

An Administrative History of the
National Cancer Institute's Viruses and Cancer Programs, 1950-1972
By Carl G. Baker, M.D

To my wife,

CATHY

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Preface

Although the major advances of the science aspects of viral oncology are recorded in various histories, the science-administrative aspects and the managerial decisions behind the program developments have not been well set forth. This book discusses these elements in relation to the Viruses and Cancer Programs of the National Cancer Institute during the period, 1953-1972. The staff members who conduct the science-administrative efforts that lay behind the science have rarely received recognition of their contributions. Moreover, with the widespread use of advisory groups, the record makes it appear that the Federal Government staff has not been able to conduct the work without the advice of committees composed of non-Government individuals. Most of the time, however, the staff has formulated the program proposals, new guidelines and policies, *after* which advice was obtained. To be sure, many groups of outstanding experts can provide helpful advice in specialized areas. However, in broader areas (such as determining the value of various components in cancer research as a whole) those who work full-time on the total picture of cancer research may well have a better grasp of the subject than a committee that deals with the subject at three-day meetings held three times a year.

In addition, this book illustrates how the NCI Viruses and Cancer Programs added to the foundations of molecular biology and biotechnology and provided techniques, resources, and concepts important for research on AIDS. They funded, through contracts, production of developmental research resources that were otherwise not available. Currently, many of these resources and techniques, which are now available commercially, are outgrowths of the contract funding of these NCI R&D contracts.

This history of the NIH viral oncology program describes the activities of senior NCI staff and gives an accounting of scientific and administrative events; it shows the interweaving of

the two components. I have provided an account of key management decisions and actions for the period, 1953-1972. I have also described Congressional actions in relation to the National Cancer Act of 1971 and the various aspects of planning that went into it.

Prior to 1960 the NCI viral oncology extra-mural efforts were funded by grants for individual projects. During the period 1959-1960 efforts were made to begin to define the scientific problems and the resources needed. Staff also developed various options for managing the new viral oncology activities. The Viruses and Cancer Panel of the National Advisory Cancer Council (NACC) was formed and scientific-technical committees were appointed. As a whole, the internal NCI viral oncology efforts were enlarged.

From 1960 to 1966 there was a change in the NCI philosophy of cancer research from emphasis on project support of individual investigators (grants) to complementing the grants funding with broad multi-discipline, integrated programmatic efforts. This also encompassed a greater focus on defining goals and objectives. In order to do this, systems planning—under the name “the Convergence Technique”—was utilized as a means of giving proposed program operations more central direction. In addition, NCI staff and NACC committees were reorganized to reflect the new philosophy. Contracts, integrated into the systems plan, became the major tool for implementing the program. Quality controls were instituted to ensure that contamination from interfering bacterial or viral presence in tissue cultures, and other deficiencies were corrected. After these changes, the Program picked up its pace in terms of accomplishments. Important research results were achieved on a regular basis, scientific information was exchanged between scholars, and there was increased availability of defined standardized resources. While the extensive annual reviews of the Program before the Scientific Directorate and the NACC required the NCI staff to generate large—even excessive—amounts

of documentation, they nonetheless signaled that NCI was committed to making the viral oncology programs a success.

Introduction

The National Cancer Institute (NCI) Viruses and Cancer programs laid the groundwork for the development of molecular biology and biotechnology. The Special Virus Leukemia Program, and later the Special Virus Cancer Program, was especially significant. In 1982, Nobel Laureate James Watson, who was a member of the National Advisory Cancer Board, told Vincent DeVita, former Director of the NCI, *“Given the still prevalent unfair public misconception that the NCI Tumor Virus Program was a failure, and the strong possibility (fact?) that most if not all of viral oncogenes have their human counterparts, the time is more than ripe for NCI to point out how well the public purse has, in fact, been used.”* (NCI Monograph 64, May, 1984, page 1).

The NCI viral oncology programs provided the basis for the discovery of AIDS and supplied concepts, techniques, and tools for subsequent research on AIDS. In the January 18, 1999, issue of *The Scientist*, NCI geneticist Stephen J. O’Brien was quoted: *“The development of our sophistication in virology and immunology, and the relationship between genetics, virology, and cancer, all came out of this infusion of money in the virus-cancer program; it did empower us ... to recognize that [AIDS] was a virus -- and how it worked.”* Anthony Fauci, Director of the National Institute of Allergy and Infectious Diseases, added: *“Now that AIDS has really opened up whole new fields of research, there is cross-fertilizing back to cancer. But what we know about AIDS really emanated from a lot of creative people many years ago investigating the relationship between viral genes, cellular genes, and cancer transformation.”* The NCI viral

oncology program produced a new set of research tools necessary to further development of the field.

This document sets forth the programmatic history of the Viruses and Cancer Programs of the National Cancer Institute 1950-1972. Although the history of the scientific aspects of the viruses and cancer area has been well documented, the associated administrative aspects have not been well documented. This latter aspect includes the history of the development of the required quality resources: tissue culture cell lines; virus preparations; antibodies; special animals and animal model systems; hazard containing facilities; banks of human tissues and sera and other resources; low temperature storing equipment; and special instrumentation. Today most of these resources are commercially available, but in the early years of the Programs they were not available in the quantities needed, and many of the materials were of insufficient quality.

These programs in the early years, when the focus was on the scientific and technical matters, were illustrative of the cooperative relationship between NCI expert scientific and administrative staff and advisors outside the Government. They jointly analyzed the main problems to solve, set forth the strategic directions to go, identified the resources required, and outlined the administrative structures needed to implement the expanded effort. While the relationship was excellent at first, it deteriorated to some extent over the years as outside advisors became more heavily oriented to political factors, especially those resulting from appointments made to the National Advisory Cancer Council (NACC). The NCI staff was mostly responsible for implementing the administrative program; this included the review of project proposals, evaluation of program development, making actual *decisions* about the program and the approval of projects, the development of budget, and defending the program higher levels in the Executive Branch and the Congress. Some of the pioneering efforts in systems planning of

biomedical research programs derived from the search for better ways to develop the budget, which included the Viruses and Cancer Programs. Individual outside advisors made some important implementation steps. With respect to advice, it is often better to have advice from an individual who is very knowledgeable than from a committee that usually must compromise to reach a conclusion. The Foreign Minister of Israel recently said, “*Compromise is failure.*” The January 2003 issue of *Reader’s Digest* quoted British Prime Minister Margaret Thatcher as saying: “*Consensus is the negation of leadership.*” Also, to advise is easier than to implement.

Chapter 1: Background and Initiation of Viral Oncology Activities

Little interest in viral oncology research was shown before 1953 when Ludwik Gross demonstrated that cell-free extracts of mouse leukemic tissues contained one or more viruses that caused cancer in animals. This finding led to the possibility that viruses caused *human* leukemia and perhaps other *human* tumors and that vaccines capable of preventing such cancers could be produced. Several other animal virus-caused tumors were soon identified; these results strengthened the possible significance for man.

These dramatic discoveries changed the views of cancer investigators from no interest to excitement in cancer virology research; the number of investigators interested in cancer virology began to increase. By 1958 the accumulated research findings led the Director, National Cancer Institute (NCI), and Nobel Laureate Wendell Stanley at their testimony before the Congressional Appropriation Committees to emphasize progress in cancer virology and to seek additional funds for this work. The Congress subsequently called for vigorous stimulation of research and training efforts in the study of the possible viral origin of human cancer. To emphasize the importance of this research, the Congress appropriated an additional \$1 million

for added viral oncology efforts. The NCI science-administrators decided these funds would be spent as research and training grants.

The National Advisory Cancer Council (NACC) recommended that long-term support be given to outstanding investigators, some of whom were active in poliomyelitis research. The Virology and Rickettsiology Study Section (V&R SS) concurred and invited grant proposals in four categories: 1) basic research on viruses and animal hosts, utilizing tissue cultures, electron microscopy (EM), and model systems with reference to man; 2) training; 3) distribution of living host and viral materials, and 4) expansion of the research grant mechanism to support large-scale inter-disciplinary explorations over a long period of time.

The NCI, with endorsement of the NACC, established an expert Panel on Viruses and Cancer to provide advice to the Council and staff, working with the V&R SS. At the request of NCI, The V&R SS agreed to an expedited review of grant proposals. to speed up the initiation of new cancer virology research.

After NCI expanded the virology grants program, the next task was to define the aim and scope of the effort, the primary scientific problems, and the resources required; the focus would be on the search for human tumor-causing viruses. The aim of the effort was to determine if any human tumors were viral induced and, if so, whether they could be prevented with vaccines. The scientific problems at this stage primarily dealt with techniques for isolating, identifying and classifying viruses from tumors and studying the effects of viruses on animals and cells, including tumor causation. A variety of resources would need to be produced to conduct the scientific investigations.

Tissue culture techniques are major tools in virology research, and NCI brought together in mid-1959 experts in the growth, characterization, and preservation of animal cells. However,

before the tissue culture techniques could be profitably used in human virus research, several problems needed to be worked out. Because individual investigators had carried out their research largely independently, tissue culture cell lines developed with little coordination between these efforts. The cell lines needed to be standardized. In addition, other problems plagued researchers who used tissue culture systems, such as lack of standardization of tissue culture growth media, mislabeling of cell lines, contaminations with bacteria or viruses, and improper storage.

The experts developed a plan to address the most pressing problems: standardizing the tissue culture methods and cell lines; organizing a central tissue bank, and ensuring proper coordination and quality control. The Viruses and Cancer Panel, appointed earlier, delineated several immediate objectives for a more direct attack rather than the usual more general, long-term support of the basic research projects approach.

Over the course of several meetings, the staff and advisors refined and prioritized the list of other scientific problems that needed to be tackled. By the early 1960s, interest in cancer virology had increased dramatically. The integration of the scientific aspects and the resources into one program had its beginning at this time.

Although research advances were progressing rapidly, research tools needed to be made more reliable. By 1961, the staff and their advisors had developed a charter of very broadened scope for creating an enlarged program. Research advances were progressing rapidly. In addition, research concepts and approaches, techniques and methods, new resources, and data and knowledge gained from animal studies were being vigorously applied to the search for human tumor viruses. Problems with the quality control over resources still plagued the viral oncology efforts, but these problems would largely be solved over the next few years.

Early Cancer Work

Very little interest was shown in viruses and cancer research prior to 1953. In 1911 Peyton Rous produced sarcomas in chickens with cell-free extracts of the tumors and demonstrated that a virus was the causative agent. In the 1930's a few additional viral-induced tumors were identified in rabbits (Rous and Beard; Shope), mammary tumor in mice (Bittner and Andervont), and kidney tumors in the frog (Lucké). The study of viruses and cancer was not even considered as part of cancer research in the 1938 report of the committee appointed by Surgeon General Parran to advise on the research to be funded by the newly established National Cancer Institute (Report: Fundamental Cancer Research, *Public Health Reports*, 53: 2121-2130, 1938). Members of the Committee were: S. Bayne-Jones; R. G. Harrison; C.C. Little; J. Northop; and J.B. Murphy, Chairman. Despite the unpopularity of work in the field, Joe Beard, Ray Bryan and Ben Burmester, and Rous himself, continued research on the Rous sarcoma agent.

Virus Causation of Leukemia

A dramatic change occurred (akin to the concept of the “paradigm change” of the historian Thomas Kuhn) in 1953 when the work of Ludwik Gross was confirmed by other investigators (Thomas S. Kuhn, *The Structure of Scientific Revolutions*, Chicago: University of Chicago Press, 1970). He produced leukemia in mice with cell-free extracts containing a virus. Soon after this (1953-1957), other leukemia producing viruses were found in mice by A. Graffi and by Charlotte Friend, and Sarah Stewart and Bernice Eddy isolated from mice a polyoma virus that produced twenty-three different tumor types in hamsters. Following this work Frank Rauscher isolated another leukemia virus, Henry Kaplan found another leukemia virus from

irradiated mice, and John Moloney isolated a sarcoma virus from a sarcoma and later another leukemia virus. These research findings produced great excitement among cancer investigators as the results from the laboratory with animals suggested the possibility that some human tumors were caused by viruses and might be prevented with vaccines. The field quickly became very complicated with the finding that some of the viruses required “helper” viruses for them to produce their effects. Moreover, many of the animal systems and tissue culture cell lines were contaminated or even mislabeled.

1958

In the spring of 1958, NCI Director Rod Heller gave special emphasis in his testimony on recent developments in viruses and cancer research before the Appropriations Committees of Congress. He reported that several animal cancers had been induced by injection of cell-free extracts from leukemic tissues and tumors. These extracts had been filtered to remove all particles the size of bacteria or larger. Viruses were shown to be involved in the induction of the cancers. He also reported that the notion that viruses could cause cancer in man was of growing acceptance among cancer investigators. Nobel Laureate Wendell Stanley, who was a member of the National Advisory Cancer Council (NACC) and later a member of the NCI Board of Scientific Councilors (for NCI Intramural Research Programs), also testified before Congressional Appropriations Committees in favor of a larger budget than the one proposed by the Administration. He called for expanded research in viruses and cancer work and presented scientific evidence supporting the call for the expansion. Based on these presentations, in part, the Congress called for vigorous effort to stimulate research and training efforts in the study of the possible viral origin of human cancers. The aim of the effort was an expansive one: to search

for viruses causing human cancers and their prevention. To the regular appropriation for the NCI of \$27.814 million, the Congress appropriated an additional \$1 million for added viruses and cancer efforts.

One of the earliest symposia that covered work on viruses and cancer was “Perspectives in Virology,” held in February 1958. The Program Committee consisted of Joe Beard, René Dubos, Bob Huebner, Morris Pollard, Richard Shope, and James Steele. There were 117 attendees (*Perspectives in Virology*, edited by Morris Pollard, John Wiley & Sons, Inc., 1959).

At the June 16, 1958, meeting of the National Advisory Cancer Council, the Council recommended long-term support (up to ten years in some cases) for outstanding investigators, with emphasis on the individual rather than on a submitted detailed project proposal. Grant support for viruses and cancer research was about \$698,000 in fiscal year 1958 and \$2,000,000 in 1959 (about half the increase resulted from the special activities of the NCI Program on viruses and cancer).

The Virology and Rickettsiology Study Section (V & R SS), the regular NIH Study Section that reviewed grant proposals in the area of virology, sponsored a meeting on September 16, 1958, on “The Role of Viruses in Relation to Human Malignancies.” Fifteen expert investigators were invited to the meeting. They were: Joe Beard; Ray Bryan; John Enders; Charles Evans (Chairman); Hilary Koprowski; Salvatore Luria; Dan Moore; Alfred Prince; Stanfield Rogers; Harry Rubin; Albert Sabin; Jonas Salk; Richard Shope; and Jerry Syverton. Harvey Scudder, Executive Secretary, V & R SS, and Robert Backus, NCI, provided staff support from the National Institutes of Health (NIH). The group discussed expanding the research through technological, educational and institutional means. The members focused on four major categories:

1) basic research on viruses and animal hosts, utilizing tissue culture, electron microscopy, and model systems with reference to man;

2) greater emphasis on training;

3) improvement of the sources and distribution of living host and viral materials; and

4) expansion of the research grant mechanism beyond the current project concept to support large-scale inter-disciplinary explorations over a long period of time (Internal document, September 1958).

On September 18 the V & R SS itself endorsed the conclusions reached at the September 16 meeting and the statement from the June 16, 1958, NACC meeting that long-term support of investigators would be required.

The NACC Panel on Viruses and Cancer

At the November 1958 NACC meeting, the NCI established, with Council endorsement, a Panel on Viruses and Cancer with Council member Stanhope Bayne-Jones as Chairman. Robert Backus of the staff of the NCI Grants and Fellowships Branch was appointed Executive Secretary. The Panel, consisting of experts in virology and in cancer, was formed to provide advice to the Council and the NCI staff. Its function was to supply broad policy guidance, survey the field of viruses and cancer, identify areas needing greater emphasis, consider training needs, and give counsel on program needs and means of accomplishing goals. In performing these functions, the Panel would work closely with the V & R SS.

NCI science-administrators decided to use most of the \$1 million special appropriation for grants to individuals. For the first time in the viruses and cancer area, NCI made a portion of the funds available for contracts should it become necessary to provide a mechanism for

supplying tissue culture stem cells and human tumor tissues to investigators throughout the country. Administrators decided not to use contracts at that time for support of research work. Industrial organizations instead could apply for grants. During the initial stages, responsibility for the conduct of the Program was given to Carl G. Baker who recently had become the NCI Assistant Director after nearly two and a half years as Assistant to Dr. Joe Smadel, Associate Director for Intramural Research, NIH. This NCI assignment involved coordination of the various viruses and cancer activities, and close cooperation would be maintained with Ralph Meader, Chief of the Grants and Fellowships Branch and his staff, and with Harvey Scudder, Executive Secretary, V & R SS.

Following extensive discussions, the NCI asked the V & R SS to follow a precedent set on a few other occasions when Congress had earmarked funds for specific diseases. The Study Section was asked to nominate individuals for whom area grants might be recommended for long-term support. These grants were to be based on the individual rather than on a submitted detailed project description. To speed the process and allow new research to begin at once, letters of intent (to be followed by full grant proposals) were invited from outstanding investigators in the field. At the suggestion of the Study Section Chairman, Dr. John Dingle, staff of the NCI, along with Study Section members and its Executive Secretary, telephoned many investigators in the virology and cancer fields. Dr. Smadel, who knew most of the virologists who had worked in poliomyelitis research, telephoned them to invite their participation in the accelerated program.

