nucleic acids. Both the nucleic acids and nucleohistones are being studied by a variety of physicochemical methods.

2. A new micro-spectrophotometric method for measuring the state of titration of the acidic and basic groups of nucleic acids has been developed. The method is also applicable to study of the nucleic acid component of nucleohistones. It was shown by the spectral method that the anomalous titration, a property associated with the native hydrogen bonded macromolecular structure, is found

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with nucleohistone as well as with purified nucleic acid. This was demonstrated for the components derived from calf thymus, the lymphoma, and the lymphosarcoma. The method provides a new criterion for definition of the native state of desoxypentose nucleic acid, whether free or in combination with protein. The mechanism and kinetics of the denaturation of nucleic acid by heat, acid, and alkali was investigated by the spectral titration method, and correlations were established with changes of other properties such as viscocity, double refraction, solubility, and electrophoretic mobility.

3. Studies have been made of the electrophoretic properties of calf thymus desoxypentose nucleic acid and of derivatives prepared by treatment with acid, alkali, and heating and drying. Results indicate a strong binding of cations. Similar studies with tumor nucleic acids are in progress.

4. An investigation of the binding of ions, dyes, and proteins by nucleic acids has been initiated. This should contribute to the establishing of distinctions between different nucleic acids and to an understanding of the chemistry of intracellular staining. A study of the binding of sodium chloride by calf thymus desoxypentose nucleic acid has been completed. Results show negligible binding of chloride but strong binding of sodium. It has been concluded that

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the combination of dyes and proteins with nucleic acid derivatives;

competition with sodium ions for the binding sites.

A series of papers dealing with the above [illegible] is in an advanced state of preparation. The first has been [illegible] for publication.

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Radio-iodated antibodies and other proteins.

The dynamics of certain aspects of protein synthesis and utilization, as a corollary to the general problem of protein chemistry of human tumors, have been approached by the development of techniques for the labelling of proteins with radio-active iodine.

1. Drs. S. Vanouradis and F. R. Melchor have worked with immune globulins for these studies. Immunochemical criteria have been used for evaluating specificity of antisera after trace I^{131} iodination. It has been shown that antibodies can be labelled by trace I^{131} iodination (about two iodine atoms per protein molecule) without altering immunologic specificity of the protein.

2. The *in vivo* stability of the I^{131} protein label has been studied by trace iodinating a rabbit antibody and introducing the labelled antibody into a heterologous host, guinea pig. The antibody was then specifically isolated immunologically from the serum proteins of the guinea pig over a period of 10 days. It was shown that the antibody recovered contained the same amount of I^{131} activity per unit weight of antibody over this period as did the preparation before guinea pig administration. This is evidence that the I^{131} protein label does not undergo a metabolic fate independent of the protein molecule.

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The work demonstrates that proteins can be labelled with trace I^{131} iodination without affecting protein specificity and that the I^{131} protein label is stable *in vivo*.

3. Applications of these studies, in animals as well as in man, which are now underway include: the turnover of rabbit antibody in non-immune and immune animals, the introduction of labelled anti-bovine serum albumin into guinea pigs which receive bovine serum albumin intramuscularly to demonstrate *in vivo* localization of antibody, and the turnover of labelled albumin and gamma globulin in patients with cancer.

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Other activities.

1. A number of additional research activities, not specifically noted in this report, are usually being pursued by members of the staff. These are of an exploratory nature, and are either expanded if the preliminary data appear of interest and correlated with the major objectives of the laboratory, or are terminated if they do not appear to be fruitful. Mention is made of the study of electric potentials in developing eggs, by Dr. E. P. Bierman and Dr. R. W. Sperry; constitutive compounds in determinations in the urine, by Dr. [illegible] and H. E. [illegible]; the study of temperature and [illegible] by Dr. H. I. Petrakis; the study of the [illegible] activity induced in [illegible] with cold on tumor formation by [illegible] and [illegible] Melchar; and carcinogenic [illegible] from canine urinalysis by Drs. [illegible] and M. P. [illegible].

