THE PROBLEM:

THE PREVENTION, EARLY DETECTION, AND SUCCESSFUL TREATMENT OF CANCERS IN THE HUMAN POPULATION

The cancer problem is sufficiently serious that it cannot await the ultimate elucidation of every step in its causation, progression, and successful treatment. Continuous improvements in diagnosis and therapy are needed. Many future improvements will have to be based on empiricism or on incompletely understood leads provided by laboratory research. At present the lag period between a significant laboratory finding and its application in therapy, diagnosis or prevention in human populations is too long. All too frequently a discovery is made in a department or institution that lacks both the capability to extend it and the medical personnel to apply it. Often biomedical scientists have little or no insight into the clinical problem of cancer. In fact, they may never have seen a human cancer and may have little appreciation of the clinician's needs for improved methods of detection and treatment.

Some Premises

Thus the existing patterns of cancer therapy and cancer research tend to isolate one from the other. We need new structures organized to eliminate this obstacle. Enormous numbers of lives can be saved by enhancing current detection methods and by eliminating the roadblocks now existing for optimum treatment.

Ultimately, the greatest promise for the conquest of cancer will come through its prevention by new methods, not yet available. There is too little understanding on the underlying nature of the cancer process; indeed, different cancers may be due to different processes. A cardinal task of cancer research is to state with precision the etiological factors applicable to man and to devise preventive measures.

Proposed Approach

We are proposing that a comprehensive Cancer Center be established in Oak Ridge to provide a coherent and balanced attack on the problem at all levels from new and innovative treatments of patients to laboratory research revealing insights for new approaches. It would integrate into a single operation the existing treatment and research activities and would expand such activities into additional important areas of effort. The broad technological and scientific capabilities of the Oak Ridge National Laboratory would be available in support of the operation along with the clinical research facilities of Oak Ridge Associated Universities. Special features of these organizations and of the Oak Ridge community which would contribute to the success of a center include:

1. An active cancer research program of considerable size (ORNL) in the setting of a large modern biology laboratory; unusual competence to maintain large colonies of animals under defined environmental conditions and evaluate toxic and carcinogenic effects of chemical, physical, and biologic agents.

2. A research hospital unit (ORAU) of 25 beds concerned for over 20 years with problems in cancer detection, applied radiobiology, and beneficial applications of radioactivity.

3. Sizable resources in the full spectrum of physical sciences and engineering; a mathematics and computer facility well beyond the capacity of most institutions.

4. A science community with a record of intramural cooperation that cuts across specialties, and a history of defining specific problems and planning and implementing effective attacks for their solution.

5. A tradition of effective science management of large interdisciplinary programs.

6. A graduate school of biomedical sciences in Oak Ridge; close proximity to the University of Tennessee; and long established collaborative programs among the region's science and academic community.

With this defined perspective, with the extensive work now under way in Oak Ridge and with the regional need for a center, we propose a broad based but coherent program. A comprehensive plan is envisioned that will:

Reorganize the present relevant research activities in Oak Ridge under a single new organizational framework dedicated to the cancer effort.

Describe a significantly enlarged clinical cancer research center that will provide a dynamic interface between laboratory and bedside.

Assure flexibility in pursuit of new leads. Organize task groups as required to attack targets of opportunity.

Eliminate any compartmentalization that tends to inhibit interactions of people of different disciplines assigned to one or another aspect of the cancer problem.

This approach is designed to answer some of the needs stated by the National Panel of Consultants on the Conquest of Cancer. That report states on page 6 that:

> "(c) Existing cancer centers should be strengthened and additional cancer centers in different parts of the country should be created. The solution of the cancer problem lends itself to a multidisciplinary effort, where teams of highly qualified specialists are available to interact on problems of research, both clinical and nonclinical, teaching, diagnosis, preventive programs, and the development of improved methods in the delivery of patient care, including rehabilitation. . ." (p. 6)

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> ". . the comprehensive cancer center offers the best organizational structure for the expanded attack on cancer. . ."

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> "The new centers should have appropriate geographic distribution and should, wherever possible, be created where a nucleus of scientific, professional and managerial personnel already exists and preferably where a university or a medical school (teaching) affiliation exists or is planned."

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> "It should be emphasized that the strengthening of existing cancer centers and the creation of new cancer centers does not mean that under this program general responsibility should be undertaken for the care of the Nation's cancer patients. The delivery of patient care in cancer cases is a part of the general problem of the delivery of patient care and should be dealt with. However, this inhibition must not prevent the cancer centers from including such patient care facilities as are necessary for clinical research and teaching and for the development and demonstration of the best methods of treatment in cancer cases."

The heart of the Oak Ridge proposal lies in creating a much larger patient treatment facility, buttressed by teams of basic scientists. To reach a "critical mass" we calculate the need for a hospital-laboratory complex of 150 beds. The advanced techniques would span from early detection through curative therapies and rehabilitation to palliative methods for those not curable. The dominating atmosphere would be concern for the individual person, intermeshed with the continuing question, "What new light can this case shed on the cancer problem?" The laboratories under one roof would provide not only for comprehensive management of cancer patients but would also include those laboratory elements that use patient samples for research and those close to the stage of clinical trials. In addition, the existing laboratory resources in Oak Ridge will be exploited fully; expansion of certain of these specialized facilities is envisioned.

Task groups would be designated by directed assignments by scientific management with the authority to create and terminate priorities as leads looked promising and results failed to materialize. Such task groups are expected to have well defined narrow objectives and a lifetime limited both by their achievement and by their being supplanted by objectives of potentially greater importance.