1959

At a January 5, 1959 meeting, the V & R SS, in response to a request from NCI to expedite review of grant proposals, moved to speed up the process and help create a new

accelerated program of research on the relation between human cancers and viruses. The Study Section circulated a statement to the scientific community on four areas that the Study Section would be interested in receiving grant applications. The statement read as follows:

RESEARCH ON THE RELATION OF VIRUSES TO CANCER

The Study Section has been informed of the desire to establish a special mechanism for allocating funds with the intent of expediting research on the problem of the relation of viruses to cancer with special consideration of human malignancies. After thorough consideration, the Study Section expresses unanimous approval of the principle of all possible support of this field and wishes to make the following suggestions with respect to the procedure for implementing the program: 1) that funds allocated for this purpose be employed for the support of long term programs designed for the systematic approach to the direct study of viruses in cancer with special emphasis on human malignancies as rapidly as the development of knowledge and methods permit; 2) these funds shall be made available to any investigator judged to be competent to work in the field; 3) that the funds may be regarded as support for area research described in terms of general direction of approach; and 4) that the applications be processed by the Study Section and that a Subcommittee be appointed by the Chairman of the Study Section to expedite implementation of the special program (Minutes of V&RSS, January 1959).

At this meeting twelve “letters of intent” were discussed. The study section had accepted these abbreviated proposals for research, as a way to speed up the bureaucratic process. Six proposals (totaling \$325,442 for fiscal year 1959) were recommended for approval, and six others (totaling \$613,941) were deferred until additional information could be obtained. At another meeting on February 21 the Study Section met in special session to review twenty more applications totaling \$1.332 million (first year only). With recommendations from the Study

Section, the NACC at its March 2-4, 1959, meeting recommended approval of nineteen proposals for a total of more than \$1 million (Minutes of the V&RSS Meetings).

NCI Tissue Culture Consultants Meeting

One of the major tools in virology research is *in vitro* cultivation of cells and of viruses. The effects of viruses on cells can be studied with profit in such systems. However, because investigators had generally worked largely independently, the tissue culture cell lines had been developed with little coordination or standardization. Thus, cell line names were not always accurately applied, cultures could be contaminated with viruses or bacteria, and the cell lines might not be properly characterized and stored. The staff of the NCI asked seventeen consultants to come to the NIH May 15-16, 1959, to discuss the need for, and possible technical problems involved in, coordinating the characterization activities of investigators working with cytological materials. These consultants were selected for their competence in various aspects of cell growth, characterization and preservation. At the meeting, the consultants generally agreed that coordination was rapidly becoming necessary: an overwhelming amount of information had been accumulated, but the data was nearly impossible to correlate because researchers had used varying methods and nonstandardized resources. They agreed that a tissue culture bank should be organized around contributions that would be made available to investigators who were participating in the program. This Consultants Conference was Chaired by Council member Dr. Charles Evans, University of Washington. Dr. Jerome Syverton, University of Minnesota, presented an opening statement on the "Characterization, Preservation and Supply of Tissue Culture Cell Lines." Most of the members of the Viruses and Cancer Panel attended the meeting. The Panel met the day after the Conference and concluded that *a clear need existed for*

a coordinated cell-characterization program and that a program should be given sufficient impetus and administrative guidance and support to assure the success of a self-sustaining program. A second Conference of the expert consultants was called for to determine how best to undertake a cooperative effort for initiating and sustaining a mammalian cell bank with insurance of quality control (Minutes of the Virus and Cancer Panel, May 1959).

The Second NCI Tissue Culture Consultants Meeting

The second Conference of the expert consultants was held June 3, 1959. A plan developed for the creation of one or more centralized tissue bank facilities and a number of participating ancillary laboratories. Provision should be made for a long-term, low-temperature preservation of valuable materials characterized for future reference and for regularly scheduled cultivation for distribution as starter cultures. It would be expected that investigators utilizing banked materials would provide detailed data and contribute information that would add to the characterization of the registered and/or repositored materials. Such a facility could serve to accelerate the pace of productive biological research by minimizing the duplication of effort and by integrating pertinent information on a cumulative scale. Two of the participants, Drs. Cy Stulberg and Lou Coriell, voluntarily submitted detailed applications to organize centralized laboratory facilities for the coordinated characterization and banking operations. Nearly all of the participants in the meeting volunteered services within their individual areas of competence in a cooperative program (Minutes of the Second Meeting of the Expert Tissue Culture Consultants, June 1959).

The First Meeting of the Viruses and Cancer Panel

The first meeting of the Viruses and Cancer Panel was held February 11, 1959. The Panelists focused on the best way to uncover the relationship between viruses and cancer. The members focused on several immediate objectives for a more direct attack, rather than broad, general long-term basic research projects. They delineated the following objectives:

1) that opportunities for better communication among investigators in various disciplines should be made available.

2) that arrangements be made for anticipated source material needs including: a) a registry of tumor-viruses and specific antisera; b) registration and retention of tissue cell lines to be available to investigators; and c) encouragement through grants if possible, or contracts if necessary, of research specifically directed to characterization and stabilization of tissue culture cell lines (the staff was requested to explore with The American

Type Culture Collection the extent of undertaking these items by the Collection with funding by grant or contract).

3) that available primate animal resources be determined for studies of inter-species transmission of viral agents from human sources.

4) that the needs for technical personnel and professional investigators for the present and future be reviewed.

5) that consideration be given to meeting certain specialized service needs such as immune sera preparation, instrument development, electron microscopy, etc. (February 1959, Minutes of the V&C Panel).

The recommendations were sent to the NACC.

The Second Meeting of the Viruses and Cancer Panel

The second meeting of the Viruses and Cancer Panel was held June 31, 1959. At this meeting members decided to recommend to the NCI and the NACC specific proposals to implement a coordinated cell characterization program. They felt that the Panel should not engage in any direct effort to “organize” a program of the magnitude and complexity envisioned at the first meeting. They also thought that NCI should form a “Cell Culture Collection Coordinating Committee.” The committee was to be made up of individuals particularly sensitive to the problems and needs of the Program. The NCI Director appointed Dr. Syverton Chairman of the Committee. The applications of Drs. Stulberg and Coriell and of Dr. Clark from the American Type Culture Collection were reviewed by the Pathology Study Section and subsequently assigned to the NIH Division of Research Grants for review. Favorable recommendations were made by the Pathology Study Section. An application from Dr. Clark for a matching funds facilities grant was recommended by the Health Research Facilities Council at \$90,278. This Council was fully informed of the programming interests of the Viruses and Cancer Panel and the NCI staff. Robert Coghill (Special Assistant for Industrial Relations to the NCI Director and to the Head of the Cancer Chemotherapy National Service Center) and Carl G. Baker (NCI Assistant Director) assisted Dr. Clark in finding the matching funds required by the facilities grant. This grant allowed the move of the extensive invaluable collection of bacterial strains, fungi, virus preparations, and cell lines from a modified frame house fire hazard to a modern brick structure designed to meet functional requirements (Minutes of the Second Meeting of the V&C Panel, June 1959).

1960

By 1960 the interest in cancer virology had increased dramatically as evidenced by the support given by public institutions such as Congress and private public health organizations such as the American Cancer Society. At the Appropriation Hearings for fiscal year 1960 the Congress again expressed strong interest in viruses and cancer work. Funds appropriated for additional cancer research increased more than 30% for 1960 over 1959 to \$37 million. For viruses and cancer research there were 108 grants totaling \$3.6 million. For viruses and cancer training the amount of funding was \$847,565. Another indication of the growing interest in cancer virology was the sponsorship by the American Cancer Society of a major symposium on “The Possible Role of Viruses in Cancer” held November 19-21, 1959. The meeting was organized by a committee of Richard Shope (Chairman), Joe Beard, Hilary Koprowski, Ted Puck, and Peyton Rous. Twenty-nine scientists were invited to attend (*Cancer Research*, 20, 669-830(1960)).

A New NCI Director

On July 1, 1960, NCI Director Rod Heller became Director of the Memorial Sloan-Kettering Cancer Center in New York City. Ken Endicott, who had been Chief of the NCI Cancer Chemotherapy National Service Center and then NIH Associate Director for Training and earlier, succeeded Rod Heller as NCI Director. Bo Mider, NCI Scientific Director, succeeded Joe Smadel as NIH Deputy Director for Laboratories and Clinics. On September 13, 1960, Ken Endicott made the following appointments: Ralph Meader, Associate Director for Grants and Training; Mike Shimkin, Associate Director for Field Studies; Stu Sessoms, Associate Director for Chemotherapy (and Chief, Cancer Chemotherapy National Service Center); Eli Nadel, Assistant Director; Gordon Zubrod, Clinical Director, with responsibility for

intramural clinical research; and Carl Baker, Assistant Director, with responsibility for intramural non-clinical research. Dr. Baker was also made NCI Acting Scientific Director and represented the Institute at the NIH Scientific Directors meetings. Dr. Zubrod represented the Institute at the NIH Clinical Directors meetings. Dr. Endicott had experience in the grants philosophy of supporting individual scientists with project grants when he was Executive Secretary of the Pathology Study Section (while also conducting laboratory research on blood cell formation) and later Scientific Director of the NIH Division of Research Grants. When he headed the CCNSC he also gained science-management experience in developing defined multi-discipline programs aimed at solving specific problems (in this case discovering and developing new drugs useful in the treatment of cancer patients). While he strongly endorsed the support of basic research, he also believed the NIH research programs should include directed research target programs aimed at solving important disease problems. He brought this philosophy to the Directorship of the NCI and would proceed to reorganize the NCI to reflect this philosophy. This change was a shift from a largely *reactive* to an added *proactive* stance on the part of the management style of the Institute. The NCI Assistant Director, Dr. Baker, later the Associate Director for Program, was in agreement with this philosophy and would give Dr. Endicott strong support in bringing about the change.

The Third Meeting of the NACC Viruses and Cancer Panel

It had become evident by early 1960 that *in vitro* and whole animal systems as well as viral and antibody preparations were contaminated with various viruses. Characterized and standardized antisera and animal and tissue culture systems had to be developed to ensure sound quality controlled experimental systems comparable from one laboratory to another. The Viruses

and Cancer Panel met September 29-30, 1960, and developed an outline for how the program should operate:

“Statement of Current Program Interests”:

- 1) Use of known tumor viruses in model systems for virus-cancer research, and the search for unknown tumor viruses in man and other animals.*
- 2) Mammalian cell culture characterization, certification, distribution, and long-term preservation through a group of cooperating laboratories.*
- 3) Procurement, certification, and distribution of virological typing reagents for human and experimental animal viruses, with establishment of typing centers.*
- 4) Arrangements to facilitate provision of normal and neoplastic human tissue, including blood, for virus-cancer research, with establishment of collection centers.*
- 5) Development of “defined” animals for laboratory research as characterized by viral experience and genetics (including tumor susceptibility).*
- 6) Inquiry into studies of newborn primates as experimental animals for virus-cancer research, especially with reference to candidate human tumor viruses.*
- 7) Utilization of primates with neoplastic diseases for virus-cancer research, with provision for harvesting primate tumors at whatever age they exist.*
- 8) Encouragement of training in virology and related disciplines, especially as applied to neoplastic diseases.*
- 9) Improvement in communication in the interdisciplinary area of cancer virology.*
- 10) Development of special research equipment considered essential to the advancement of virus-cancer research (Minutes of the Third V&C Panel, September 30, 1960).*

The rapidly enlarging activities related to resources needed for the research led to the formation of a new Virology Research Resources Branch (VRRB). The above list of the ten items was drafted by Harvey Scudder who had recently joined the NCI Division of Grants and Training under Dr. Meader and was made Chief of the newly created Virology Research Resources Branch. Robert Stevenson was to join the Branch from his position as Head of the Cell Culture Section at the National Naval Medical Center. The Branch was to have three Sections: Cancer Virology; Cell Culture and Tissue Materials; and Laboratory Animals.

The Viruses and Cancer Panel also passed several resolutions:

1) The Viruses and Cancer Panel should report directly through its Chairman to the Council, rather than to the Research Review Board which is the present arrangement.

2) Contract proposals serving the Viruses and Cancer Program should receive dual review for their scientific need and merit. The Panel unanimously recommends primary review by a competent technical committee and final review by the Panel itself, with communication to the Council. The advisory groups for the primary review might be such technical committees as the Cell Culture Collection Coordinating Committee, the Enterovirus Committee, and the proposed Committee on Laboratory Animals.

3) In addition, the Panel passed the following resolutions concerned with implementation of the new program in viruses and cancer research. The Panel recommended that the National Cancer Institute take the measures to:

a) Liquid nitrogen equipment: Encourage the design and production of liquid nitrogen refrigerator and accessory equipment suitable for individual laboratory use, for the purpose of long term preservation of mammalian cells, tissues, and other biologic reagents, for which

satisfactory equipment is not now commercially available; grant or contract mechanism to be used, if necessary, to facilitate this aim.

b) Human material supply: Arrange at one to five hospitals or medical centers for the collection, preservation, and distribution of human tissues, including blood, both neoplastic and normal, properly processed and diagnosed; grant or contract to be used, if necessary, to accomplish this.

c) Committee on Laboratory Animals: Appoint a technical committee, preferably chaired by member of the Panel, to serve as an advisory group on laboratory animals, in order to undertake planning and technical guidance in the general areas of laboratory animal definition, provision, and techniques insofar as their development is considered essential to progress in the virus-cancer field. The Committee should be concerned with the development of facilities for handling virus-defined animals.

d) Typing reagents for mouse viruses: Encourage the development and procurement of typing reagents for mouse viruses, with independent confirmation as needed; grant or contract mechanism to be used, if necessary, to accomplish this.

e) Virology investigations at primate centers or stations: Encourage a cooperative program of viral investigation in the primate centers, which are currently being planned and financed by the National Heart Institute.

f) Primates for virus-cancer studies: Determine what must be done to make available primates of known background, especially new-born primates, for work in the virus-cancer field, and proceed in cooperation with other interested Institutes in achieving this goal.

g) Typing reagents for human viruses: Arrange for the production of adequate quantities of typing reagents (several liters) for any of the human viruses for which the production protocols are fully developed, using contracts or grants, if necessary.

h) Standardization of viral typing reagents: When considered necessary by the Viruses and Cancer Panel, arrange by contract or otherwise for the independent confirmation, standardization, and certification of viral typing reagents (antisera and antigens) produced under contract or otherwise.

i) Virology training: Establish two or more regional summer training centers, on west and east coast areas, for the training of experienced researchers in the virus and cancer field. These centers should represent institutes for advanced study, making provision for lectures, seminars, and laboratory sessions of various types. Some courses in basic techniques of virology and cancer research could be taught yearly, other courses in new techniques or development given as expedient (Minutes of the Third V&C Panel, September 30, 1960).

All these items, which indicated the broad scope of the effort, were essential for carrying out the viral oncology activities, and they would have to be integrated with the research activities into one total program.

At its November 14-16, 1960, meeting, the NACC recommended that the recommendations of the Panel be accepted in principle and that the various facets pointed out be utilized for furtherance of this program as seems appropriate. At that time 153 viruses and cancer projects totaling \$5.6 million were supported by NCI grants (NACC Minutes, November 1960).

1961 - Enlarged Scope of Viruses and Cancer Research Programs

The acceptance of these recommendations developed by the NCI staff and advisors thus provided a charter of very broadened scope for development of an enlarged viruses and cancer program. This charter laid out the future general development of the research. The implementation of the new efforts, especially development of resources (largely under contract), required intensive effort by the NCI staff over the next decade. The volume of work required for developing invitations for contracts, evaluating contract proposals along with establishing review committees, justifying decisions on contractor selection, and monitoring contractor performance was extremely heavy. Many of the Federal Government procurement regulations and some auditing rules were not well suited for research. While over the next couple of years many advances were made, such as discoveries of additional animal cancer viruses and identification of various virus particles with the electron microscope, considerable confusion still existed as to identifying characteristics of tissue culture cell lines, virus and antibody preparations, animal test systems, and even animals themselves. Progress was made in the development of portable liquid nitrogen refrigerators for storage and transport of cell lines and tissues and in improving viability success in freezing and thawing specimens. Problems remained, however, for the selection, removal, collection, preservation, and distribution of mature and embryonic tissues. Human tissues were still in short supply. Quantification of viruses was improved through developments in complement fixation and other immunological techniques. A major step forward was the plaque assay developed by Renato Dulbecco, which allowed much better quantitation of virus levels. Production and certification of mouse virus reagents still had many problems (spelled out in detail in a July 27, 1961, memorandum sent by Wally Rowe to members of the program). Extensive efforts to overcome the confusion were made by NCI administrators and investigators, contractors, and grantees. Dr. Robert Huebner sent another comprehensive memoranda to the

directors of NIAID and NCI proposing joint research efforts of NIAID (Huebner) and NCI (Shimkin) (“Collaborative Studies of viruses and Cancer as an Inter-Institute (NCI-NIAID) Effort,” February 20, 1961.)