In the field of experimental therapy of tumors in animals, [illegible] chemicals are screened for their effect on the growth of primary carcinoma and lymphoma in mice and their toxicologic and histologic effects. Interest [illegible] in two investigations on the Pacific Coast, and consultative [illegible] have been furnished to the investigators involved. [illegible]

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of certain placental preparations on animal tumors, being studied by Dr. W. Steele Livingston, D.V.M., of Hollywood, California, and the effect of arginase on tumors in mice by Mr. Vad Vrat of the American Institute of Radiology, Belmont, California.

2. Drs. H. R. Bierman and J. N. McClelland are continuing the project on the evaluation of cancer teaching and knowledge by means of a standardized multiple-choice examination. Annual examinations are now conducted in 57 medical schools and in 28 dental schools, a total of 27,000 students being tested this year. The work, supported by NCI Grant CS-1020(C), occupies no less than one month's time per year by Dr. Bierman and is a full-time endeavor in statistical analysis by Dr. McClelland.

3. Dr. M. B. Shimkin, since 1947, has acted as Secretary of the Cancer Research Coordinating Committee of the University of California, which allocates approximately $280,000 for cancer research projects throughout the University of California in Berkeley, Los Angeles and San Francisco.

4. Teaching activities at the School of Medicine, particularly by Drs. Shimkin and Bierman, include participation at the Consultative Tumor Board, occasional lectures to classes, participation in various clinical rounds, and instruction of medical students assigned to the Laboratory during summers. Dr. Shimkin

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is a member of the Cancer Board, and Dr. [illegible] of the [illegible] Committee of the Medical School. As outside activities, Dr. Churchill participates in the Tumor Boards of the Marine Hospital and Letterman Army Hospital, while Dr. Bloomer participates in the Tumor Boards at Stanford University School of Medicine and the Veterans's Hospital. Cooperation in terms of lectures is also afforded to the American Cancer Society and other educational and medical groups of the area.

Respectfully submitted

Michael B. Shimkin

Michael B. Shimkin, M.D., Chief
Laboratory of Experimental Oncology

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ADDENDUM I

PROFESSIONAL STAFFS
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JANUARY 1, 1951

1. Professional Staff: Laboratory of Experimental Oncology

MICHAEL B. SHIMKIN, M.D., Medical Director, USPHS, and Chief of the Laboratory (NCI); Clinical Professor of Oncology (Medicine) and Director of the Laboratory (UC).
HOWARD R. BIERMAN, M.D., Medical Officer, GS-14, and Asst. Chief of the Laboratory (NCI); Assoc. Clinical Professor of Oncology (Medicine) (UC).
LEO R. MELCHER, Ph.D., M.D., Surgeon, USPHS (NCI); Asst. Clinical Professor of Oncology (Medicine) (UC).
JOSEPH SHACK, Ph.D., Biochemist, GS-12 (NCI); Asst. Clinical Professor of Oncology (Medicine) (UC).
BERNARD SHACTER, Ph.D., Biochemist, GS-12 (NCI); Asst. Clinical Professor of Oncology (Medicine) (UC).
NICHOLAS L. PETRAKIS, M.D., Sr. Asst. Surgeon (R), USPHS (NCI); Clinical Instructor in Oncology (Medicine) (UC).
KEITH H. KELLY, M.D., Damon Runyon Research Fellow; Clinical Instructor in Oncology (Medicine) (UC).
SERAFEIM P. MASOUREDIS, M.D., National Cancer Institute Research Fellow; Clinical Instructor in Oncology (Medicine) (UC)
PAUL ORTEGA, M.D., American Cancer Society Research Fellow; Resident in Pathology (UC).
PAUL F. NORDIN, M.D., Asst. Resident in Medicine (5-8/50) (UC)
LLOYD E. SMITH, M.D., Asst. Resident in Medicine (9-12/50) (UC)
FREDERICK W. KING, M.D., Asst. Resident in Medicine (1-4/51) (UC)
JACK E. KAHOUN, M.D., Asst. Resident in Medicine (5-9/51) (UC).
BRUCE W. SHUMWAY, B.S., Physicist, GS-9 (NCI).
ROBERT J. JENKINS, B.S., Engineer (Electronics), GS-7 (NCI)
MARJORIE F. BROWN, R.N., Chief Nurse, GS-7 (NCI).