Highlights of existing work and potential resources will be described according to the following outline of the main parts of the cancer problem and promising avenues for their solution:

1. Diagnosis: early detection, localization and staging, classification and tumor typing.

2. Therapy: surgical, radiation, chemotherapy, immunologic, combined, and supportive.

3. Prevention: identifying human carcinogens, eliminating carcinogens from environment, and preventive measures.

4. Information analysis and exchange: clinical data reduction systems, information exchange among research workers, to clinical professionals, to the public.

5. Training: predoctoral, postdoctoral (Ph.D. and clinical), and ongoing staff training.

CANCER DIAGNOSIS

I. The Problem

To improve cancer cure rates with present therapeutic methods we need better ways to detect early lesions, or to identify the precancerous state. With a few exceptions, tumors less than 1 to 2 cm are not palpable or detectible by X ray. Realistically, we can expect to double cure rates with the existing methods of treatment if earlier detection were possible.

After cancer is diagnosed, optimum therapy at present depends on precise localization of the lesion, its size, extension, and metastases. Ways for better staging are required, and some therapeutic failures can be attributed to inadequate tools for these studies.

To a significant degree, optimal treatment depends on precise classification and typing of the neoplasm, and to an unknown but probably greater extent, future ways of treatment also may hinge on cancer taxonomy. Cancer has been classified traditionally by primary organ (or tissue site), cell type of origin, and degree of de-differentiation; sometimes by biochemical characteristics, occasionally by behavior in tissue culture, and once in a while by suspected etiology.

II. Current Programs in Oak Ridge

a. Tumor-localizing radioindicators

The discovery of the ORAU Medical Division that gallium-67 concentrates in some kinds of human cancers and animal tumors has renewed interest (once widespread) in the development of scanning agents and methods for detecting and staging tumors. Current efforts include clinical trials to determine its value as an adjunct in planning therapy, as a method for assessing the success of therapy, and to determine its value as a diagnostic agent. In the laboratory, efforts are under way to elucidate its mechanism of uptake, to seek ways of enhancing uptake and detectability, to compare this agent with other tumor-localizing substances, and to seek even better radiopharmaceuticals.

b. Instrumentation

Unsurpassed electronic and engineering talents exist in Oak Ridge and have been applied to nuclear medical instrumentation. For example, P. R. Bell, of Oak Ridge National Laboratory, and his colleagues developed the first medical spectrometer, which initially was field tested at the ORAU Medical Division. His group also contributed significantly to collimator theory and design. Currently, with the emergence of tumor-localizing agents, better tomographic scanners are critically needed and a project to design and build prototypes is under way. Associated with the attempt to provide better focusing techniques is application of computer-assisted analysis of data that cannot be visually interpreted. The Mathematics Division and the computer facilities in Oak Ridge are an uncommon resource of talent and hardware.

c. Exfoliative Cytology

At ORNL Biology Division, animal work is under way to characterize the cell changes during experimental carcinogenesis in the respiratory tract. Methods are being developed to obtain tracheal washings from rats and hamsters; studies are in progress to describe the progressive cytological changes that occur during the onset of chemically induced lung cancer. This is a part of a much larger effort on respiratory carcinogenesis described later in this document.

d. Tumor Antigens

The carcinoembryonic antigen of Gold and other antigens associated with various cancers has stimulated much interest here and elsewhere in the possibility of early detection by assay of tumor antigens. Recent work at ORNL and elsewhere demonstrates that most cancers in animals contain antigens which are normal constituents of fetal cells. Current work in the Molecular Anatomy Program jointly supported by NCI-AEC is focused on the role of fetal antigen expression in animal cancers.

e. Biochemistry of Cancer

The Medical Division of ORAU is credited with discovering a major biochemical characteristic of cancer cells, the presence of increased amounts of glyceryl ethers; the metabolic pathway for this accumulation has been elucidated. At the Biology Division of ORNL, several lines of inquiry relate to metabolic requirements of specific tumors, thereby providing an additional promising tool in tumor taxonomy as well as avenues for novel therapeutic approaches.

III. Proposed Expansion

Our principal objective will be to develop and apply new techniques for early detection of incipient cancers, localizing and staging existing cancers, and improving the classification and typing of human cancers.

a. Early Detection

In the course of the present carcinogenesis work at ORNL, tools are expected to appear for human screening for cytologic and biochemical alterations. These changes predict which members of a population are threatened with development; e.g. of lung cancer. Thus a smaller "at risk" population can receive intensive periodic screenings in anticipation of a malignant transformation. Trials will be done within the framework of an enlarged cancer center and in cooperation with industrial health clinics where sizable populations of workers with specific risks can be monitored.

A major task group, or series of task groups, will be assembled to exploit the strong program in immunology aiming for <u>immunologic tools for early detection of cancer</u> (and ultimately possible therapy). Undoubtedly many tumor antigens will be present in very low concentrations, thus the most significant component will be continuing current development of precise and sensitive methods for detecting antigens, purification from human tumor materials, and large scale tissue tissue culture. The schematic flow chart is an example how the GeMSAEC system can be used with immunofluorescence methods. It demonstrates how systematic engineering can be used by task groups to attack well defined questions. (See chart 1.)