Reorganization of the NCI

On February 27, 1961, Ken Endicott sent forward a memorandum containing an agenda for discussion with the Deputy Director, NIH on NCI reorganization of the “Grey Areas.” They were programs in the Field Investigations and Demonstrations Branch (FIDB), the Biometry Branch, the Cancer Chemotherapy National Service Center (CCNSC), and the Cancer Control Program in the Bureau of State Services (BSS), PHS. In the reorganization:

1) The Chief of CCNSC became Associate Director for Chemotherapy and also assumed responsibility for the virus program.

2) The Associate Director for Field Studies assumed responsibility for the Biometry Branch as well as for three new Branches (Epidemiology, Carcinogenesis Studies, and Diagnostic Research).

3) The FIDB was abolished and its activities were transferred, modified, or abolished, as appropriate.

4) Epidemiology, Diagnostic and Environmental activities of FIDB were moved to the Associate Director for Field Studies.

5) All grant activities of FIDB were transferred to appropriate branches under the Associate Director for Grants and Training. Field Investigation Grants became regular Research Grants. Traineeships and Clinical Training Grants were combined with Research Training Grants.

- 6) The Cancer Nursing Section would be transferred to BSS.
- 7) The Uranium Miners Study would be transferred to BSS.
- 8) NACC review of grants to States and Special Project Grants were discontinued.

The Virology Research Resources Branch, headed by Harvey Scudder, was shifted from the Division of Grants and Training under Dr. Meader to the Division of Chemotherapy under Dr. Sessoms (requested March 1, 1961 and approved by the Director, NIH, April 18, 1961). The main reason for this transfer was that the Chemotherapy staff had extensive experience in managing large projects on resources production funded with contracts. It was anticipated that the VRRB effort would expand in this direction.

The NCI Policy Group

The reorganization was effected to allow the senior staff to focus on the science aspects and program planning and less on administrative details. The NCI Policy Group was the focal point for bringing about the science-management changes. On May 10, 1961, Dr. Endicott sent a memorandum to the NCI senior staff establishing a NCI Policy Group consisting of Dr. Endicott as Chairman; Mr. Learmouth; and Drs. Baker, Zubrod, Sessoms, Shimkin, Meader, and Sloan. Dr. Baker was to serve as Executive Secretary. The initial paragraph of the memorandum was:

“For some time, there has been a need for the Director to discuss in a systematic fashion with members of the staff who have major program responsibilities, certain aspects of operations and plans of the Institute. The need is especially great in the area of long-range planning and in those aspects of operations that necessitate coordination, and indeed integration, among the major segments of the Institute. The key to successful approaches to these problems lies in: 1) periodic, structured discussions by a small group of senior program

leaders, and 2) careful, orderly, systematized selection of agenda items of major import and the appropriate staff work in conjunction with each meeting.”

To begin to make clear what was wanted, specific agenda items had to be formulated and selected. Further in the Memorandum:

“Dr. Baker has suggested that the following topics might be worthy of discussion:

I. NACC activities:

A. Organization and functions of Council Boards and composition of Council, Boards, Panels and technical subcommittees.

B. Council agenda.

C. Periodic reports to the Council, including their timing.

1. Design of the reports to ensure usefulness in overall Institute operating effectiveness and improved communication within NCI and NIH.

D. Extent of Council participation in long-range scientific program planning.

E. Role of Council in the review process in the face of large numbers of regular project grant applications, initiation of new grant programs, and the fact that the decisions on awarding most grants rest predominantly with the Study Sections since the Council rarely changes the Study Sections recommendations (how closely does the collective action on grant applications relate to Institute programmatic interests?).

II. Institute operations.

A. What are the most effective means of coordinating and integrating the activities of different segments of the Institute programs?

1. Participation of intramural scientists in programs of Field Studies, CCNSC and international activities:

- a. Epidemiology.*
- b. Carcinogenesis.*
- c. Viruses-Cancer.*
- d. Geographic Pathology.*
- e. Cancer Diagnosis.*
- f. Chemotherapy.*

2. Programmatic relationships:

a. Epidemiology and epizootology studies in Field Studies, Intramural and Viruses and Cancer programs.

b. Dynamics of the CCNSC programs and their relation to the viruses and tissue culture programs.

c. Carcinogenesis studies in Field Studies and in the Intramural area.

d. Enzymology and immunology studies in the Diagnostic Research Branch and the Intramural Branch.

B. Will work scheduling documents aid in accomplishing better Institute coordination of programs?

C. What should the nature of the Institute be five years from now?

Ten years?

1. What mechanisms should be employed to move toward the long-range goals?

2. What new programs should be instituted?

3. How can modern data processing methods help?

D. What should be the Institute training goals?

1. How large should the training programs be?

2. What types of training programs?

3. How best to move toward the training goals?

E. How should NCI relate to the BSS cancer programs?

1. Should a program of research on cancer patient care and rehabilitation be initiated?

F. How should NCI relate to the Bureau of Environmental Health?

G. How can the NCI weekly report and annual Highlights be improved?

1. The Policy Group can serve as a convenient mechanism for selection of appropriate scientific topics or areas.

H. What international programs should be engaged in by NCI?

I. Should more attention be given to awards for NCI staff?

1. How can the mechanics of award submittal be simplified?

J. Additional broad decisions on the new building.

III. Relationships with NIH:

A. What are the best mechanisms for dealing with the multiple channels for communication (and “semi-authority”) between the Institute and NIH staff?

1. What should NCI do, if anything, about the lack of clarity on the “grey areas” at the NIH level?

2. Should NCI seek to decrease the action channels outside the Director (NIH) -- Director (NCI) route?

a. Should NCI seek organizational changes in the non-Institute part of NIH?

B. What should NCI’s position be on NIH dealing with bigness?

1. Should we seek greater autonomy?

2. *Should other types of decentralization be favored?*

a. *Decentralization of grants and fellowships activities.*

b. *Establishment of major field stations.*

(I) *In university settings?*

(II) *Relatively independent major Branches?*

3. *What are the alternatives to the continuing proportional expansion of NIH central services?*

C. *How should NCI programs and plans relate to the NIH farm and other animal activities?*" (Internal NCI document, May 10, 1961).

Other suggestions were invited. This action initiated a management tool (the NCI Policy Group) that would form the basis for participation in policy formulations and operational decision-making by the knowledgeable senior staff of the Institute. It also developed into a forum through careful selection of agenda items and associated staff work for considering high priority subjects in cancer and dealing with problems needing attention that arose. Funding considerations and review actions on program plans and on contracts were ongoing functions of the Group.

The NCI Scientific Directorate

Later in 1961 Dr. Endicott further reorganized the Institute to strengthen functions of the NCI Policy Group. The Group was renamed the Scientific Directorate [much later called the Executive Committee]. Dr. Baker was appointed Associate Director for Program with enlarged Executive Secretary directorate staff and functions, plus added coordination and analysis and planning responsibilities. Dr. Zubrod was appointed Associate Director for intramural activities

and NCI Scientific Director and was made Chairman of the Scientific Directorate. The Scientific Directorate became the NCI focus for program developments and direction (with final decision-making authority with the NCI Director).

NACC Boards and NCI Boards Advisory to the NCI Director

On May 22, 1961, Ken Endicott requested approval for reorganization of the NCI Advisory Committee Structure (approved by the NIH Director June 7, 1961). Partly, this action to change the NACC committees was taken because the Kennedy Administration wished to decrease conflicts of interest problems. However, Dr. Endicott had discussed with the NACC in closed sessions how the actions of the NACC and its committees might be improved, and the proposed reorganization carried NACC general agreement. The change constituted a shift of emphasis to science-technical oriented units from mostly administrative-mechanics orientation. The memorandum on this reorganization to NCI staff included:

1. All standing subcommittees of the National Advisory Cancer Council (Planning Board, Research Review Board, Training Review Board, Cancer Control Board, and Chemotherapy Review Board) are abolished.

2. Three Boards of the National Cancer Institute advisory to the Director, NCI, on programs that utilize research contracts in combination with direct operations for the three major collaborative research programs in virology, chemotherapy, and field studies were established.

These Boards and the technical Panels associated with each are as follows:

1. Viruses and Cancer Board

- (a) Cancer Virology Panel*
- (b) Cell Culture Panel*
- (c) Laboratory Animal Panel*
- (d) Human Studies Panel*

2. Chemotherapy Board

- (a) Chemistry Panel*
- (b) Drug Evaluation Panel*
- (c) Endocrinology Panel*
- (d) Clinical Studies Panel*

3. Field Studies Board

- (a) Biometry-Epidemiology Panel*
- (b) Carcinogenesis Studies Panel*
- (c) Diagnostic Research Panel*

ROTATION PLAN

1. Boards: Three or four members of the National Advisory Cancer Council will be asked to serve on each Board, one of whom will be asked to serve as Chairman. These Council members will rotate off at the time their Council appointment terminates. The remainder of each Board will consist of the several technical Panel chairman advising that Board and such members-at-large as might be required. The members-at-large will be appointed for one-year terms, renewable indefinitely.

2. Panels: The chairman and members of the Panels will be

appointed for one year at a time, renewable indefinitely (Internal NCI document, June 1961).

Dr. Endicott explained in his requesting memorandum that turnover of advisors on a yearly basis (renewable at the option of the Director) rather than on a four-year basis would ensure new talent and better advice. As indicated in a memorandum footnote, at the time there was expectation that NIAID would be given responsibility for diagnostic virus typing reagents program for all of NIH.

Laboratory of Viral Oncology

In February 1961, the NCI had established in its intramural programs the Laboratory of Viral Oncology with Ray Bryan as Chief. This Laboratory was to include such outstanding investigators as Frank Rauscher, Jack Dalton, John Maloney, Sarah Stewart, Mary Fink, Guy de Thé, Bob Manaker, John Bader, Ruth Merwin, Giancarlo Rabotti, Lou Sibal, and Robert Zeigel. Ray Bryan prepared a detailed plan dated July 6, 1961, for expanding studies on human tumor viruses; space and position slots were the greatest shortages. Also projected were requirements of animals for the intramural programs. Gordon Zubrod, in his role as head of clinical activities and his special interest in leukemia, proposed collaborative studies with the Laboratory of Virology staff to learn for example if John Maloney's findings in mice could be duplicated in human leukemia patients. With electron microscopy, virus particles like those found in mice were seen in some leukemia patients. The status of the viruses and cancer program was reviewed on July 6, 1961, by Ken Endicott with senior staff (Gordon Zubrod; Stu Sessoms; Carl Baker; Margaret Sloan; Bob Learmouth; Walter Magruder; and Ray Bryan). Background information for the review was provided by Dr. Bryan (his July 6 memorandum), and Dr. Zubrod added information

on intramural projections and needs (Dr. Zubrod summarized proposals for intramural expansion of viruses and cancer investigations in a July 27 memorandum). Again shortages of space needs and position slots were prominent. Laboratory animals and tissue culture resources would need great expansion. The CCNSC could help with these animal needs by enlarging the outputs from contractors earlier established to increase animal production required for screening in chemotherapy assays. Carl Baker had prepared for review a preliminary program plan for a full-scale NCI program. It was in the form of an organization chart with functional headings suggestive of flow charts of the viruses and cancer activities that would be developed later. Very fruitful collaboration was established between NCI and Bob Huebner's group in NIAID, which included Wally Rowe and Janet Hartley. A proposal for a field epidemiology study on viruses and cancer in the Hagerstown, Maryland, area as a collaborative effort between the Huebner group and the Epidemiology Branch in NCI Field Studies Division under Bob Miller led to establishment of a base laboratory and animal holding facilities (house-type trailers). This arrangement was temporary; future movement of the activity to the NIH farm at Poolesville would be explored. In addition to joint funding of the collaborative venture, the NCI would provide virus diagnostic reagents for cancer investigations to Bob Huebner and coworkers.

Panels of the NACC Viruses and Cancer Board and Coordination

The NACC Viruses and Cancer Panel was enlarged June 13, 1961, to become the NACC Viruses and Cancer Board with four panels: 1) Virology Panel (Joe Melnick, Chairman; Marvin Harris, Executive Secretary); 2) Cell Culture Panel (William Scherer, Chairman; Robert Stevenson, Executive Secretary); 3) Laboratory Animal Panel (George Poppensiek, Chairman; Robert Holdenried, Executive Secretary); and 4) Human Cancer Panel (Charles Evans,

Chairman; Robert Stevenson, Executive Secretary). Priorities and coordination among the Panels needed better definitions. Staff of NCI had some concern that perhaps too many permanent committees were being established. It is difficult to eliminate such committees. Special attention was given in the Director's Office to coordination of the various viruses and cancer activities funded with contract, grant, and intramural monies. The central focal point was Dr. Baker who worked closely with NACC members and other advisors, Panel members and Executive Secretaries, senior program leaders, and, at times, grantees and contractors. The Executive Secretary position of the NCI Scientific Directorate provided other important coordinating functions.

Virus Typing Reagents

Virus typing agents had been produced under National Foundation for Infantile Paralysis auspices for the poliomyelitis effort by Herb Wenner and the Kansas University Endowment Association. Supplies of these reagents, consisting mostly of those for enteroviruses and adenoviruses, and the focus of programs to develop reference and diagnostic reagents for virology, were moved to the jurisdiction of the NIAID. The NIH movement of these reagents to NIAID without consultation with Dr. Bayne-Jones, who was head of the Viruses and Cancer Panel of the NACC, led to his resignation from the NACC. On July 1, 1960, NCI awarded a contract to the Association to produce virus typing reagents for the viruses and cancer program of NCI. NCI would maintain development for programs in cancer virology for the time being, though consideration was being considered to place all NIH virus activities under the jurisdiction of NIAID. Ken Endicott proposed that a NIH Division of Research Resources be established to provide essential research resources and that a Viral Diagnostic Reagents Program be a part of

the Division. Such a Division was later established, but the expansion of tumor viruses reagents was developed by NCI.

Review of VRRB Program Philosophy

On August 15, 1961, Dr. Endicott notified NCI staff of the transfer of the Virology Research Resources Branch (Harvey Scudder as Branch Chief) from Dr. Meader (Grants and Training) to Dr. Sessoms (now NCI Associate Director for Collaborative Research). In a communication in early November 1961 to Dr. Scudder, Dr. Endicott expressed a growing concern that the NCI viruses and cancer effort was fragmented and diffuse. He expected some difficulties in communication because of rapid growth and subdivision of effort. However, he came away from the meeting of the Viruses and Cancer Board with a feeling that the viruses and cancer efforts were not as clearly organized and on course as they should be. Though there were many examples of superb staff work, they seemed to be somewhat off target and fell short in leading to concrete action. Dr. Endicott was also concerned over the apparent lack of communication between the VRRB staff and those in other parts of the Institute who were working on essentially the same problems. There appeared to be a difficulty of communication between Ken Endicott and Harvey Scudder and a difference in philosophy as to the administration of the VRRB Program. Dr. Scudder saw the Branch Program as an *enabling* activity to provide grantee scientists resources needed for their research. Reagents produced under the Program would be available upon request. Dr. Endicott saw the Branch Program as producing resources based on a *defined* need of the various resources. The Program should be a planned effort that integrated the various scientific, managerial, and resources components into a unified entity. Dr. Endicott wanted a clear spelling out of what the VRRB was trying to do and

how it was proposed to accomplish the tasks. A meeting was held to review the status of the Program, and Dr. Endicott, perhaps partly because of the discussions at the NIH level on the centralization of viruses reagents programs in NIAID, asked Dr. Scudder how long it would take to close down the VRRB Program. Dr. Sessoms sent forward on January 8, 1962, to the Director's Office Dr. Scudder's F.Y. 1963 professional judgement budget for VRRB requesting \$7.417 million for contracts, an increase of \$3.507 million. The F.Y. 1963 apportionment figure for VRRB contracts was \$6.150 million.

1962 - Cancer Facilities Construction Needs

In January 1962, Dr. Endicott responded to Dr. Shannon's request to the Institute Directors for construction needs in their respective areas. The response referred to a two-year old sample survey of ten cancer research institutes made by Dr. Heller. Reported building plans for 1960-1965 totaled \$29 million of which over half were for immediate needs (land costs and space for research beds and non-research clinical laboratories were not included). In F.Y. 1961 NCI received 33 applications for \$23,982,816; the NACC recommended 15 applications for \$11,506,581. The \$10 million appropriated in 1961 and 1962 met immediate needs. Dr. Endicott expressed dissatisfaction with respect to disease categorical research and on the separation of funds for operations, manpower and facilities unrelated to cancer and other diseases. Although construction needs are tied to program requirements in NASA, DOD, and AEC, in PHS, funding for facilities for the most part had not been related to cancer research. Advisors to the NIH Health Research Facilities Branch had shown no special interest in furthering cancer research. Moreover, only the wealthiest cancer research institutes could meet the 50:50 matching requirement. Dr. Endicott proposed that NIH seek legislation similar to that of NASA, DOD, and

AEC that would make construction funds directly related to program needs. The viruses and cancer activities did indeed require additional construction and renovation funds.