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2. Active Collaborating Staff: University of California School of Medicine

PAUL M. AGGELER, M.D., Asst. Clinical Professor of Medicine
EDWIN B. BOLDREY, M.D., Assoc. Professor of Neurological Surgery
LeROY H. BRIGGS, M.D., Professor of Clinical Medicine, Emeritus.
RALPH L. BYRON, M.D., Instructor in Oncology (Surgery).
LEONID S. CHERNEY, M.D., Clinical Instructor in Surgery.
WAYNE CHESTLETON, M.D., Asst. Resident in Radiology.
NORMAN E. FREEMAN, M.D., Assoc. Clinical Professor of Surgery.
EMERY M. GAL, Ph.D., Research Associate in Biochemistry.
RUTHERFORD S. GILFILLAN, M.D., Clinical Instructor in Surgery.
M. ALICE GRADY, M.D., Clinical Instructor in Radiology.
DAVID M. GREENBERG, Ph.D., Professor of Biochemistry.
MICHAEL J. HOGAN, M.D., Assoc. Clinical Professor of Ophthalmology.
BERNARD KORDAN, M.D., Asst. Resident in Radiology.
ELIZABETH LOWENHAUPT, M.D., Asst. Clinical Professor of Pathology
ESCHSCHOLTZIA L. LUCIA, Ph.D., Lecturer in Oncology (Biometrics).
WILLIAM R. LYONS, M.D., Assoc. Professor of Anatomy.
JAMES M. McCLELLAND, Ph.D., Instructor in Oncology (Medical Education).
EARL R. MILLER, M.D., Professor of Radiology.
STACY R. METTIER, M.D., Professor of Medicine.
CLAYTON D. MOTE, M.D., Assoc. Clinical Professor of Medicine.
HOWARD C. NAFFZIGER, M.D., Professor of Neurological Surgery.
LLOYD E. SMITH, M.D., Asst. Resident in Radiology.
FRANCIS A. SOOY, M.D., Asst. Clinical Professor of Otorhinolaryngology.
ROBERT S. STONE, M.D., Professor of Radiology.

3. Other Active Collaborators:

DAN H. CAMPBELL, Ph.D., Assoc. Professor of Chemistry, California Institute of Technology.
MAURICE FISHLER, Ph.D., M.D., Chief, Biology Section, Naval Radiological Defense Laboratory, Hunters Point.
ARTHUR FURST, Ph.D., Assoc. Professor of Chemistry, University of San Francisco.

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ADDENDUM II

CLINICAL WORK OF THE RESEARCH WARD, LABORATORY OF EXPERIMENTAL ONCOLOGY

July 6, 1948 to April 30, 1951

	July - Dec.	Jan.-Dec.	Jan.-Dec.	Jan.-April
	1948	1949	1950	1951
Hospital Days	179	365	356	120
First Admissions	52	86	106	36
Readmissions	21	141	176	73
Total Admissions	73	227	282	109
Patient Days, Total	1530	4375	4094	1402
Mean Daily Census	8.5	12.0	11.5	11.6
Out-Patient Visits	68	363	681	262
No. of Deaths in Ward	15	30	59	22
Autopsies*	15	36	66	25

* Including autopsies on LEO patients dying outside of Research Ward

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ADDENDUM III

PUBLICATIONS

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LABORATORY OF EXPERIMENTAL ONCOLOGY

January 1947 to June 1951

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