<u>Biochemical aspects of cancer</u> will present another major focus in interest. Specific attacks will be made on the biochemistry of membranes of cancer cells as compared with normal cells. The goal will be to clarify the role of glycolipids and glycoproteins in plasma membranes of cancer cells as compared with normal cells. All membranes (both surface and intracellular) consist of a variety of specific protein and lipid constituents that serve structural and functional roles. The outermost molecules located on the surface of the cell provide a molecular basis for cell recognition, i.e., association or rejection. Results from limited biochemical research on this subject suggest that glycoproteins and glycolipids in the plasma membrane are probably responsible for regulating cellular interactions. The technology for isolating plasma membranes coupled with biochemical studies of enzymic and structural constituents of biomembranes provide an unusual expertise for pursuing this topic.

b. Localization and Staging

Another major task group built on existing strength will be devoted to <u>tumor indicators</u>. The objective will be to improve diagnosis and treatment of cancer by means of better localizing labeled compounds, specifically, 1) screening for suspected disease, 2) staging disease for treatment protocols, and 3) evaluating treatment results. A large number of new labeled compounds should be synthesized, evaluated for efficacy, and tested for toxicity. A model for the proposed work and expertise is demonstrated by the current work on gallium-67 wherein a variety of animal tumor models are available, together with modern tools for defining the subcellular sites and biochemical processes involved in the phenomenon.

Closely related with the preceding development is the instruments development work. Limited resolution and sensitivity of current instrument systems are a roadblock to earlier detection and localization. Progress in solid state detectors, electronic circuitry, and computer hardware, as well as comparable advances in other detection systems suggests a new era of detection may be in sight. For instance, the use of thermography and of ultrasonics has been disappointingly limited, but new principles and a new generation of apparatuses may offer renewed promise. Such approaches, in conjunction with radioisotope scanning, need to be examined from the viewpoint of information theory to determine their individual and combined detection efficiency. A cadre of skilled persons available for such a team effort exists in Oak Ridge.

Collaborative clinical trial is an important and difficult phase in the evolution of an idea translated into an effective diagnostic tool. Under the sponsorship of Oak Ridge Associated Universities, a Cooperative Group to Study Localization of Radiopharmaceuticals has been formed. The initial membership of 17 institutions, mostly from the Southeastern region, has embarked on a study of the place of gallium-67 in managing lymphoma and lung cancer. Joint support comes from the Atomic Energy Commission and the National Cancer Institute. When a common protocol is followed, uniform data can be more rapidly collected to determine the value of a new agent, thereby significantly shortening the time that is required via the conventional methods of isolated reports from individual institutions. We envision that the clinical Cooperative Group can serve an important function in any broadened effort toward the conquest of cancer, not only in testing new tumor-localizing radioindicators but in larger volume screening procedures. It also can operate with highly experimental therapeutic protocols where suitable candidates are scarce at any one institution.

Biochemical monitoring of patients is another promising avenue of research for which Oak Ridge capabilities are well suited. The MAN program at ORNL has been concerned with high resolution chromatographic analysis of blood and urine, and with developing fast analyzers to accommodate large numbers of patient samples. The flow diagrams (charts 2, 3) show two task group examples: 1) high resolution chromatography in a search for new compounds in known cancer patients and unique compounds that appear in the patients undergoing radiation therapy or chemotherapy; 2) as a system for detecting changes in serum levels of substances such as enzymes which may be tumor-associated or therapy-associated.

CANCER THERAPY

I. The Problem

In the foreseeable future, surgery will be the most widely used form of curative therapy. Increased cures through earlier detection and better staging procedures are within reach. For lesions not curable by surgery, radiotherapy will remain as a second major modality. Failures are related to: 1) radiation damage to normal tissues with restrictions thereby imposed, 2) imprecise staging so that fields do not include all neoplasm, 3) limited radiosensitivity of some tumor sites. Chemotherapy has emerged as the third modality but suffers with drawbacks parallel to radiotherapy: 1) restrictions imposed by damage to normal tissues, 2) acquired cell resistance, 3) susceptability of the patient to infection and hemorrhage, 4) absence of assay systems to predict responsiveness in individual tumors.

While one can guarantee increased cancer cures and survivals by refining these methods, clearly the rescue of currently fatal cancers will rest on some new and innovative therapy based on biochemical manipulations, by exploiting an immunologic phenomena involved in the cancer process, or perhaps a new combined attack exploiting current and new methods.

II. Current Programs

a. Radiotherapy

An important task in the earliest days of the Medical Division of ORAU was the design of the first teletherapy units. Trials have been completed that defined the place of radioactive colloids in the treatment of malignant serous effusions. Current work emphasizes total-body irradiation therapy. Experimental protocols are designed to find the optimum schedules of fractionation and protraction (dose rate) in the control of selected patients with lymphoma, chronic lymphocytic leukemia, chronic granulocytic leukemia, polycythemia vera, essential thrombocythemia, and closely related disorders. Interest in the radiotherapy community in using total-body irradiation has been rekindled as clinicians are becoming disappointed with results of long-term chemotherapy for certain patients. Combined radiation and chemotherapy can offer significant survivals not obtainable by either alone.

b. Surgery

While no major experimental cancer surgery has been pursued, certainly the efforts here are closely allied to this treatment modality. As mentioned above, the need for better tumor localization is a roadblock in surgical cure, and the gallium-67 project contributes both to radiotherapeutic and surgical management. For many years, combined approaches to thyroid cancer have been under investigation using surgery for primary total thyroidectomy followed by therapeutic doses of radioiodine for control of metastasis and for detection of residual thyroid tissue. In a given patient, multiple non-mutilating surgical excisions have been successful in control of disease. A surgical probe has been designed to assist the surgeon in locating small bits of cancer.

c. Immunologic Approaches

Over 10 years ago, marrow transplants were attempted in patients with acute leukemia. Recently, after significant advances in immunosuppression and tissue typing, this effort has been resumed with success at the ORAU Medical Division. Close collaboration with the ORNL Biology Division in this area has been productive. Work in that Division for many years has been directly concerned with marrow transplantation, the factors involved in rejection of foreign marrow.