American Type Culture Collection Committee

An advisory committee to the American Type Culture Collection (ATCC) had been meeting for over a year. In preparation for the seventh meeting on April 15, 1962, a Policy Statement had been developed. The ATCC would serve as a repository for cell lines certified by the Cell Collection Coordinating Committee (CCCC or the C-4 Committee). Certification would be based on criteria developed by the Committee: history or genealogy; sterility; morphology; media and growth factors; species specification; viral susceptibility; and specific characteristics. Quality controls were to be based on the certification criteria. Nomenclature and sample handling were spelled out in the Policy Statement. The members of the Committee were: W. Scherer, Chairman; H. Morgan; T. Hsu; D. King; H. Meryman; K. Sanford; John Shannon; C. Stulberg; and R. Stevenson, Executive Secretary. The Policy Statement was approved. Dr. Stevenson reported that the sample handling guidelines were suitable for government regulations regarding shipment in the U.S. Storage and shipments with the liquid-nitrogen refrigerators and freezing and thawing instructions were working well. Consideration was given to a contract proposal from Melpar, Inc. for establishing standards and analyzing samples from other contractors and grantees for components of chemically defined cell culture media.

The Chemically Defined Tissue Culture Media Committee

On May 11, 1962, a meeting was held by another committee concerned with tissue culture: the Chemically Defined Media Committee, a group constituted at the request of the

CCCC to make suggestions for more thoroughly characterizing and improving cell culture media. Members of this group were J. Morgan; W. Swim; C. Weymouth; V. Perry; T. McCoy; D. Pace; H. Eagle; D. Merchant; R. Parker; R. Holmes; R. Hull; R. Pumper; K. McCarty; C. Rappaport; and R. Stevenson, Executive Secretary, CCCC. The Melpar proposal, which called for producing five 2000 liter lots of media (standardized with advice of the Committee based on data) was discussed. The participants each discussed their experiences, including problems with purity of chemicals, e.g., *allo*-isoleucine contaminating leucine. Dr. Eagle was skeptical that group effort could be as good as the same number of individuals working individually, a view he still held in 1971 with respect to planning for implementation of the National Cancer Act of 1971. A second meeting was called for the fall of 1962.

In May 1962 Lou Carrese joined Carl Baker to enhance the systems analysis and planning efforts in the Director's Office. Dr. Baker had been seeking better ways to develop and present budget priorities and documents, and he had found that systems developments in other agencies offered possible improvement. In addition, systems networks were good for considering program priorities. Lou Carrese, who had a master's degree in industrial psychology, had experience in Department of Defense contract work in smaller companies where he had had to integrate various functions. A productive collaboration developed that led to expanded planning efforts in cancer research.

NCI Staff Planing Conference

In mid-June, 1962 a two-day Planning Conference attended by the NCI senior staff was held at Airlie House Conference Center, Warrenton, Virginia. In attendance were: Ken Endicott; Bob Learmouth; Ralph Meader; Mike Shimkin; Gordon Zubrod; Stu Sessoms; Nat Berlin; and

Carl Baker. Review of the science and management aspects of all programs of the NCI was made. Philosophic bases, current status and future projections for the different NCI program areas were discussed. The general conclusion was that NCI needed to spell out more clearly what problems should be selected for emphasis and what should be done to try to solve the selected problems. Resource requirements should be defined. The NCI Scientific Directorate should make the selections and decide on the courses of action. Underlying the Scientific Directorate considerations should be planning documents prepared by a secretariat in the Office of the Associate Director for Program. Programs for Viruses and Cancer, Carcinogenesis, and Cancer Diagnosis should be structured to function along the lines of the CCNSC. These units, along with Biometry and Epidemiology, would constitute the Collaborative Research of NCI. It was evident that internal shortages in positions and space were limiting program development. As had been demonstrated by the CCNSC effort, contracts increased the ability to expand research in cancer. More investigators could be engaged and added resources could be brought to bear on solving problems. Different scientific disciplines could be integrated into defined efforts, and resources could be more precisely defined and applied to specific problems. Another example of engaging scientists outside NCI was collaboration with Bob Huebner and his group in NIAID by transfer of some NCI funds and positions [Mike Shimkin's comment about the Huebner collaboration was, "Give Huebner the funds and let him go"]. It was agreed the program planning did not mean telling investigators what experiments they should do. At the program and Institute levels, leadership by NCI staff should be shown and the scientific community should be kept informed of developments and the rationale behind them. The Institute should continue to work closely with the NACC. It was perceived that there was a need to move away from details of individual

projects and to move to broader program reviews. The workload on Council members was becoming unmanageable. Program reviews by the NACC would require better documentation.

VRRB F.Y. 1963 Program Proposal

On August 2, 1962, a memorandum to the Director, NCI, over the signature of Randall Thompson, Acting Chief of the VRRB, set forth Branch Program Recommendations for F. Y. 1963. Proposed were 19 projects in 7 areas: 1) Modification of resistance of experimental animals to tumor viruses; 2) Selection of reference strains of tumor viruses; 3) Serological survey of laboratory workers; 4) Comparative susceptibility of types and species of animals to tumor viruses; 5) Search for tumor-associated viruses in animal tissues; 6) Search for tumor-associated viruses in human tumors; and 7) Establish a Cell and Organ Culture Task Force. Because much was already being done in other places, less emphasis would be given to: a) Large scale attempts to isolate viruses from human tumor specimens; b) Extensive serological surveys of human and animal populations; and c) study of immune mechanisms associated with human cancer. The need for integrating various contract efforts was noted; one example was the testing by Microbiological Associates of germ-free animals produced by Carworth Farms. Special emphasis would be given to leukemia with close collaboration with the Leukemia Task Force under the Chairmanship of Gordon Zubrod. VRRB would fund some of the Task Force costs generated by supplying of human tissue specimens and possibly by studies of anti-viral chemotherapy. Projected funding for viruses and cancer research for F.Y. 1963 was \$6.457 million for grants and \$6.150 million for contracts. The need to relate more closely to other viruses and cancer efforts by others was recognized and would become clearer after the NCI reorganization was completed.

On August 16, 1962, Dr. Endicott responded to the August 2 memorandum from the Acting Chief, VRRB. After review of the Program proposals, Dr. Endicott considered the document to be an excellent review and a comprehensive survey of possibilities. However, with limited resources available, everything could not be done. Hence, priorities would need to be established. For this, advice would be sought from the Viruses and Cancer Task Force which would be convened a short time later. No contracts would be transferred from VRRB to the new NIH Division of Research Facilities. No personnel would be taken from VRRB except Dr. Thompson would move to CCNSC where he could work on virus chemotherapy, an area of special interest to Dr. Thompson.

Collaboration with Dr. Huebner's Group in NIAID

Dr. Robert Huebner was very well known as an outstanding productive investigator. Not so well known was his ability to construct excellent incisive memoranda on laboratory and organizational operations. They were concise, but comprehensive, placing the subject in a broad background perspective. The problem was clearly stated, and the effort aimed at solving the problem was outlined. Resources required for the proposed program were also spelled out. One such memorandum was his August 22, 1962, one entitled "The Oncogenic Virus Program in the Laboratory of Infectious Diseases" [in NIAID]. It was addressed to the Directors, NIAID and NCI. Drs. Huebner, Rowe, and Hartley of the LID had decided to devote their efforts to the viruses and cancer field. The earlier work of the LID was briefly summarized to show that the LID had unusual capabilities to contribute to this field. In the *laboratory*, focus had been on characterizing the biological properties of tumor viruses and adapting conventional viral techniques for use in defining their natural behavior. In the *field*, the approach was similar to that

in previous studies of rickettsial diseases (rickettsialpox and Q-fever), Coxsackie diseases (herpangina and pleurodynia), and respiratory virus diseases (due to adenoviruses, para-influenzas, R.S., Eton Agent, etc.). In addition to direct searches for tumor viruses, Dr. Huebner and coworkers (with aid of Microbiological Associates contracts) were able to conduct serological procedures for 120 human and animal viruses, including the well known oncogenic viruses (adenoviruses type 12 and 18; bovine, rabbit, and canine papillomas; polyoma; and SV40). Also available for pilot sero-epidemiological surveys of cancer patients were group and specific antigens for all known myxoviruses, poxviruses, adenoviruses, reoviruses, salivary gland viruses, enteroviruses, and others. The prime obstacle again was shortage of space and positions. NCI had provided to the LID some contract funds and 10 positions (and possibly 4 more for the coming year), but space needs could be met only partially with contracting with commercial organizations. Dr. Huebner, in his memorandum, had proposed a new building to meet the space problem. Nearly five years would pass before it was possible to transfer Dr. Huebner to NCI. Space then had to be taken from other NCI activities.

Additional Resources for Dr. Huebner's Viruses and Cancer Program

As a follow-up on Dr. Huebner's memorandum of August 22, a meeting was held on September 5, 1962, of NCI senior staff (K. Endicott; C. Baker; M. Shimkin; R. Bryan; P. Kotin; and R. Stevenson) with Bob Huebner. To carry out the expanded viruses and cancer efforts projected for the future, expansion of resources was required (in addition to space and positions): 1) animal production, including large animals; 2) long-term animal holding; 3) virus identification services; 4) histopathology services (central services and special technologies); 5) electron microscopy; and 6) training. Grants or intramural programs could not meet these needs.

The use of contracts offered solution to the problems. The group discussed possible contractors who might be able to help: Microbiological Associates; Pfizer; Bionetics; Hazleton Laboratories; Walkersville; Flow Laboratories; Melpar; AEC-Union Carbide; Fort Detrick; Pennsylvania State University; University of Pennsylvania; University of Tennessee-Oak Ridge National laboratories; and Michigan State University. Some of the CCNSC contracts could be modified to help in meeting VRRB needs. A new building was not required. Indeed, a single building would invite cross-contamination. Rather, 10-15 trailers (about 100 square feet) separated from each other would allow Dr. Huebner to begin expansion of high priority work. Dr. Bryan would develop data on the projected needs.

Chapter 2: Cancer Research Philosophy, Systems Research Planning, and Reorganization of the National Cancer Institute

The primary device used by the National Institutes of Health (NIH) for funding biomedical research during the period under discussion was a research grant made to an individual investigator. Two groups reviewed the grant proposal: first, a Study Section for excellence in a scientific discipline (such as biochemistry or immunology); and second, a Council for relevance to a disease (such as cancer or diabetes). The Council usually concurred in the recommendation of the Study Section. Recommendations for approval were given priority scores, and grants were paid down the ordered list of scores until the funds were exhausted. The National Cancer Institute (NCI), since Congress established it in 1937, continues to fund much of cancer research by this mechanism.

Dr. Kenneth Endicott, who was appointed Director of NCI in 1960, believed that many problems in cancer research required broader, multi-discipline efforts and that better planning of such efforts was needed. He took steps to complement the philosophy of the grants approach supporting projects with defined problem-solving research programs. Contracts were used to fund much of the new work since some central control was necessary to ensure coordination to achieve the integration of parts into a program systems whole. The NCI Office of the Director reviewed the state-of-the-art of systems planning and made modifications to accommodate the research aspects, developing the "Convergence Technique." The staff began development of an overall systems plan for the NCI.

The Director also began a reorganization of the Institute and the NACC to reflect the change in research program philosophy. It proved to be difficult and took six years to fully complete (though planning and reorganization are on-going and are never final). Within the Institute the reorganization was effected with a series of management memoranda detailing general guidelines, responsibilities, structural changes and lines of authority, and requirements for reviews of programs and contracts. With respect to the NACC, difficulties were encountered with some Council members in gaining acceptance of the new research program philosophy and in reaching agreement on what and how much information the NCI should provide to the Council.

NCI Review of Program Plans and Contracts - Standing Committees

To improve the functions of NCI and ensure sound quality of contracts, in a September 10, 1962 memorandum (drafted by Carl Baker) Dr. Endicott informed the NCI staff of the abolishing of all panels and boards consisting of outside consultants in accordance with President

Kennedy's concerns about conflicts of interest (see above). Instead, Review of contracts would be done by internal committees. Dr. Endicott suggested that two standing committees be established to review program plans and provide preliminary review of contracts: (1) the Committee on Etiology and Prevention; and (2) the Committee on Diagnosis and Treatment. According to his plan, the final review of program plans and contracts would rest with a staff group of senior NCI program leaders under the chairmanship of Dr. Endicott. Two advisory groups corresponding to the two committees would be established from the NACC, and a large roster of additional outside consultants would be established and maintained. The memorandum continues:

Through this mechanism we intend to provide sound review of contracts within a framework of well thought-out, broad program plans, with appropriate attention to their interrelatedness, importance and significance to the mission of the National Cancer Institute.

In addition to providing: a) broad, long-range support in wide segments of biomedical sciences through the grants mechanism and b) broad support for certain types of research effort requiring a more coordinated effort through the contracts mechanism, we need a mechanism to ensure not only the support for, but forceful and rapid execution of research programs focused on specific problems of high priority and importance, urgently in need of solution.

To provide this latter mechanism, I am establishing Task Forces (only two initially) which will be constituted of scientists from both within the Institute and in outside research organizations who are particularly suited to work together and execute the research aimed at solutions of particular problems, both because of their particular interest, knowledge, skill and motivation and their ability to utilize effectively the types of resources required. Task Forces are

expected to concentrate efforts and resources on the problems selected, within a plan formulated by them that calls for a termination of the Task Forces within a finite period of time, most usually not longer than about three to five years. It is important, therefore, that the Task Forces develop their objectives in a concrete manner with a sense of exerting concentrated effort on specific, important and urgent problems, solutions to which are expected within a relatively short period of time. To work with the Task Forces will be a Secretariat consisting of additional Institute Staff, and to assist the group will be contract monies available if needed and justified, in addition to resources already available for operations of the Task Force members. In some respects the Task Forces will operate in a manner similar to that followed by the World War II Commissions of the Armed Forces Epidemiological Boards.

One of the Task Forces will be the Human Cancer Virus Task Force. This group will be asked to pose specific cardinal questions directed toward examining the possible role of viruses in the etiology of some types of human cancer, to formulate plans suitable for the Task Force operation for obtaining answers to these questions in the earliest possible time, to implement the plans, and to assess periodically progress made under the plan. This will involve:

- 1. Identification of the specific problems involved in relating viral agents to the etiology of human cancer.*
- 2. Assessment and evaluation of the present efforts directed toward establishing the viral etiology of human cancer.*
- 3. Delineation of feasible approaches which could be used to augment current research and to explore new areas and to establish priorities for their implementation.*

4. Determination of factors that are impeding progress along such feasible approaches.

5. Initiation and implementation of programs to overcome obstacles and to speed progress in exploiting to the maximum the most attractive avenues of approach.

Those invited to become members of the Task Force have already made a prior commitment to the study of the human cancer problem and have established programs commanding relevant ideas, trained personnel and appropriate resources (Internal NCI document, September 10, 1962).

This memorandum was a further effort to complement the philosophy of the grants approach supporting projects of individual investigators with multi-discipline, defined problem-solving research programs involving collaborating investigators and large-scale production of needed defined resources.

Dr. Endicott asked Ray Bryan to be Chairman of the Human Cancer Virus Task Force and Bob Stevenson to be Executive Secretary. Initially, it was planned that the membership include R. Huebner; R. Miller; J. Melnick; P. Kotin; J. Grace; and F. Horsfall. Others could be added later. The second Task Force, chaired by Gordon Zubrod, was on Leukemia, mostly on its treatment research. Collaboration between VRRB and the Leukemia Task Force developed effectively.

VRRB Progress Report - September, 1962

The production of high quality resources was as essential as the conduct of sound viral oncology scientific research. On September 17, 1962, the Virology Research Resources Branch,

now headed by Bob Stevenson, sent the NCI Director a ten-page report on the activities of the Branch. The report was well prepared and overcame concerns of Dr. Endicott that the Branch program was too diffuse. The section entitled Progress to Date included the following highlights:

- 1) three tissue banks of characterized cell cultures and a distribution system to supply cell lines to cancer virologists had become operational (a contract for testing for PPLO and other contaminants was initiated);
- 2) a system for obtaining and supplying characterized human tissues had been developed for two sites (difficult legal and ethical issues had been addressed and dealt with);
- 3) in addition to the NIAID program on virus antigens and antibodies, NCI, under contract, produced antigens and antisera for six mouse viruses and would expect seven more paired reagents in the next year; these reagents were candidates for certification by the ATCC;
- 4) as part of the program to produce viral-defined laboratory animals, one commercial breeder had succeeded in production of significant numbers of germ-free mice on a weekly basis;
- 5) the value of larger animals (goats, marmoset) was being explored for improved production of viral reagents in addition to other systems;
- 6) VRRB staff brought together information for distribution to investigators on containment of laboratory infections;
- 7) a contract was let to ensure the availability of “gradacol” membranes, at the time the only way to size virus particles;
- 8) the Branch made a survey of training needs and initiated joint program efforts with the NCI Training Branch;
- 9) a program was instituted to search the literature for publications pertinent to cancer virology and make the results available to investigators in the field; this effort included grants and intramural research in addition to VRRB direct activities; and
- 10) the problem of inadequate facilities for work requiring control of viral infections was expected to grow and would be restrictive of progress unless regulations on renovation and new construction were to be modified.