The marmoset project of ORAU represents a unique study of natural chimerism in the only known primate which almost uniformly carries cells from its twin. (Twinning occurs in high incidence in this species.)

Work in the MAN project mentioned earlier, dealing with fetal antigens, is potentially quite important. While clinical trials are still distant, the current systems approach is designed to be ultimately applicable in immunotherapy.

III. Proposed Development

a. Radiotherapy

Test groups in four main topics have current priority; 1) radioprotective agents. Promising new agents under study at the Biology Division, ORNL, are nearing the phase where clinical trial is feasible. Animal studies show it is possible to increase the radiation resistance of certain normal sensitive tissues such as skin, bone marrow, gastrointestinal epithelium, by as much as 100% while increasing the resistance of a transplantable mammary tumor by only 15%. Current development of model systems using the experimental lung tumors and radiotherapy with this class of compounds is a continuing high priority topic of study. 2) Application of radiobiologic knowledge from the wealth of data generated from many radiobiology laboratories. Relatively little of this information has been translated into protocols for human experimental therapy. Based on diverse data, such as mitotic cycles of tumor cells, differences in repair rates of normal and neoplastic cell systems, effects of fractionating doses, protracting dose rates, we are confident that improved cure rates and better palliation can be achieved than presently possibly by conventional radiation therapy. 3) New modalities — the possibility of using particle beams for improving radiotherapy has not been exhausted. Elsewhere, major projects in testing pi mesons is envisioned. Oak Ridge has excellent particle accelerator facilities at the Physics Division of ORNL, particularly the Oak Ridge Isochronous Cyclotron (ORIC), and the 6MV and Tandem Accelerators at the High Voltage Laboratory. 4) Improving the staging of patients for radiotherapy: the promise of tumor-localizing agents in this application has been described above. Closely coordinated team effort exploiting the skills of nuclear medicine, diagnostic radiology, and surgery (and other modalities) will provide the experimental radiotherapists with much better descriptions of tumor site and extent. One can characterize this as staging-team research.

b. Surgery

Larger scaled clinical research in the proposed center depends on broader cancer surgery resources. We would form a team of cancer surgeons who would work closely with the preclinical scientists to test innovations. For example, we see the electronics engineer in close collaboration with the surgeon to work out new detection probes and an attack based on new experimental tumor-localizing techniques. For the immunologist, the surgeon would cannulate the thoracic duct to collect large numbers of lymphocytes, or excise tumor metastases for recovering antigen for assaying immunologic responses. For a variety of combined approaches, surgeons would perform preliminary excision of surgically resectable masses before the immunotherapy or chemotherapy is undertaken; with the radiotherapist they would be a part of the staging team performing the laparotomies or cannulations for new diagnostic procedures.

c. Immunotherapy

The talents in Oak Ridge have special application in this largely unexplored aspect of cancer management. Because of increasing evidence that malignant cells have antigens different from those of normal host tissues, immunotherapeutics is an attractive avenue of inquiry. The objective will be to treat cancer by stimulating or giving antibodies, or sensitized cells that would attack malignant tissue, or by giving therapeutic radioisotopes that would localize on immunoglobulin receptor sites of malignant cells. Proposed work would include greatly expanded animal experiments on immune factors related to tissue transplantation and blocking antibody. When appropriate laboratory evidence has been gathered, expanded clinical trials will be designed. These would include work currently under way in marrow transplantation attempts: (a) to support cancer patients who have marrow insufficiency due to cancer or vigorous therapy, (b) to transplant an immune system that would be hostile to host malignant cells. For example, a task group could work on cell fusion as a means of improving antigenicity to malignant cells. A second example would be a task group to produce quantities of pure antigens and antibodies, a prerequisite for experimental immunotherapy studies.

d. Biochemical Adjuncts to Therapy

Initially we envision three task groups, exploiting existing talents and projects under way in Oak Ridge:

1. Biochemical group to monitor effects of chemotherapy and radiotherapy. A new high volume, high resolution assay system, such as the GeMSAEC would make it possible to identify quantitative changes in serum and urinary breakdown products produced during chemotherapy, irradiation therapy. Identification and quantitation of these compounds could provide an important clue for evaluating patients' status, and for new promising modes of treatment.

2. As mentioned in the section on diagnosis, to attack the question of the biochemistry of membranes of cancer cells, with the view to determining the role of viruses, antigens, and antibody-binding sites on the cell wall.

3. A group to determine the specific needs for amino acids, essential fatty acids, and other building blocks of particular types of cancer, with the view of blocking tumor growth by depriving cells of the substances or substituting nonfunctioning analogs (metabolic antagonists).

e. Supportive Treatment in Cancer Therapy

The threat of infection and hemorrhage limits intensive treatment by radiation or chemotherapy. Sustaining patients through periods of extreme thrombocytopenia, leukopenia, and immunosuppression, is an important objective. In Oak Ridge, two task areas are identified: (a) Instrumentation. Cell separation methods to provide large quantities of leukocytes and platelets from healthy donors. (b) Research on infections that affect cancer patients. This includes a complete description of shifts in patients' flora under various intensive therapies, and the role of endogenous versus exogenous organisms in infections. To this end a laminar air flow sterile patient facility is already in use at the Medical Division of ORAU. Further work on common pathogens in the immunosuppressed state, particularly pseudomonas infection and candida infection is under way and should be greatly expanded, perhaps toward development of appropriate vaccines.

CANCER PREVENTION

I. The Problem

Epidemiological and other data suggest that a large fraction of human cancers are induced by environmental agents. Cancer mortality could be reduced appreciably by identifying the cancer-inducing agents and either developing the means of removing them from the environment or protecting the population against their action. A strong program in cancer prevention, based upon existing ORNL programs in chemical, viral and radiation carcinogenesis and cancer immunology, would be a major unit of the proposed Oak Ridge Cancer Center.

II. Current Programs

The following are capsule summaries of ongoing ORNL programs related to cancer prevention. Much of this work is supported wholly or in part by interagency agreements between AEC and the Etiology Program of NCI.

1. Biology Division

   a. Carcinogenesis Program - A broad interdisciplinary program in chemical and viral carcinogenesis. Emphasis on interaction of environmental factors in development of lung cancer, development of appropriate animal models for lung cancer and other cancers, with special inhalation facility holding 5,000 mice and facilities for rearing and maintenance of pathogen-free rodents. Development of methods for assessing mutagenic capacity of carcinogens, correlation of mutagenicity with carcinogenicity. Host factors in carcinogenesis: role of immune system in chemical and viral carcinogenesis, repair mechanisms in carcinogenesis, cellular and molecular level analyses of factors determining susceptibility to chemical and viral carcinogens, repression mechanisms and their role in development of cancer.

   b. Radiation Carcinogenesis and Other Basic Programs - Analysis of carcinogenic effects of low levels of radiation, various types of irradiation, host factors in radiation carcinogenesis. Basic research in differentiation, protein and nucleic acid structure and metabolism, chromosome structure and function, mechanisms of protein synthesis, mammalian genetics, transplantation immunology.

2. Molecular Anatomy Program

   Cancer immunology, emphasis on fetal antigens and their relationship to antigens of cancer cells, potential in cancer diagnosis and therapy as described elsewhere. Development of centrifuges and methods for virus isolation, containment engineering. Capacity of fetal antigens to immunize against cancers a central concern in current research.

3. Analytical Chemistry Program

a. Identification of Environmental Carcinogens - Development of methods for complete analysis of chemical constituents of commercial cigarettes and cigarettes formulated by joint NCI-industry program to develop less hazardous cigarette. Collaborative with Carcinogenesis Program in development of animal model for bioassay of carcinogenicity of cigarette smoke.

III. Proposed Development

These research efforts will be extended with particular attention to the following areas:

1. Identification of Carcinogens

a. Epidemiology

Identification of agents acting to increase the incidence of human cancer is best made through epidemiological analysis; to our knowledge little or no capacity for cancer epidemiology exists in the Southeastern United States. This lack would be remedied by the establishment in the proposed Cancer Center of an epidemiology unit working closely with the existing ORNL biometry and biostatistics group and using ORNL computer facilities.

b. Environmental Factors in Lung Cancer

The existing inhalation facility should be doubled in capacity (to 10,000 mice) to permit intensive investigations into key questions such as the conditions under which environmental contaminants such as SO_2 and NO_2 enhance carcinogenesis in the respiratory tract, the extent to which these agents enhance the effect of a given dose of chemical carcinogen, and the role of respiratory infections in development of lung cancer. That the inbred mouse is a satisfactory animal model for these studies is suggested by our recent demonstration that bronchogenic squamous carcinoma is readily elicited in mice given carcinogens intratracheally. This points to the need to develop inhalation chambers for the study of carcinogenic aerosols. Engineering experience at ORNL in problems of biological and radiological containment is extensive and will contribute appreciably in this development.

Inhalation of cigarette smoke is now recognized as the primary factor in the steadily increasing incidence of lung cancer. Two ORNL components are currently engaged in the effort to develop less hazardous cigarettes, one in a comprehensive chemical analysis of the components of the smoke of various cigarettes and the other to develop methods for bioassay of the carcinogenicity of cigarette smoke. When these methods have been perfected an expanded joint effort will seek answers to such pressing problems as the degree of carcinogenicity of experimental cigarettes, the cocarcinogenic effects of cigarette smoke and of various fractionated components, and the role of host factors in smoke carcinogenesis.

c. Improved Carcinogen Testing Procedures

The major barrier to rapid identification of chemical carcinogens is the requirement for exposing large numbers of animals for long periods; thus current screening procedures are both inordinately expensive and depressingly slow. Several routes toward a solution are currently under way. These should be strengthened and other alternatives initiated. Current approaches, under way or planned, include a study to determine if immunologically-suppressed animals can be used in carcinogen testing. Many carcinogens are immunosuppressants; the immune system is known to play a highly significant role in determining the response to carcinogens. Since the fundamental question asked in screening assays is: Is this compound carcinogenic?, a functional immune system can be regarded as an unnecessary complication which probably prolongs carcinogen testing assays appreciably. Use of immunologically-suppressed animals (e.g. by neonatal thymectomy) may shorten testing time and divorce the factor of immune suppression by test chemicals from the primary question of carcinogenicity. The existence of specific pathogen-free animal facilities is essential here.