Items under the heading 1963 Program Plans included the following: 1) the VRRB would become the staff focus for implementing program and administrative decisions that result from the Scientific Directorate and the Human Cancer Virus Task Force activities (implementation would involve an extensive coordinating role); 2) instead of developing program for general provision of virus resources, the VRRB would now have an integrated effort on programs focused on a) detection, isolation, characterization, growth and evaluation of viruses in human tumor tissues, with emphasis on leukemia (collaboration with the Acute Leukemia Task Force); b) determination of the viral experience of human subjects and the possible relationship to human cancer and studies on the ecology of viruses in man and animals (collaboration with Bryan's and Huebner's groups and Bob Miller); c) provision of animal virus resources with emphasis on oncogenic viruses; and d) carcinogenesis studies including attempts to clarify interrelationships of viruses, chemicals, and radiation (collaboration with Huebner's, Kotin's, and Bryan's groups and possibly staff of Oak Ridge National Laboratory); 3) VRRB would be heavily involved in contract supported work; it would: a) serve as a means of bringing together at one point in the Institute on a continuous basis cancer viruses information required by the Scientific Directorate and the Human Cancer Task Force to make proper judgements and decisions for integrating and coordinating the various program and administrative decisions; b) make recommendations to these two groups on program implementation; c) provide Project Officers on contracts concerned with animal viruses resources, and on some contracts developed in conjunction with the Task Force; d) suggest new program developments to the Scientific Directorate, including possible programs for new Task Force implementation; e) assist in developing the facilities necessary for implementing the planned program areas, including animal quarters which would prevent viral contamination of the animals and possible hazard to

the workers involved; and f) assist in coordinating the virus activities within the NCI, between NCI and NIAID, and between NCI and groups outside NIH. It was anticipated that the work of the Human Cancer Task Force would require the resources that had been developed through the Virology Research Resources Branch programs. The Branch staff would continue to develop, through the contract mechanism, additional resources required for animal virus studies and would serve as Contract Officers on the projects. Projected were collaborations with Drs. Huebner, Kotin, and Miller on epidemiology studies and on carcinogenesis investigations with viruses, chemicals and radiation [these investigations did not become fully developed].

At this time (1962), the Virus Contracts totaled \$2,704,992 and the Cancer Virus Grants totaled \$ 7,593,000; the Branch staffing was down to 9 positions (of 14 authorized). Space shortages continued as critical, and extensive analysis and planning steps were taken to begin to ease the shortages. Efforts were initiated to develop non-human primate resources. Consideration of holding animals in isolation was begun should isolated viruses prove to be hazardous to humans. Agreement with Oak Ridge National Laboratory was made for NCI funding of Norman Anderson to develop special centrifuge rotors for preparing virus and antibody reagents of higher purity.

The VRRB Progress Report included the following:

Continuing analysis of grant supported research, assisted in part by the analysis by the NCI Grants and Training staff was made. In addition to several grants made in conjunction with the cooperative program on cell culture characterization and certification, a major effort is underway in many laboratories attempting to evaluate the role of viruses in human cancer. The finding of Trentin that human adenovirus-type 12 induces tumors in hamsters (confirmed by Huebner and Rowe along with the demonstration that adenovirus-type 18 also is oncogenic in

hamsters) and confirmation of the oncogenic nature of SV-40, further characterization of its properties in tissue culture (e.g., growth of virus and transformation with chromosomal changes in human cells in culture), and delineation of the nature of the PAPOVA viruses (especially by Melnick, Koprowski, and Hilleman) represent important highlights resulting from grant supported research. Production of tumors by combinations of viruses and chemical agents (e.g., lung epidermoid carcinoma induction in mice with influenza virus and an ozonized gasoline fraction) has provided base information for NCI program expansion aimed at clarifying interrelationships among chemicals, viruses, and radiation in their roles in carcinogenesis. Production of Shope papilloma tumors with highly purified nucleic acid by Ito and Evans adds to the growing body of information indicating that bare nucleic acid can produce disease (polyoma, poliomyelitis, phage, etc.). Knowledge of the type of nucleic acid and the intracellular sites of virus production for several oncogenic viruses has now been determined. The studies of Rubin on avian lymphomatosis which showed that chickens carrying the virus from the egg stage did not develop antibodies against the virus (presumably because of immune tolerance) have important implications for approaches to be employed in studying human cancer. These same studies showed that chickens free of virus at birth could become infected when placed in a flock containing chickens with the virus, but that the incidence of disease was six times lower in these chickens than in those which contained the virus in the egg stage. Studies on virus interference phenomena are throwing further light on the problems in need of solution for the detection of viruses in tumor and other tissues, and some leads have been developed in viral chemotherapy (fermentation producers, e.g., statolon, xersin; naturally occurring products, e.g., interferon; synthetic products, e.g., iododeoxyuridine, thiosemicarbazones, etc.)(Internal NCI document, September 10, 1962).

Additional Guidelines for NCI Standing Committees

On October 16 the Associate Director for Program sent a memorandum on “Additional Guidelines for the NCI Standing Committees” to the Chairmen of the Standing Committees (Carcinogenesis and Prevention and Diagnosis and Treatment). It provided information supplemental to Dr. Endicott’s earlier memorandum and its attached functional statements on procedures to be followed for contract reviews by the Committees and the Scientific Directorate. The intent was to provide helpful guidance for initiating the Committee meetings. The Committees were to become operational on November 1, 1962. The memorandum further stated:

The Committees are being asked to do two things;

(a) To review, evaluate, and report on the major developments of cancer research for their respective areas, indicating the major streams of development, the most important developments in broad terms, and scientific areas receiving too little or too much attention. In essence, the Committees are being asked to do the difficult job of distilling from a very large body of information the important broad aspects in cancer research. They are also being asked to review the NCI program activities, again in broad terms, and relate the information gleaned from the review to that obtained from the broad review of cancer research. From this they are being asked to provide advice to the Director on how well current NCI activities are going and where future emphases should be placed. The purpose is to evaluate the broad areas in ways which do not give undue emphasis to any particular discipline or other segment of cancer research, but rather place each in an appropriate over-all perspective; and

(b) with the above evaluation and background, provide advice to the Scientific Directorate on each contract proposal brought before the Committee for preliminary review.

It is obvious that these are difficult assignments to the Committees. Nevertheless, it should be pointed out that the need for this kind of advice for the Director has been exceedingly difficult to obtain in the past, even though most of the Advisory Committees were made up of some of the best scientists. The reason for this lack seems to be derived from: 1) The Committees tended to spend so much time on details of individual proposals that they were unable to deal with the broad subject, and 2) most of the Committees were brought together to advise on rather specific and somewhat narrow aspects of cancer research, rather than to look at the broad aspects of cancer research as a whole. The Council was mainly affected by the former problems and the Study Sections by both. It will take sustained attention to the assignments of the Committees as stated above to prevent these new Standing Committees from evolving the same way as the earlier advisory committees.

Although the Committees will wish to determine for themselves how they are to accomplish the difficult tasks before them, the following suggestions may be of help in putting the Committees into operation. While the major responsibility for the operation of the Committee will fall on the Chairman, a very key individual in making the Committees function well is the Executive Secretary for each Committee. Under guidance of the Chairman, it will fall to the Executive Secretary to see that the agenda for the meetings are properly developed with attention to what is most important for the Committee activities, to see that appropriate information is brought to the Committee membership prior to the meetings, and to follow up on the implementation and coordination required by actions taken by the Committees. The degree of

success of the Committee functioning will depend to a great extent on how well the Executive Secretary can carry out these functions.

Initially, the Committees will need to spend considerable effort on reviewing their respective areas of cancer research in the broad framework of the assignment. To do this, it seems likely that segments of these broad areas will need to be reviewed in turn. The Committees were constituted to include individuals who have considerable knowledge of major segments of cancer research, and the Chairmen may wish to make assignments to members within the Diagnosis & Treatment Committee or within the Carcinogenesis & Prevention Committee. In this responsibility for summarizing for the full Committee, broad segments should include the highlights of current cancer research activities plus summarization of the corresponding NCI program activities. Those reporting will depend upon their own knowledge, their familiarity with the scientific literature, and certain materials produced by NCI, such as the Annual Reports. In some cases the Annual Report statements will be adequate; in others, totally inadequate. It will be very important for future Annual Reports to be strengthened in order to assist the Committees and the program operators in meeting their responsibilities. In a number of instances, broad critical reviews may be available which can help summarize important aspects of an area. It is expected that in the future additional sound critical reviews will be sought with actual payment for the writing done by means of the contract mechanism. Committees will probably also wish to invite individuals who are not on the Committees to present summarizations for particular areas to the Committee.

It is anticipated that once each year the Committees will prepare a written report for the Director which will summarize the state of development of cancer research in their respective areas plus proposed new developments, both scientifically and program-wise.

[These standing committees did not carry out their difficult assigned responsibilities. On the other hand, the Human Cancer Virus Task Force did very well in meeting its assignments. Much credit for this success should go to Dr. Stevenson, Executive Secretary of the Task Force, and to Dr. Charles Evans, the Chairman.]

The procedures to be followed in review of contracts are outlined in the material attached to Dr. Endicott's memorandum. It should be noted that some of the continuation contracts which are proceeding satisfactorily without change (for example, straight animal procurement contracts) will not need to be brought before the Committees every year. This should save some time of the Committees in the contract review process.

It seems desirable for the Committees to have an initial organization meeting prior to the full-scale operations of program and contract reviews. If I can be of assistance in helping to clarify the system outlined by Dr. Endicott's memorandum and the attached materials I will be glad to do so. If you wish me to attend the organizational meetings of the Committees please let me know (Internal NCI document, October 16, 1962).

Ray Bryan was appointed Chairman of the Carcinogenesis & Prevention Task Force and Gordon Zubrod Chairman of the Diagnosis & Treatment Task Force.

The First Meeting of the Human Cancer Virus Task Force

Also on October 16, 1962, the Associate Director for Program sent a memorandum to members of the Human Cancer Virus Task Force intending to provide information that might be helpful in preparation for the first meeting of the Task Force (October 25, 1962). Dr. Endicott's letter of invitation was included in the memorandum. Dr. Endicott was unable to attend the meeting and asked Dr. Baker to meet with the Task Force to provide background information, orientation for the group, and clarification of what the National Cancer Institute was asking the Task Force to do. The memorandum continued:

In Dr. Endicott's invitation of September 10, 1962 [drafted by C. Baker] was the following:

"Task Forces are expected to concentrate efforts and resources on the problems selected, within a plan formulated by them that calls for a termination of the Task Forces within a finite period of time, most usually not longer than about three to five years. It is important, therefore, that the Task Forces develop their objectives in a concrete manner with a sense of exerting concentrated effort on specific, important and urgent problems, solutions to which are expected within a relatively short period of time." And further, "This group will be asked to pose specific cardinal questions directed toward examining the possible role of viruses in the etiology of some types of human cancer, to formulate plans suitable for the Task Force operation for obtaining answers to these questions in the shortest possible time, to implement the plans, and to assess periodically progress made under the plan. This will involve:

1. Identification of the specific problems involved in relating viral agents to the etiology of human cancer.

2. Assessment and evaluation of the present efforts directed toward establishing the viral etiology of human cancer.

3. Delineation of feasible approaches that could be used to augment current research and to explore new areas and to establish priorities for their implementation.

4. Determination of factors that are impeding progress along such feasible approaches.

5. Initiation and implementation of programs to overcome obstacles and to speed progress in exploiting to the maximum the most attractive avenues of approach.”

The October 16 memorandum continues:

As a means of providing a framework for discussion, of attempting to sharpen the definition of the Task Force activities, and perhaps of stimulating thought prior to the meeting, the following is offered as types of specific problems:

1) Should the general initial objective of the Task Force be: “To identify viruses obtained from human tumor tissues, grow them in tissue culture and in animals, and learn if preparations made from human tumors, inoculated tissue cultures or animals will produce tumors when introduced into different species and strains of animals”? Some other statement of the general objective?

2) What justification and assumptions underlie the Task Force objective?

3) Will the general plan be: Obtain specimens of human tumor tissues of various morphological types (emphasis on acute leukemia) handled by different methods of preservation;

prepare the selected specimens in a variety of ways (with due attention to preventing viral contamination) for inoculation into animals of defined strains and species and into defined tissue culture cell lines grown in defined media; apply various methods of virus identification to the animals and tissue culture materials; and hold inoculated animals sufficiently long to determine if increased tumor incidence occurs in an environment that will prevent contamination of the animals with extraneous viruses?

(a) What types of human tumor tissues should be selected and what criteria of selection should be utilized? (b) What methods of preservation of the tissues should be employed and why? (c) What methods of preparation may be employed for the selected specimens and what orders of priority should be given to the various methods as regards implementation? (d) What strains and species of animals should be selected and by what criteria? (e) Which cell lines and media may be employed and what is the order of priority for implementation? (f) What methods of viral identification should be employed? (g) How long should inoculated animals and tissue culture preparations be observed? (h) To what extent should the environment be controlled to avoid contamination by extraneous viruses?

4) What resources are required for the Task Force that are not now available?

5) Assuming that the laboratories of Task Force members will maintain their independence and autonomy, how can they best work together to insure integrated exchange of materials and information that will allow the Task Force as a group to move toward its objective more effectively than the individual members might do were they not members of the group?

6) How can the Task Force best evaluate periodically the progress made by the group in moving toward the objective?

7) In view of the sizable research effort already under way in attempting to evaluate the possible role of viruses in human cancer, why have results so far been so meager?

We hope by joining together and focusing thought, effort, and resources on this important area of cancer research that we may clarify the role of viruses in human cancer more rapidly than would be done by a less concentrated and cooperative venture. Each of you has already indicated your high interest in this problem by your ongoing research activities. We look forward to discussing with you the best ways to plan and implement the Task Force activities (Internal NCI document, October 16, 1962).

The members appointed to the Task Force were: Ray Bryan, Chairman; Jim Grace (Roswell Park Memorial Institute); Frank Horsfall (Sloan-Kettering Institute); Bob Huebner; Paul Kotin; Joe Melnick (Baylor University School of Medicine); Bob Miller; and Bob Stevenson, Executive Secretary.

In preparation for the first meeting of the Human Cancer Virus Task Force (October 25, 1962), the Associate Director for Program on October 16, 1962, sent a memorandum to members of the Task Force which might give a means of providing a framework for discussion, of attempting to sharpen the definition of the Task Force activities, and perhaps of stimulating

thought prior to the meeting. The memorandum offered types of specific problems that the Task Force might need to address:

“1. Should the general initial objective of the Task Force be: ‘To identify viruses obtained from human tumor tissues, grow them in tissue culture and in animals, and learn if preparations made from human tumors, inoculated tissue cultures or animals will produce tumors when introduced into different species and strains of animals’? Some other statement of the general Objective?

2. What justification and assumptions underlie the Task Force objective?

3. Will the general plan be: Obtain specimens of human tumor tissues of various morphological types (emphasis on acute leukemia) handled by different methods of preservation; prepare the selected specimens in a variety of ways (with due attention to preventing viral contamination) for inoculation into animals of defined strains and species and into defined tissue culture cell lines grown in defined media; apply various methods of virus identification to the animals and tissue culture materials; and hold inoculated animals sufficiently long to determine if increased tumor incidence occurs in an environment that will prevent contamination of the animals with extraneous viruses?

(a) What types of human tumor tissues should be selected and what criteria of selection should be utilized? (b) What methods of preservation of the tissues should be employed and why? (c) What methods of preparation may be employed for the selected specimens and what orders of priority should be given to the various methods as regards implementation? (d) What strains and

species of animals should be selected and by what criteria? (e) Which cell lines and media may be employed and what is the order of priority for implementation? (f) What methods of viral identification should be employed? (g) How long should inoculated animals and tissue culture preparations be observed? (h) To what extent should the environment be controlled to avoid contamination by extraneous viruses?

4. What resources are required for the Task Force that are not now available?

5. Assuming that the laboratories of the Task Force members will maintain their independence and autonomy, how can they best work together to insure integrated exchange of materials and information that will allow the Task Force as a group to move forward toward its objective more effectively than the individual members might do were they not members of the group?

6. How can the Task Force best evaluate periodically the progress made by the group in moving toward the objective?

7. In view of the sizable research effort already under way in attempting to evaluate the possible role of viruses in human cancer, why have results so far been so meager?

We hope by joining together and focusing thought, effort, and resources on this important area of cancer research that we may clarify the role of viruses in human cancer more rapidly than would be done by a less concentrated and cooperative venture. Each of you has

already indicated your high interest in the problem by your ongoing research activities. We look forward to discussing with you the best ways to plan and implement the Task Force activities.

At the first meeting of the Human Cancer Virus Task Force considerable time was spent on clarifying the charge to and the role of the Task Force. Dr. Baker, in Dr. Endicott's absence, provided additional background and answered questions. In response to Dr. Grace's question about a planning function of the Task Force, he stated that the Task Force was appointed to be a working group on a cooperative basis. If the group could see any merit in planning approaches, exchanging data and information, and sharing material or resources on a mutual assistance level, then there was a need and justification for a task force. Otherwise, there was no reason for the existence of a task force. Dr. Melnick asked about research facilities. NCI had limited construction authority for the time being; however, in some cases, contracting with commercial firms could provide more space for the viruses and cancer activities. The Task Force might wish to become a recommending body for programs when they did not wish to become involved directly in the work. Examples of cooperative work could include obtaining clinical material from human leukemia patients and screening for virus-like particles, with division of positive specimens among the members of the Task Force.

Dr. Bryan presented an outline of specific problems for Task Force consideration in three broad areas: 1) virus dependent reactions (RNA viruses); 2) viral transformation of cells through induction of quantal type change (DNA viruses); and 3) joint action of ordinarily nononcogenic viruses with other carcinogenic agents in the induction of neoplasia. At Dr. Bryan's request, each member discussed current work and specific problems in their own laboratories. Dr. Horsfall felt that the Task Force might make a mistake in suggesting that there is a satisfactory systematic

approach for discovering things presently unknown. He urged that the Task Force increase the probability of discovery by increasing the dimensions of the effort and suggested that the history of scientific advance is linked to individual effort, a view expressed by Dr. Eagle at the May 11, 1962, meeting on Chemically Defined Tissue Culture Media (and again in 1971 at a meeting of outstanding scientists constituted by the Director, NCI, to discuss plans for the expanded cancer research effort called for by the coming Cancer Act of 1971 - signed by President Nixon on December 23, 1971). Dr. Bryan suggested that increasing the productivity of investigators by freeing them of routine tasks would, in effect, increase the dimensions and the probability of discovery. Screening of specimens to be used in elaborate experiments and holding animals for observation were concrete examples of ways of increasing the individual's capabilities. Dr. Huebner offered to provide the diagnostic virology service with Dr. Melnick's help for the other members of the Task Force. Dr. Stevenson reported that six antigens and corresponding antisera had been produced on contract and seven more pairs were to be done in F.Y. 1963. Higher yields and sharper specificity of antibody titers were being met with use of germ-free animals (which did not seem to have antibodies to a number of viruses commonly encountered in the mouse colonies as Dr. Huebner described). Possible topics for the agenda of the second meeting of the Task Force included: 1) Inbred hamsters; 2) Establishment of a serum bank from cancer patients; 3) Facilities (laboratories, animal holding, etc.); 4) Electron microscope screening service; 5) Viral diagnostic service; 6) Histopathology service; and 7) Epidemiological support. Dr. Baker asked how these needs of individuals expressed in their presentations might be tied together to establish priorities of effort so that available staff would not be diluted in their efforts to provide essentials.

Five Year Projection of Dr. Huebner's Viruses and Cancer Program

On November 6, 1962, Dr. Huebner, at NCI's request, submitted to the NCI Director a memorandum setting forth his projected viruses and cancer program and resources needs for a five-year period. He also outlined the links to the Human Cancer Virus Task Force. The memorandum again was a model document that laid out the scientific basis of the program and management needs, as well as ways to develop solutions to key problems. The full package for the Frederick facility totaled for F.Y. 1963 \$791,500 (including contracts for management of the Frederick facility; for developmental work; and for tissue cultures, experimental animals, and other serological materials). A contract with Microbiological Associates was let for viruses characterization, identification (or typing), and viral diagnostic services, using complete complement-fixation, cross neutralization and hemagglutination-inhibition tests on various groups of viral diagnostic reagents. About 50 percent of the effort would be developing and applying virus typing techniques and 50 percent on production of satisfactory viral diagnostic reagents. At this time co-carcinogenesis studies were included, though these were never pursued after Dr. Kotin moved to head the Environmental Health Programs in North Carolina. Dr. Huebner's long-term view (or *vision*) projected a tripling of personnel (50 professional and 150 technical workers) and provision of 25,000 square feet for tissue culture work and 5000 square feet for pathology plus outside space for animal quarters. He showed prescience in pointing out the likely need for elaborate and expensive facilities to insure safety and protection for those working with and exposed to oncogenic viruses. Attached to the memorandum was a chart of animal tumor viruses indicating: the natural host; other hosts; nucleic acid types; cellular location of viral inclusions; and other features. The viruses were grouped by seven families (the papova

group; adenoviruses; the poxvirus group; the “leukemia” group; the avian leukosis group; mammary carcinoma; and frog kidney carcinoma).

The Second Meeting of the Human Cancer Virus Task Force

The second meeting of the Human Cancer Virus Task Force was held on December 14, 1962. Dr. Robert Miller, Chief, Epidemiology Branch, NCI, discussed epidemiology aspects of the Task Force efforts. Other items on the agenda included: a) Discussion of Task Force Objectives and Methods of Achieving Them; b) Further Consideration of the Seven Operational Problems Identified at the First Meeting: 1. Inbred hamsters and SPF animals; 2. Establishment of a serum bank from cancer patients; 3. Facilities (laboratories, animal holding, etc.); 4. Electron microscope screening service; 5. Viral diagnostic service; 6. Histopathology service; and 7. Epidemiological support); and c) Other Business.

The Chairman had suggested that the members put down their thoughts about the Task Force activities in memoranda for the record. Drs. Bryan, Melnick, and Huebner brought their memoranda to the meeting for discussion. Dr. Melnick suggested three target areas: 1) Acute Leukemia of Childhood; 2) Papovavirus; and 3) Viruses and Antigens Present in Normal Human Tissues and Human Tumors. Dr. Huebner made several points. Standard certified prototype viral seed and monovalent reference typing serums were and should be handled by committee decisions on protocols and through contracts for production. Diagnostic reagents for identification of viruses and for studies of antibody responses relevant to virus isolation and to controlled sero-epidemiological investigations of viral antibody prevalence and incidence in cancer still required much developmental research. The Task Force might find it necessary to

accept responsibility for much of the developmental research that needed to be done on diagnostic reagents. Unlike the standard viral reference reagents, these reagents could not be developed and evaluated through formulation of protocols by committees, but must be handled through contracts and grants for developmental research in which the commercial contracting agencies work hand-in-glove with specific government supported research groups in designing and carrying out research protocols. He agreed with other members that the emphasis in research should be placed on acute leukemia. He expected to place higher emphasis on *in vitro* rather than *in vivo* methods for demonstration of a human leukemia agent because of the complex viral picture in animals. Germ-free animals might be helpful for the animal inoculation approach. Survey tools designed to define the natural histories of animal leukemia viruses in their natural ecologies can and should be developed and used. The information provided would be invaluable in the design of similar studies of human leukemia, and might even disclose immunological and zoonotic relationships. He pointed out that the most profitable approach to the definition of the causes of acute viral diseases has been the virus in search of disease approach and epidemiological studies of their clinical and pathological behavior. It is a matter of documented fact that most of the newer human viruses were first isolated in situations that gave little indication of their true clinical behavior. The important concept to be derived from this fact is that the role of most of these viruses in natural disease could not even be suspected from the circumstances in which they were first found. This could be true of viruses found in temporal and spacial relationships to human cancer. Regardless of where suspect viruses are found and what they do in the laboratory, machinery must eventually be set up for studies of the natural history of these agents in their human host, and epidemiological studies capable of distinguishing “real” from “spurious” associations.

Other materials related to presentations of VRRB staff at the Task Force meeting were distributed with the Agenda: 1) Materials Produced by VRRB Programs; 2) Development of Embryonating Eggs Free of Known Poultry Microorganisms; 3) Information on Numbers and Kinds of Tumors in Swine; 4) Syrian Golden Hamsters; 5) Production of Virus-Free Mice; 6) Cancer in Subhuman Primates; and 7) Large Germ-Free Animals.

By the end of 1962 the NCI viruses and cancer activities, especially those of the VRRB, were well defined as to philosophy, main objectives, and organizational patterns. The quality-controlled resources needed to move ahead with the research were beginning to be produced in sizable quantities and made available to investigators requiring them. Discussions were held on additional steps that should be taken in the coming years.

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Dr. Huebner's Suggestions on the Conduct of the Activities of the Human Cancer Virus Task Force and Staff

On January 8, 1963 Dr. Huebner wrote another thoughtful and thought-provoking memorandum to the Human Cancer Virus Task Force members and NCI staff on the future activities of the Task Force. He pointed out that the Task Force had spent too much time discussing at length details on equipment and personnel instead of new ideas and approaches. So much time had been spent discussing the use of the electron microscope for screening of leukemia specimens, he thought that other approaches to screening would not be made until the scopes were working in the participating laboratories. This narrow concept was not the view of the staff. He also misconstrued the meaning of "focus down" in staff documents as narrowing the Task Force activities. The meaning intended was to call for *prioritizing* among the many possible

lines of work, since at the time funds would not allow pursuit of every possibility. The staff was not looking to narrow the scope of the Task Force's area of consideration, but asking the Task Force to make specific priority selections within the very broad scope of possibilities. Also the participating laboratories should each pursue different directions of their research while collaborating on approaches requiring joint efforts. Dr. Huebner discussed the role of staff in helping to carry out the work of the Task Force. At the time he was not aware of how much the staff agreed with his comments on staff activities. The memorandum stated:

When a certain research approach is approved and certain laboratories are designated as the key ones for carrying it out, I suggest that staff be instructed to take over without further discussion of details. It is a staff function to figure out with each research group their particular needs to accomplish task force objectives. I doubt very much that it is the Task Force's prerogative to act on such matters anyway - except in an advisory fashion after the planning is completed and only if the staff requests review of specific questions and/or information is needed for justifying certain items.

Further:

I suggest that it is the function of the staff to find specific justification for requirements of the Task Force's program in the recommendations of the Task Force. I suggest further that the proposals for support of each group be worked out separately on the basis of particular needs (they can't all be the same) to meet Task Force commitments, and that they be circulated by mail and approved as quickly as possible when we get together. We should reserve most of the time available to the Task Force for discussing new approaches, for building new programs, and supporting them as necessary with published and unpublished data.

The final paragraph:

After all, the only justification of this Task Force will be what it accomplishes in the end, and to this end it must spend most of its time and effort on building programs and on achieving program objectives; this, strangely enough, means working. The chief function of staff is to facilitate this end by assuming as much responsibility as possible for administrative details, leaving the investigators to get on with their work. This is also the best way to serve the best interest of the NCI staff, since it will assure maximum opportunities for achieving something worthwhile. In a five- year race against time, the bearings must be greased, not filled with repetitive consideration of gritty details concerning specific justification (Internal NCI document, January 8, 1963).

The Second Meeting of the CCCC

On January 24, 1963, the Second Meeting of the Cell Culture Collection Committee was held in Bethesda. The meeting focused on media problems, including characterization of media and definition of terms (chemically defined media; characterized media; and maintenance media). Composition of defined media currently in use was discussed. Currently available information on reagents was next taken up (current criteria of purity, analytical procedures, and evaluation of current suppliers). Stability and shelf-life of media and their components were discussed, as was the type of storage required. Could media be frozen or lyophilized? What about interaction of components that compromise the media?

Proposed Sero-Epidemiological Survey

On January 24, 1963, Dr. Huebner sent a memorandum to the Chairman of the Human Cancer Virus Task Force entitled “Sero-epidemiological surveys of human cancers for antiviral antibodies”. He proposed establishment of a “Cancer Serum Center” (in three phases) for surveying numbers of serums from patients with representative different types of cancer for antibody reactions to various viruses. Such a Center should prove useful to the Task Force for serological confirmation and epidemiological testing of specific hypotheses deriving out of current efforts to identify human cancer viruses. An overall center could not be established at the time because of inadequacy of facilities, reagents, personnel, or informational storage. However, a beginning could be made with a pilot program in the Laboratory of Infectious Diseases, NIAID, coupled with supply of specimens from Sloan-Kettering Institute added to the leukemia specimens already being received from the Leukemia Task Force activities (Dr. Zubrod) (Phase 1). Phase 2 would be double-blind controlled studies and Phase 3 would be broader investigations in populations with greater varieties of characteristics. Phase 1 would only need advisory and moral support from the Task Force and a modest amount of funds to Sloan-Kettering Institute for a serum and information collection unit. Phases 1 and 2 would require additional resources.

The Third Meeting of the Human Cancer Virus Task Force

The Third Meeting of the Human Cancer Virus Task Force was held on January 25, 1963. Dr. Stevenson, as Executive Secretary of the Task Force and Head of the Virology Research Resources Branch, supplied several documents to the members of the Task Force. In his memorandum accompanying the agenda he requested policy decisions to initiate the

collaborative program agreed to by the members at the second meeting because the program would require a variety of resources to be obtained. The memorandum went on:

“The first specific problem is that of obtaining clinical material and making it available for Task Force use. After the Task Force has decided on the policies and procedures for this aspect of the program, details will be worked out with individual groups. Future topics will include selection or identification of needs for test systems such as animals and cell cultures, sera, etc.”

“Whenever possible, the Virology Research Resources Branch will provide the Task Force with the resources or the administrative mechanisms such as contracts which are identified as being necessary to the collaborative program.”

“At this point, your help and participation in planning are necessary and a suggested program for acquisition of clinical material, its identification and distribution is presented along with suggested data needed for definition of the leukemia patient.”

“We have not attempted to do more than outline the basic aspects of the protocol which will require policy decisions. Specific details of individual items can be worked out by the staff scientists of the respective members programs.”

The VRRB also presented a set of questions for the Task Force:

“1. What criteria are to be used for selection of leukemia patients and controls? (See Zubrod’s protocol).

2. What kind of protocol should be established for the selection of various types of human specimens - blood, urine, etc. (These procedures should be standardized).

3. *How are specimens to be allocated to laboratories other than source of specimen?*

What percent is retained? What percent is distributed? What percent is stored for later reference?

4. *How to establish minimum size of specimen if it is to be distributed to other laboratories?*

5. *How many patients are to be examined per year, and how many specimens per patient? ”. (Internal NCI document, January 25, 1963).*

Other materials were supplied by Dr. Stevenson: a statement of “Proposed Policies for Collection and Distribution of Clinical Specimens”; the Acute Leukemia Task Force “Protocol #2, Cooperative Study in the Chemotherapy of Acute Leukemia”; a report on the current status of “Development of a Nucleus ‘Germ-Free’ Hamster Breeding Colony”; and details of John Moloney’s procedure, “Preparation and storage of human leukemic blood, blood fractions and bone marrow aspirates.” The pioneering work of the Acute Leukemia Task Force in developing defined procedures for collaborative efforts, including those for handling specimens, was of great help for the Human Cancer Virus Task Force. Other items on the agenda included: a Proposal for Sero-Epidemiological Survey of Human Cancers (Dr. Rowe for Dr. Huebner); a status report on Surveillance of SV-40 Inoculated Patients; and an open discussion of Strategic Approaches to Virus-Cancer Targets. “Identification of and Needs for Specific Test Systems to be Obtained under VRRB-Task Force Contracts” was selected for discussion at the next Task Force meeting. Four days after the January 25 meeting Dr. Melnick submitted a contract proposal to implement Task Force efforts by the Baylor group.

Status Report to the Scientific Directorate

On February 5, 1963 Ray Bryan presented a status report on the activities of the Human Cancer Virus Task Force to the NCI Scientific Directorate. A summary statement was distributed to the Directorate members. It follows:

1. Major objective and purpose of the Task Force.

To determine the relationship of viruses to the etiology of human neoplasms.

2. Working concept of the nature of neoplasia.

A general type of cellular and tissue reaction, rather than a single specific disease entity.

3. Categories of virus-host (or host-cell) interactions associated with neoplasms of animals.

I. Virus-dependent reactions in which specific viruses (or related types of viruses) are the direct continuing causes of certain specific neoplastic diseases. Examples: Rous sarcoma; leukemia of fowls; leukemia of mice.

II. Viruses-initiated reactions in which viruses of different types act as biological carcinogens in the production of a variety of autonomous neoplasms of different tissues and in different species, but the virus is not associated with continuation of the neoplastic reaction (at least in a detectable form). Examples: tumors, or in vitro cell transformations, induced by the polyoma and SV-40 viruses and by adenoviruses 12 and 18.

III. Co-carcinogenic reactions in which not only viruses of dependent neoplasia (e.g., Shope papilloma), but also ordinarily non-tumorogenic viruses (e.g., vaccinia, influenza) act together with chemical or other carcinogenic agents to initiate autonomous neoplasms, but neither type of agent is associated with continuation of the reaction (at least in detectable form).

IV. Other reactions (this category to include future types of interaction not now known or recognized).

4. Major problems common to all categories of tumor viruses and interactions.

(1) Detection (identification) of candidate virus.

(2) Propagation of the virus in the laboratory.

(3) Proof of tumorigenicity of the virus.

(4) Establishment of etiological relationship of the virus to human neoplasia.

No human virus of category I has yet been discovered. Initial work in search of agents of this type is therefore confined to the problems of (1) Detection and (2) Propagation. Unless and until these objectives are accomplished there will be no basis for proceeding to problems (3) and (4).

On the other hand, many viruses unassociated with known disease have already been detected and propagated in the laboratory, and may be considered as candidates for tumorigenic agents of category II. The work on these known agents can therefore proceed immediately to problems (3) and (4). The search for new viruses of this category, however, involves problems (1) and (2).

5. Major segments of the over-all human-cancer-virus-problem (i.e., "targets") embraced by the Task Force to date.

A. Leukemia and lymphomas (including Hodgkins disease).

The comprehensive task has been embraced of determining whether or not viral etiological agents comparable to those that cause leukemia in fowls and mice are associated with human leukemia and lymphomas. The fowl and mouse agents fall in category I of the types of interaction listed under 3 above. The planned actions for implementation of the Task Force study will therefore follow, initially, the avenues of approach that have given success with the animal model systems of category I.