A second approach is via in vitro systems. Organ cultures of respiratory tract tissues are being developed for this purpose, and we hope to implement soon a comparable facility using cell cultures of hamster, mouse, and human tissues.

A third approach is based on the presumed relationship between mutagenicity and carcinogenicity. If such a relationship could be established (a current objective) it may become possible to reject a suspect chemical by inexpensive and rapid tests for mutagenicity in microorganisms and in cultured mammalian cells. As most carcinogens are active only after metabolic transformation, we have developed a variety of procedures for assessing the products of transformation in microbial and cell culture systems; these need to be improved and extended.

A fourth approach would be based on recent observations that cultured cells, superinfected with non-transforming leukemia viruses, are rendered highly susceptible to carcinogenic chemicals. These synergistic effects, with radiation as an additional variable, could be analyzed in tissue culture, and in animals when appropriate. An existing dormant animal facility housing 25,000 mice which can be operated as a "specific pathogen-free" farm will be of particular value in developing this and other large-scale carcinogenesis experiments using conventional means of carcinogen exposure.

d. Mechanisms of Chemical Carcinogenesis

Carcinogen testing procedures will be immensely improved and rational preventive measures may become possible when the details of carcinogen activation and inactivation in vivo and of the essential reactions involved in transformation to malignancy are known. We will develop a major biochemical unit seeking answers to these questions; this unit will also investigate the threat of apparently innocuous substances being rendered carcinogenic by virtue of interaction in vivo (e.g. nitrosamine formation by reaction of amines with nitrite).

2. Carcinogen Removal

How this will be accomplished depends on the nature of the carcinogen and no general description of an approach is possible. If the problem is one of separation from other materials or of removal from water, for example, the technology of ORNL is admirably suited to attack the problem. The ORNL Environmental Studies Program is available to coordinate these efforts, as well as to assess the impact of changing established practices and to advise on the best means of bringing about such change.

3. Preventive Measures

a. Vaccines

Cancers can be initiated in laboratory animals by a variety of viruses, and it seems certain that viruses are of etiologic significance in several human cancers. Virus disease can often be prevented by appropriate vaccines, given a favorable benefit/risk ratio. Vaccine production may therefore become a significant component of cancer prevention. The ORNL Molecular Anatomy Program has pioneered in developing centrifugal techniques for virus isolation, and continues to refine both centrifugal hardware and the methods used to isolate purified virus. The proposed Cancer Center would continue development work and could construct production facilities as necessary. ORNL experience in containment engineering will be vital in this effort.

b. Measures Based on Host Factors

Much of our current program in cancer prevention deals with host factors operating to determine both the onset and the course of carcinogenesis. This long-range approach may ultimately provide control measures based on understanding of host factors such as the immune system, repair processes, cellular repression mechanisms, etc.

System-wide analyses of changes occurring in the various components of the immune system are being made in the course of chemical and viral carcinogenesis to determine the factors acting to limit the success of the immune system against development of cancers. This may lead to a more definitive immunotherapy or to preventive regimens, allowing the promotion of effective components (e.g. cell-mediated cytotoxicity) and/or the eliminating ineffective or blocking components. Similarly on current trial is the use of adjuvants to enhance tumor antigenicity and to prevent metastasis.

Our analyses of cellular mechanisms for repairing radiation damage to DNA in mammalian cells now permit description of the enzymatic steps involved in the repair process. The first of these is deficient in the genetic disease Xeroderma pigmentosum, characterized by multiple skin cancers, emphasizing the significance of repair processes in carcinogenesis and pointing to the possibility of preventive measures based upon control of repair. Current efforts to define repair mechanisms operative on chemically-damaged DNA should be broadened and extended to include mechanisms controlling integration of viral nucleic acids.

The expression of a wide variety of fetal characteristics in cancers of various kinds is rapidly being documented and may quickly lead to improved methods of diagnosis and therapy. More fundamentally, these aberrant characteristics indicate changes in gene expression which may be common to all cancer and thereby may provide the ultimate means of contro. Put very simply, this reduces to the questions What genes, normally "off", determine malignancy when "on"?, What are the cellular mechanisms determining whether these genes are "on" or "off"?, and, How can these mechanisms be manipulated to ensure that the appropriate genes remain "off"? This long-range goal is being approached at present in several ways, including basic studies of repression mechanisms governed by steroid hormones in mammalian cells and the development of somatic cell genetics; experience in microbial systems clearly shows that genetic tools are indispensable in delineating mechanisms of gene regulation. More direct approaches to gene regulation in cancer are being made in studies of the factors governing expression of the oncogenic RNA viruses. Strains of mice and cultured cells of widely differing susceptibilities are being analyzed in both biological and biochemical terms. Cell fusion studies involving fusion of "non-producer" cells with those actively synthesizing virus may help to identify repression mechanisms operative in one cell type and inoperative in the other. Cellular mechanisms governing expression of viral antigens and enzymes are being analyzed; in the course of these studies it was recently found that single-stranded ribopolymers are very effective competitive inhibitors of the RNA-directed DNA polymerase of leukemia viruses, a finding which may have therapeutic significance.

Further development of these long-range approaches to cancer prevention are entirely dependent upon generating greater understanding of the fundamental properties of mammalian cells. The proposed Center should therefore include units concentrating on mammalian biology and molecular biology, with particular reference to immunology, mechanisms of DNA synthesis and cell replication, the biology and biochemistry of tumor viruses, somatic cell genetics and the regulation of genetic activity, and protein and nucleic acid structure, all of which would be carefully directed toward providing information needed for cancer prevention.