Although virus-like particles resembling those associated with the animal leukemias have been observed in tissue or blood specimens from some leukemia patients (Dmochowski - published; Beard, et al., Dalton, et al., and Melnick, et al. - unpublished), no definite association of the human disease with a viral agent has yet been made. Nor has propagation in the laboratory of a candidate viral agent resembling the animal etiological agents been successfully achieved. The initial actions of the Task Force with respect to leukemia are therefore directed toward the first two major problems listed under 4, i.e., (1) detection and (2) propagation in the laboratory. If a substantial effort fails after a few years to yield positive results on these problems, the negative outcome will not conclusively prove a lack of association of human leukemia with a viral etiological agent, but will call for a reevaluation of the intensive efforts following these particular presently known animal model systems.

The presently available working approaches to problems (1) and (2) that have been developed with animal model systems (category I) may be listed under the same headings as the problems themselves, for the purpose of identifying specific Task Force projects with the

objectives toward which they are directed. The following represent the methods and indicator phenomena, or identification criteria, that may be used for detection and propagation of one or more of the animal leukemia viruses. [Approaches under which specific Task Force contract operations are currently being proposed are marked by an asterisk()].*

(1) Detection

**1. Electron Microscopy*

(a) Thin-section; staining with lead and uranium salts.

(b) Negative contrast of film preparations; staining with salts of phosphotungstic acid.

**2. Cellular transformations in tissue culture (CPE has not yet been observed for type I tumor viruses of animals).*

3. Viral interference, using known viruses as indicator agents.

**4. Inoculation of newborn or conditioned animals (mice, hamsters, non-human primates, other).*

5. (Immunological and serological methods are potentially useful, but will not be applicable to type I agents until reagents become available through successful propagation in the laboratory).

6. Co-carcinogenesis, and enhancement.

(2) Propagation in laboratory

**1. In primary as well as established cell lines in tissue culture (human, other primate, other).*

**2. In animals (non-human primates, hamsters, mice, other).*

**(a) Conventional.*

**(b) Specific pathogen free (SPF).*

B. Seroepidemiological and virus isolation studies on cancer cases in general, for the purpose of defining antibody and virus spectra. This will embrace testing for as many as possible of the known viruses as well as a search for new viruses.

** (1) The initial studies will be “pilot” in nature, for the purpose of obtaining leads for laboratory work through association of cancer type with frequency of isolation or identification of viral type. Leukemia cases will be especially emphasized, in keeping with the targeted all-out attack on leukemia.*

(2) A broader program envisioning (a) a large serum and specimen bank, (b) various epidemiologically controlled populations, and (c) collaborative epidemiological investigations, has been approved in principle, but further study and program planning will be required to develop this complex undertaking.

6. Proposed operations requiring contract support.

A. Electron microscopic studies.

Studies by Doctors Dalton and Moloney on mouse leukemia led to the development of methods for detection and rough quantitation of virus from the blood of leukemic, or pre-leukemic inoculated mice. Thin section techniques were used initially, but greater speed and

efficiency have recently been achieved through the use of negative contrast staining with phosphotungstate.

These methods were applied to the study of human blood specimens and virus-like particles resembling the mouse leukemia virus have been observed in roughly 1/3 of 51 cases of human leukemia (mostly acute lymphocytic, of children).

In comparable independent studies Dr. Melnick and associates have observed virus-like particles in blood of leukemic patients by the negative contrast procedure.

Virus can be isolated from only a small fraction of leukemic mice of strains which develop leukemia spontaneously (e.g., AK, C58); and, like other neoplasms of type I, the quantity of virus recovered from experimentally infected animals is related to infecting dose and rapidity of development of disease. It is therefore logical to expect that human specimens in which particles can be detected by electron microscopy would represent the most favorable cases for further study in attempts to isolate and propagate a human counterpart of the mouse and fowl leukemia viruses.

To provide this selection of donors and to acquire additional information on the frequency of occurrence of virus-like particles in human leukemia cases, the Task Force voted to activate Electron Microscopic Study Centers in the institutions of interested members who were willing to oversee the local operations and contribute to a collaborative program by pooling information and sharing specimens for study.

Dr. Grace's proposal and one part of Dr. Melnick's broader proposal are for activation of such electron microscopic study centers.

Dr. Melnick proposes in addition to develop, under contract, a program for the procurement of clinical specimens. Dr. Grace already has contract support for this phase of the operation that was set up previously under the Virus Research Resources Branch (VRRB).

B. Studies Involving Animals

Newborn and conditioned animals will be used in tests for virus detection and proof of tumorigenicity, as well as for propagation of large quantities of virus for further study. For all three of these purposes, the problem exists of finding a suitable (or the most suitable) species. It has not yet been determined whether specific pathogen free (SPF) animals will be better than conventional animals for the first two purposes, but for the third, namely propagation of virus in the absence of extraneous contaminating agents, SPF animals are considered to be essential.

In view of the latter fact, and the possibility that some human tumor viruses might be capable of propagating only in intact animal hosts (as is presently the case for several known animal viruses), the Task Force voted to support developmental research on SPF animals under the VRRB. Hamsters were designated as the first species to be explored for developmental research under contract (Item 2,a, on agenda).

Task Force collaboration on animal testing has been projected along two lines: (a) division of effort in exploring for possible use as test animals, various species not now included in programs already under way in the laboratories of members; and (b) joint use of primate or other large or expensive animal test-systems which cannot practicably be embraced by individual laboratories, i.e., with available resources.

C. Studies Involving Tissue Culture

As with animal test systems, various cell lines of various species (particularly human and other primate) maintained in tissue culture will be used for detection, propagation, and tests for “tumorigenicity” of viruses (tumorigenicity is in quotation marks because in vitro transformation, though suggestive, cannot alone be considered as proof of tumorigenic properties in animals, but requires confirmation in animals).

As with the animal test systems, a division of effort in trying out various cell types and conditions of culture, using common human specimen materials, has been projected, but specific joint undertakings by Task Force members have not yet been developed. Also, certain common needs for resources (e.g., human and other primate embryonic tissues, human serum, defined media, etc.) have been identified, and the VRRB has been asked to consider the feasibility of making these resources available for Task Force purposes (Internal NCI document, February 5, 1963).

This statement concisely summarized to date (1963) the status of the viruses-cancer research effort and the progress made by the VRRB and the Human Cancer Virus Task Force. Projected program efforts were also identified. The collaborative activities undertaken were uncommon outside wartime efforts; these joint efforts involved sharing of materials and information (prior to publication). The developmental research and production of defined *resources* initiated a growth of production of biomedical resources that later led to a vast array of commercially available materials, indeed to a whole new industry. During this 1963 period the programs funded with contract funds were determined from defined requirements of planned research, and not made simply to provide resources for individual investigator requests. Most virology investigators did not think large amounts of reagents could be made of sufficient quality by commercial organizations under contract. The NCI assured them that the reagents could be tested by the same methods they themselves used and, if they did not meet their requirements, they would not be used (Dr. Baker pointed out that under current practices of producing reagents in small amounts in individual's laboratories, after testing there was little material left for other studies - much greater amounts were needed for various studies). Most academic investigators objected to Government research monies going for this collaborative research instead of for support of individual's project research. Since "target research" (or problem-solving research) aimed at attacking cancer involves larger scale, multi-discipline efforts in addition to projects of individual investigators, NCI felt that the Federal Government laws regarding contracts needed modification if it was to carry out its mandate.

Request for Enlarged Contract Authority for NCI

On February 28, 1963, the Director, NCI, sent a memorandum (drafted by Carl Baker and Zelda Schiffman) to the Director, NIH entitled "Applied developmental research and research services -- Need for legislation." This memorandum presented a brief summary of NCI's position, the background, the need, and the changes in law NCI would like to see enacted. Contract authority more nearly like other Government agencies, such as NASA, Department of Energy, and Department of Defense, could allow NCI to meet its needs for additional space, positions, and added managerial capability. Despite clear justification of the need for legislative changes, this memorandum disappeared into a bureaucratic morass.

The Fourth Meeting of the Human Cancer Virus Task Force

The Human Cancer Virus Task Force met on March 8, 1963, for its fourth meeting. The agenda for the meeting included : (1) Progress Report by Dr. Stevenson; (2) Discussion of the Papova-Adeno Virus Group by Dr. Melnick; (3) Needs for Animals and Cell Cultures (Nucleus Colonies and Seed Stock); (4) Planning for Sero-Epidemiology Proposals; and (5) Date for General Meeting of the Task Force Members and their Staffs. The last item began what became a vital pattern of the NCI viruses and cancer activities: annual meetings of those participating in the activities at which information was freely exchanged well before the data were published. Dr. Holdenried presented a progress report on the contract with the Baltimore Biological Laboratory for monitoring of cell strains and virus seed stocks for PPLO contamination. One of every four cultures tested (102 specimens) was contaminated. One of every five cultures contained PPLO organisms. Of the 16 laboratories submitting specimens, two-thirds submitted contaminated specimens. Over half the laboratories submitted specimens contaminated with PPLO's. Before the evaluation of contaminations on a centralized basis for quality controls, including that on

some early VRRB contracts, much work was done without knowledge of contaminated reagents. This early contract demonstrated the necessity of quality controls on resource production contracts.

Development of an NCI Overall Program Document

During the first quarter of 1963, the Associate Director for Program and Lou Carrese, after extensive analyses of activities in cancer research and exploring many options of the form that projected research and organizational plans for NCI might take, produced for the Scientific Directorate and the NACC a preliminary overall NCI program document. The options were based, in part, on a classification scheme made up of three aspects: a *conceptual* formulation of cancer; *resources* required to meet problems in cancer research; and the *organizational components* needed to deal with the problems. This effort was a follow-up on the earlier agreed upon need, at higher NCI levels, to move away from detailed review of projects and toward broader program reviews. The conceptual base and the organizational form for setting forth the NCI program was based on a scientific conception on the nature of cancer and the current major thrusts of cancer research. This approach moved away from presenting the NCI efforts in categories such as Intramural Research, Collaborative Research, and Grants and Training, with emphasis on individual project reviews.

An overall NCI Program Review Document was presented to the NACC at its March 1963 meeting. Although various individuals complimented on the effort were made, little substantive comment resulted from these ideas. Perhaps this conceptualization was too broad for the specialized expertise of the individual Council members, or this approach was too new. Other distributions to the NACC were: The NCI Fact Book; Research and Related Programs of the

NCI; Research Grants Distribution by Facet; and Graduate Training Grants Distribution by Discipline. On the evening before the NACC meeting, the Council Subcommittee on Carcinogenesis and Prevention met on March 17, 1963. The Subcommittee consisted of: Walter Burdette (Chairman); George Cooper; Paul Gross; John Kidd; Phil Shubik; J. Walter Wilson; and William Payne (Executive Secretary). Dr. Burdette presented an analysis of the functions of the Subcommittee in relation to the NCI advisory groups. Dr. Kotin discussed the present status and future program of the NCI Carcinogenesis Studies Branch. Dr. Shubik spoke of the problems in the field of carcinogenesis and approaches to their solution. Six grant applications were reviewed; three were recommended for disapproval. Viral carcinogenesis was not discussed.

Chapter 3: Implementation and Early Program Outputs

As reorganization at the National Cancer Institute began to occur the new emphasis on planning began to have an impact, and implementation of efforts toward defined targets began to take place. Added results were beginning to show up in the scientific programs, in early production of resources, and in better coordination of managing the viral oncology activities. The research efforts were concerned largely with methods for finding, identifying, and growing viruses in animal and human tissues. This included the use of electron microscopy (E.M.) for finding various virus particles and of various innovative immunological methods. These findings were correlated with tumor induction in various animal species.

To conduct the research, it was necessary to have large amounts of resources such as antibody-containing sera and other reagents. Several animal species were developed to serve as possible test system hosts for any human tumor viruses that could be isolated, grown and able to

produce tumors. These included non-human primates, man's closest animal relatives. Tissue culture remained a key resource.

Management of the Program continued to move the Institute to greater emphasis on coordinated multi-discipline programmatic research and at the same time more clearly lay out managerial responsibilities and work loads. These modifications will be ongoing for some time in the continuing search for better management.

On May 1, 1963, NCI, in response to a request from Congress, submitted an analysis of the grants, contracts, and intramural research activities for Fiscal Year 1962. Grants totaled \$47,607,147 (1746 projects); contracts totaled \$27,573,000 (225 contracts); and the intramural programs totaled \$14,495,000 (of which \$7,185,000 was for reimbursement to NIH for central services). With grants, the largest category was treatment (\$15.651 million); for scientific discipline, the largest category was biochemistry (\$21.316 million). Virology grants totaled \$4.011 million (106 projects). Multidiscipline program project grants totaled \$3.567 million (8 projects). With contracts, the CCNSC Program totaled \$22.188 million; virus research totaled \$2.363 million. Including funds spent on intramural projects, the amounts per Laboratory were nearly equal; however, Pathology, Biochemistry, and Viral Oncology had the largest budgets.

The Fifth Meeting of the Human Cancer Virus Task Force

At this meeting held at the Airlie House Conference Center on May 12-14, 1963, twenty-six investigators from Task Force participating laboratories presented current work underway in their laboratories. The arrangement provided many opportunities for informal interchange of ideas, information, and future possibilities. The informality and common purpose encouraged the reporting of up-to-date activities well before publication. This meeting initiated a series of annual

meetings attended by leading investigators in the cancer-viruses field and their staffs. The annual congregations continued for more than a decade and are continued still under the tutelage of Bob Gallo. At the close of the first meeting five informal subcommittees of the Task Force composed of members from the participating laboratories were formed:

PPLO Subcommittee

J. Horoszewicz (Chairman)	RPMI
E. de Harven	SKI
A. Moore	SKI
R. Manaker	LVO-NCI
N. Somerson	LID-NIAID
K. Smith	Baylor U.
R. Holdenried	VRRB-NCI
R. Meyer	VRRB-NCI

Laboratory Animals Subcommittee

E Mirand (Chairman)	RPMI
F. Rapp	Baylor U.
C. Friend	SKI
W. Rowe	LID-NIAID
P. Sarma	LID-NIAID
J. Moloney	LVO-NCI
R. Holdenried	VRRB-NCI
L. Murphy	VRRB-NCI

Primates Subcommittee

J. Melnick (Chairman)	Baylor U.
C. Southam	SKI
H. Coates	LID-NIAID
F. Rauscher	LVO-NCI
E. Mirand	RPMI
R. Holdenried	VRRB-NCI
L. Murphy	VRRB-NCI

Cell Culture Subcommittee

R. Stevenson (Chairman)	VRRB-NCI
S. Stewart	LVO-NCI
D. Yohn	RPMI
M. Benyesh-Melnick	Baylor U.
A. Moore	SKI
R Chanock	LID-NIAID
R. Meyer	VRRB-NCI

Electron Microscope Subcommittee

A. Dalton (Chairman)	LVO-NCI
K. Smith	Baylor U.
E. de Harven	SKI
R. Zeigel	LVO-NCI
G. Niwayama	RPMI
J. Horoszewicz	RPMI

NCI Proposal for Contract Reviews, Program Reviews and Program Planning

On June 21, 1963, the Office of the Associate Director for Program issued for comment a draft of a major document (6 pages plus a 23 page attachment on details): “NCI Proposal for Contract Reviews, Program Reviews and Program Planning.” The document set forth the philosophy, definitions, operational and organizational guidelines, evaluation and advisory functions, and review of contracts for NCI Programs. The document was accepted as the NCI position and operating policies and practices.

Goals and Objectives of Cancer Research and their Implementation

The Associate Director for Program prepared a 32-page discussion document for the NACC and for the meeting of its Planning Committee on June 22, 1963. The title of the document was “Goals and Objectives of Cancer Research and their Implementation.” In addition to the scientific aspects, the document also covered the NCI organization and management, the program advisory committees, and review of contracts. The Closing Remarks of the document were:

A. The above discussion has presented certain research goals and objectives, analyzed some of the problems involved, made suggestions for expanding research efforts through new devices, and suggested needed changes in legislation and authorities.

B. Pressing problems include:

1. Inducing some of the best investigators to think deeply and seriously about cancer problems and to work on them.

2. *Selection of key goals, objectives and important questions needing answers of paramount significance for cancer research.*

3. *Allocation of resources, which are never unlimited, most effectively to achieve the selected goals and objectives with a minimum expenditure of time and other resources.*

4. *New legislation as indicated above will be required.*

5. *These things simply cannot be done without strengthening government staff involved.*

6. *Who will do the work even if plans, appropriate legislation, and money are available?* (Internal NCI document, June 22, 1963).

This document was also discussed at a June 22 meeting of the NCI Scientific Directorate.

Organization and Staffing Changes in the Institute

On June 25, 1963, Dr. Endicott issued a memorandum "Organization and Staffing Changes in the Institute." Several Institute Associate Director positions were created:

I. The Intramural Research area -- Gordon Zubrod would continue as Director of Intramural Research (and Scientific Director).