INFORMATION ANALYSIS AND EXCHANGE

Oak Ridge has abundant facilities for rounding out the proposed Comprehensive Cancer Center in data handling, data analysis, and information exchange. A partial list of these consists of:

1. Computer centers

   a. ORNL (Mathematics Division)
   b. Union Carbide (K-25)
   c. ORAU (Medical Division)

2. A consultation group of statistical scientists within ORNL Mathematics Division.

3. A systems programming group for medical problems ORAU Medical Division.

   A collaborative program exists between ORAU-ORNL computer groups and ORAU medical staff for developing means of reducing voluminous clinical data for easy retrieval of facts that can be used to search for dose-response relations in chemotherapeutic and radiotherapeutic trials. An IBM 1800 real time, analog-digital computer system is in operation at ORAU Medical Division where it is being used as an integrated part of clinical laboratory analyses (for example, ^{14}C and ^{3}H scintillation assays) and of physiologic patient monitoring by time-sharing. Batch processing of data from radioactive tracer studies and scans is routine. These computer staffs enjoy immediate availability of statistical consultation for data analysis from the Mathematics Division of ORNL. It is proposed that these facilities and staff will be used as fully as needed by the Cancer Center staff and augmented where necessary, to keep data acquisition and analysis on a par, available for early evaluation and dissemination to the many multidisciplinary research groups that will need to be kept informed of progress. A data-analysis task group within these facilities will need to be formed early in the development of the Center. One of its major tasks will be to find means of quickly identifying new questions or avenues of research from results of recently acquired data. Another major task will be creating new methodology for condensing the masses of clinical information contained in a difficult-to-use form in patient charts. This group will participate with other task groups in experimental design, aiding in determining the minimal amounts of data needed for demonstrating the minimal amounts of data needed for demonstrating the success or failure of a particular approach.

TRAINING AND CONTINUING EDUCATION

At present there are six programs or groups in Oak Ridge available to the Cancer Center as training resources. These are:

1. Oak Ridge-University of Tennessee Graduate School of Biomedical Sciences. Here, pre- and postdoctoral education and research in molecular biology is being provided.

2. In ORNL:

   a. The Information Centers Program — a new concept of information dissemination carried out by skilled reporters, highly knowledgeable in specialized technologies.

   b. ORNL — Postdoctoral Research Training Program.

3. At ORAU:

   a. Training Division — a group highly skilled in teaching new technologies to academic and industrial scientists.

   b. Information and Exhibits Division — a group of demonstrators, teachers, and artists whose talents combine to educate the public and the young in new technologies and their social as well as scientific importance.

   c. Medical Division — Postdoctoral Research Training Program.

Continuing intramural education for staff is an often neglected aspect. In this setting we will have a rather complete spectrum of specialized experts. In the task group approach, it is essential for every team member to understand the language of his colleagues — the immunologist must learn tumor taxonomy with the pathologist; the radiotherapist must learn from the cell biologist; the surgeon must understand what the electronics engineer can tell him. A formal program will be designed to give visability to this need, incorporating a seminar system of visitors from other large laboratories and staff as one element, preceptor bench assignments as another, and novel teaching machine approaches in addition to more conventional course offerings.

TUMOR ANTIGEN ASSAY
Based on Immunofluorescence Method

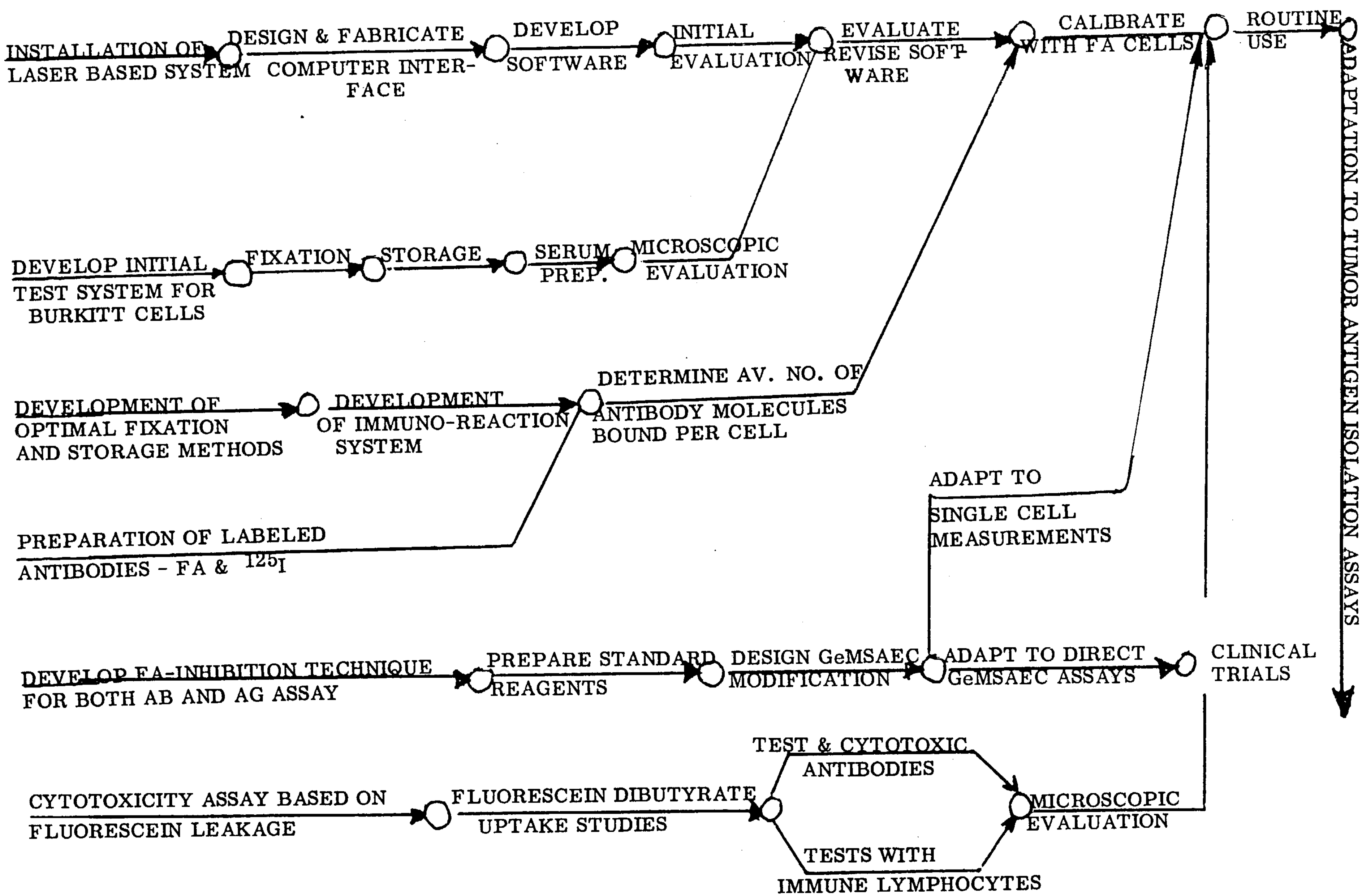

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Chart 1

June 9, 1971 NGA

GeMSAEC SYSTEM

Application to Cancer Patient Studies

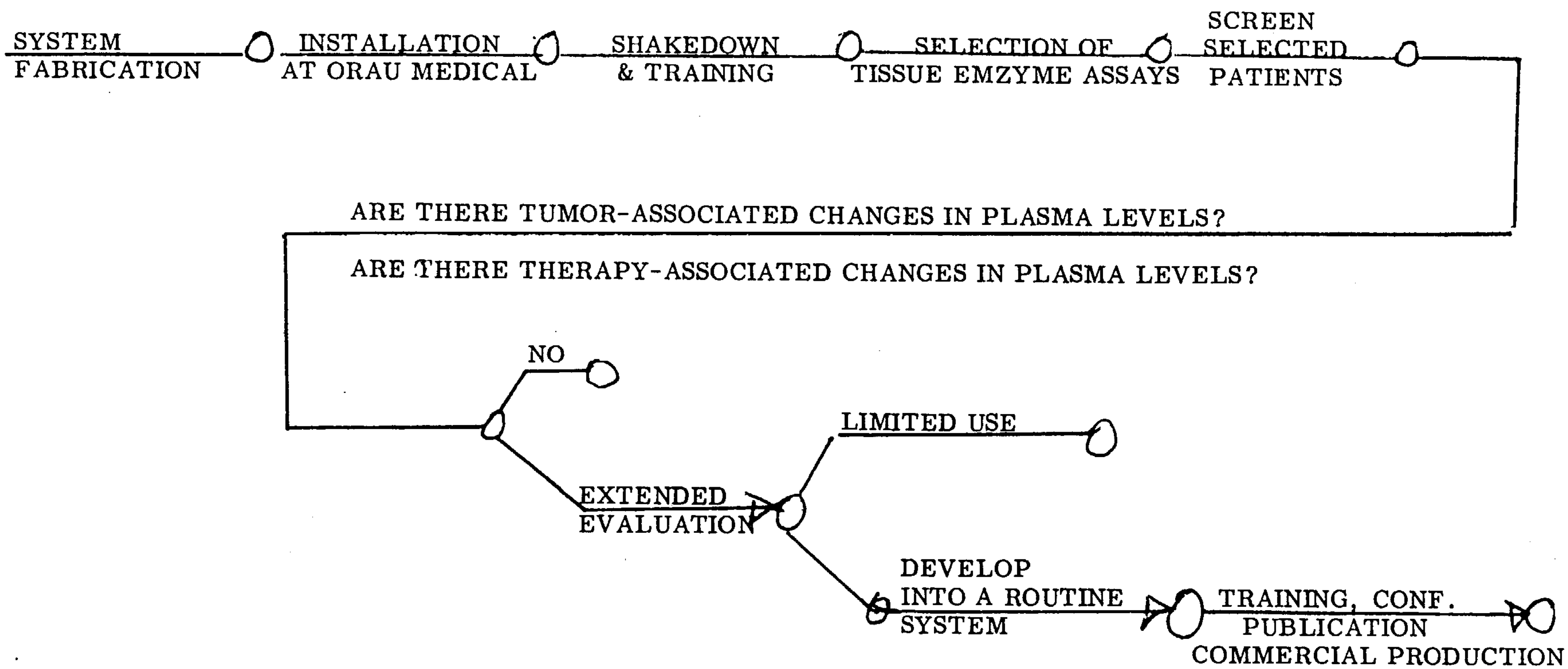

Chart 2

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