A. Associate Director for Laboratory Research - G. Zubrod.

B. Associate Scientific Director for Viral Oncology - R.

Bryan.

C. Associate Scientific Director for Experimental

Therapeutics - E. Frei.

D. Clinical Director - N. Berlin.

II. The Collaborative Research area -- T. Philip Waalkes would become Associate Director for Collaborative Research.

III. The Field Studies area -- Paul Kotin would become Associate Director for Field Studies.

The Virology Research Resources Branch, with Bob Stevenson as Branch Chief, would be transferred from the Collaborative Research Area to the Field Studies Area. These changes were approved at the NIH and PHS levels. Much of the remainder of 1963 was spent in working out the details of the reorganization of the Institute. Several key memoranda detailing the organizational relationships and procedures for program and contract reviews were issued (by the Institute Director, the Associate Director for Program, and the Chief, Research Contract Operations Branch - this Branch was transferred to the Office of the Director). Extensive Guidelines for review of programs were distributed to members of the Scientific Directorate for action. Since the VRRB had been transferred to the Field Studies Area, contracts for this Area would be reviewed by the Field Studies Task Committee. This group consisted of: Paul Kotin (Associate Director for Field Studies), Chairman; Ian Mitchell (Special Assistant to the Associate Director for Field Studies), Executive Secretary; Bertrand Brill (Chief, Epidemiology Research Branch, PHS Division of Radiological Health); Jerome Cornfield (Biometrics Research Branch, NHI); Walter Heston (Chief, Laboratory of Biology, NCI); Margaret Kelly (Medicine Branch, NCI); Edward Kuff (Laboratory of Biochemistry, NCI); Frank Lundin, Jr. (Head, Special Cancer Studies Section, Epidemiology Branch, NCI); Robert Manaker (Laboratory of Viral Oncology, NCI); Jerry Niswander (Dental Surgeon, Human Genetics Branch, NIDR); Alan Rabson (Pathologic Anatomy Branch, NCI); and Wallace Rowe (Laboratory of Infectious Diseases, NIAID). Review of animal production contracts, however,

would be reviewed by the Scientific Directorate, assisted by the Laboratory Animal Committee. This Committee consisted of: Joseph Leiter (Chief, CCNSC, NCI), Chairman; Samuel Poiley (Head, Mammalian Genetics & Animal Production Section, Drug Evaluation Branch, NCI), Executive Secretary; Walter Heston (Chief, Laboratory of Biology, NCI); Robert Holdenreid (Head, Laboratory Animal Section, VRRB, NCI); Michael Klein (Carcinogenesis Studies Branch, NCI); John Murphy (Assistant Administrative Officer, Intramural Research, NCI); and Jane Taylor (Head, Endocrine-Related Tumor Section, Endocrine Evaluation Branch, NCI).

Following discussion at a special meeting of the Scientific Directorate on June 28, 1963, additional discussion was held by the Director, the Director of Intramural Research, and the Associate Director for Program, on the subject of program and contract reviews within NCI. Based on these discussions, the Executive Secretary of the Scientific Directorate sent to the members on July 11, 1963, a memorandum for further discussion at the Directorate meeting of July 15, 1963. Considerable simplification of scope and procedure was effected by elimination of certain features of the June 21, 1963 document. The final document outlining the new contract review procedures, including forms to be used, was sent to staff by the Director, NCI, on September 17, 1963.

Conduct of the Scientific Directorate Meetings

In July 1963 the Chairman of the Scientific Directorate requested suggestions from the members on the conduct of the Directorate meetings. In his role of Executive Secretary of the Directorate, the Associate Director for Program responded to the request on July 12, 1963, with a twelve-page memorandum to the members. Five pages were concerned with the concept of cancer as might be conceived by the members and included a diagram depicting cancer in the

individual (conception at other organismic levels was invited). Items in the other seven pages included; 1) The procedural approaches to the conduct of the Directorate meetings; 2) Discussion of drug development approaches; 3) Approach to evaluation of carcinogenesis, especially screening; 4) The use of inbred animals and transplantable tumors versus random-bred animals and autochthonous tumors; 5) Immunology and cancer; implications for future NCI programs; 6) Biochemical genetics and cancer; 7) Experimental embryology; and 8) Endocrinology and cancer.

Early Systems Planning Efforts

It was about this time (September 1963) that the ideas explored on planning by Carl Baker and Lou Carrese over the past year and a half began to crystallize into concrete substance, permitting formulation of planning efforts for the total area of cancer research. In addition to extensive review of the literature on systems planning, this effort included exploration of planning structures, options for goals and objectives statements, and beginning attempts to define the criteria and associated data required to make decisions defined in the plans. Issues on monitoring, accountability and up-dating of plans were also addressed. The areas of viruses and cancer and cancer chemotherapy were examined to test the planning concepts. The concept of the linear array of the steps required in a drug development program was formulated by this stage of planning for chemotherapy (the Leukemia Task Force, Chaired by Gordon Zubrod, had been formed in 1961 and associated with it was enlarged pharmacology research). The NCI was encouraged by the Director of NIH to proceed with this pioneering systems planning effort.

A Contractor-Operated Research Facility

Much of October, November and December was spent by NCI senior staff on developing documentation on establishing a major nearby contractor-managed and contractor-operated research facility responsive to NCI requirements. The concept was briefly discussed with the NACC by the Director, NCI. The need for such a facility grew out of the constraints of shortages of space and positions (in the face of increasing budgets) and the demonstration of effectiveness of such facilities in NASA, Department of Defense, and the Department of Energy. Part of the background included listing planned contract-supported activities, Fiscal Year 1964 (November 12, 1963 memorandum). This listing included activities important for the viruses-cancer area, such as: 1). an estimated \$350,000 effort with the Human Cancer Virus Task Force and the VRRB programs for development of viral diagnostic reagents and their packaging and distribution; development of standardized serum and chemically defined tissue culture media made to specifications; additional primate species; and additional human diploid cell strain work for viral transformation, co-carcinogenesis and DNA studies; and 2). an estimated \$500,000 for additional ultracentrifuge development with the Oak Ridge National Laboratory (led by Norman Anderson); immunological studies in primates; and murine and human virus studies in germ-free mice. The listing also included potential contractors capable of meeting the complexities of such operations, including not only science and managerial expertise, but also the ability and willingness to take risks. Preliminary discussions with potential contractors were held by Drs. Endicott, Leiter, Coghill, and others. NCI planning called for \$200,000 for initiating a contractor-supported activity in the current Fiscal Year. If successful, it might serve as a prototype for similar facilities in other parts of the country. In preparation for discussion of this topic at the January 4, 1964, meeting of the NCI Executive Committee, a 27 page document on

the subject (revised based on review at the December 13, 1963, Executive Committee meeting) was distributed on December 31, 1963. The *TABLE OF CONTENTS* was as follows:

1. INTRODUCTION

1.1 Rationale for the Facility

1.1.1. High Degree of Flexibility

1.1.2. Problem-solving, Multi-discipline Orientation

1.1.3. Interchange between Biomedical and

Physical/Engineering Scientists

1.1.4. Proximity to NIH Campus

1.2 Implications to NCI Staff

1.2.1. Program Planning

1.2.2. Liaison and Coordination

1.2.3. Monitoring and Consultation

1.2.4. Overall Management

1.2.5. Summary

2. PROBLEM AREAS AND REQUIREMENTS

NCI REQUIREMENTS AND CANCER RELEVANCE CHART

3. SUMMARY OF INTEGRATED REQUIREMENTS FOR THE TOTAL FACILITY

3.1 NCI Requirements and Facility Capabilities

3.2 Basic Characteristics of the Organization and Staff

Facility

3.3 General Outline of Installations Required

3.3.1. Centrifuge and Other Separation Techniques

3.3.2. Instrumentation

3.3.3. Containment

3.3.4. Pilot Plant Operations

3.3.5. Cell and Organ Preservation

3.3.6. Electron Microscopy

3.4 Fiscal and Contractual Aspects

3.4.1. Real Estate

3.4.2. Physical Plant

3.4.3. General Contractual Arrangement

3.4.4. Subcontracting with Small Business

Concerns

3.4.5. Personnel Covenant

4. TIME SEQUENCE FOR IMPLEMENTATION

4.1 Basic Document

4.2 Immediate Research

4.3 Formal Invitation

4.4 NCI Administrative Control

4.5 Funding (Internal NCI document, December 13, 1963).

The senior staff of the NCI met with the Director, NIH, in mid-1964 to review the NCI Collaborative Research Programs. For this review an outline for discussion was prepared by NCI:

I. Definition of types of activities included under this heading in NCI

A. Research programs which provide services and things to the research community

- 1. VRRB*
- 2. CCNSC (in part)*
- 3. Biometry*
- 4. Instrumentation*
- 5. ADP and Communications*

B. Large-scale, interinstitutional, interdisciplinary target research programs with strong industrial research overtones

- 1. Chemotherapy (in part)*
- 2. Leukemia Virology*
- 3. Chemical Carcinogenesis*
- 4. Diagnostic Research*

C. Studies of human and animal populations aimed at discovering the etiology, incidence, and natural history of cancer in man and animals (Generally regarded as a normal function of governmental health agencies)

- 1. Biometry (in part)*
- 2. Epidemiology*
- 3. Carcinogenesis (in part)*

4. *Virology (in part)*

D. Miscellaneous activities funded with contracts because they do not fit conveniently into grants or “in house” operations

1. Support of research in organizations which do not qualify for grants

2. Procurement of services and things

II. Criteria for evaluating collaborative research of the above categories

A. Different categories require different criteria. For example:

1. Resource programs have merit only if they provide resources to activities of merit. To be internally efficient and effective is no great virtue in itself if the final end served is of dubious value.

2. Large-scale, industrial-type research is essential to solve certain types of problems. It cannot be evaluated by comparing it with fundamental research projects in academic institutions.

3. Study of populations is a respectable area of science which can be evaluated with the same criteria as biochemistry or physics.

4. The miscellaneous category has to be evaluated bit-by-bit and defies generalizations.

B. For purposes of this discussion, let us concentrate on large-scale target research and list important criteria.

1. Is the target worthwhile?

2. Is it technically feasible?

3. Are the resources available?

4. Is the plan adequate?

5. *Is the management adequate?*

6. *How fast should one move?*

C. Applying these criteria to the NCI programs which deal with diagnosis, treatment, and prevention of cancer, the targets are obviously worthwhile and feasible (as isolated examples show) and resources can be found (as previous experience proves). Now let us deal with points 4, 5, and 6 with each program.

III. Analysis of Chemotherapy

A. The plan. Inherent in the chemotherapy program is the orthodox linear array common to all drug development programs, but several features are importantly different.

1. A number of diseases are included.

2. Satisfactory laboratory model systems are only now beginning to emerge.

3. Drug cures are only beginning to emerge which permit the development of basic principles.

4. The total kill concept and the need for a total re-planning

B. The management

1. Recent losses of key men

2. Low morale

3. Failure in recruitment

4. Need to use intramural talents

5. Need for better support from OD/NIH and higher echelons

C. How fast should one move?

1. Program has been held practically level for some years by agreement of Shannon and Endicott.

2. Wooldridge Committee and other political pressures to cut back.
3. Technical reasons for pushing ahead at full speed.

IV. Analysis of Carcinogenesis

- A. The plan. No over-all plan has ever been set forth. Limited segments have been planned elegantly (i.e., Leukemia-Virus Program). Others more sketchily. Great potential here.
- B. The management. Excellent and getting better by leaps and bounds.
- C. How fast should one move? Kotin says should go from 10 to 50 million dollars in the next three years.

V. Analysis of Diagnostic Research

- A. The plan. Planning is not active. Existing plans developed by Nadel not accepted by Berlin. Program has been progressively cut back for five years.
- B. The management. With Nadel's retirement this summer, there will be little left.
- C. How fast should one move? Would suggest that this be quietly dropped as a line item in the budget.

VI. Some thoughts on OD/NIH, Collaborative Research and the Wooldridge Committee

- A. Director, NIH, and Surgeon General should give strong support to collaborative and intramural research without waiting for more studies.
- B. Collaborative programs should not be reviewed (from the standpoint of scientific substance) except in the context of the over-all program of an institute.
- C. Reaffirm plans for an annual total review of program by Council.
- D. Establish a committee to advise Director, NIH, on total program of NIH.
- E. Insist on adequate program review at the working level including internal and external advisors.

F. Retain power of contractor selection as an executive function.

The Diagnostic Research Program would be discontinued as a line item in the budget (Dr. Berlin to write rationale for discontinuing the Program). The virology program in Ghana would be phased out. Dr. Shannon liked the idea that Drs. Zubrod, Baker, and Schepartz and Mr. Carrese would lay out a systems plan for the Chemotherapy Program. He wished to involve the NACC subcommittees more in the program reviews and would establish review groups: 1) chemotherapy; and 2) carcinogenesis (would not include VRRB, Epidemiology or Biometry). Biometry and Epidemiology is not like other parts of Collaborative Research, but do require contract dollars. In the review, the Chemotherapy Program was considered sound. For Phase III clinical trials the single instrument grant would continue to be used; NCI would continue internal control of Phase I and Phase II trials. The Lymphoma and Breast Cancer Task Forces would continue as Prime Contractors. Staff positions requiring both scientific and managerial skills were not adequately appreciated; Drs. Shannon and Mider would meet with such staff members to reassure them.

1964

Request for Release of Bureau of the Budget Reserve NCI Funds for Funding of the Contractor-Operator Facility

The NCI Scientific Directorate and the NACC reviewed a document (January 4, 1964) justifying the establishment of a major special purpose contractor-operated research facility, along with a request to fund the facility with NCI monies that had been put into reserve by the Bureau of the Budget. The NCI then sent the document forward through the appropriate channels. The Director of NIH and the PHS Surgeon General supported the request. Although

this March 6, 1964, memorandum pointed out the need for quick action, the reply to the request received by NCI June 15, 1964, stated that “in the Fiscal Year to use the funds and release of reserves was therefore denied.”

Although sizable contracts with several commercial firms were let, it was not until President Nixon announced on October 18, 1971, the conversion of the Fort Detrick Germ Warfare Facility (at Frederick, Maryland) to a Cancer Research Facility that the large contractor-operated facility envisioned in the above document sent forward by Dr. Shannon on March 6, 1964 could become a reality. Immediately prior to the President’s announcement, Drs. Baker, Rauscher, and Zubrod reviewed the status of cancer and cancer research with the President at the Frederick facility. They emphasized the viruses and cancer research. The announcement of the awarding of a \$6.8 million contract to Litton Bionetics, Inc. was made on June 23, 1972. Litton had won the contract through competitive bidding. Several parts of the contract related directly to viruses and cancer research. William Payne was the project officer for NCI; Robert Stevenson, formerly Head of the VRRB, was the General Manager for Litton; and James Nance was President of Litton Bionetics, Inc.

Review of NIH by the Wooldridge Committee

In late 1963 President Kennedy asked Dr. Jerome Wiesner, his Science Advisor and Chief of the Office of Science and Technology, to undertake a study to assess the quality of biomedical research conducted and supported by the National Institutes of Health. Dr. Dean Wooldridge was appointed Chairman of a committee assigned the task. Dr. Shannon and the senior OD, NIH staff met with the Office of Science and Technology staff and key members of the Committee on January 9, 1964, and on June 25, 1964, to provide orientation and to answer

questions from the Committee. In March 1964 NIH staff spent a significant amount of time in preparing orientation material for the Committee. The Committee gave special emphasis to issues such as the optimal size of NIH, if the budget of NIH was “too large,” and whether the money appropriated for NIH was well spent, especially for the Collaborative Research programs. It was important to produce this orientation material because several members of the Committee were not knowledgeable in the biomedical sciences. In addition to Dean Wooldridge, other Committee members were: Dr. Wiesner (MIT); General James Doolittle (Space Technical Labs, Inc.); Dr. William Houston (Rice University); Dr. George James (Commissioner of Health, New York City); Dr. William McElroy (Johns Hopkins University); Dr. Carl Moore (Washington University); Dr. Quigg Newton (Commonwealth Fund); Dr. Joseph Platt (Harvey Mudd College); Mr. Gwilym Price (Westinghouse Electric and Manufacturing Group); Dr. Wayne Reitz (University of Florida); Dr. Julius Stratton (MIT); and Thomas Watson, Jr. (IBM). Several of the Chairmen of the eleven supporting Panels were biomedical investigators. Two Panels were concerned with administrative and policy matters. NCI produced 85 pages of material on NCI Collaborative research programs plus materials on 119 NCI contracts and staffing charts. NIH produced 310 pages on Collaborative Research programs in six Institutes and in the Division of General Medical Sciences. Fifteen pages dealt with the NCI viruses and cancer programs. Members of the Committee and the Panels also interviewed about 500 grantee investigators from over 30 major institutions, about 50 NIH investigators, and a number of contractors in the collaborative areas. In the Report to the President in February 1965, the Committee gave a favorable review to the grants area and intramural programs. Questions were raised about the Collaborative Research areas. As was usual, the recommendation from the Committee was that NIH needed more advice from committees that had members from outside Government (i.e.,

from the academic community). In the case of the CCNSC it was recommended that another committee be established to review in further depth the CCNSC (this recommendation led to the review of CCNSC by the Richardson Committee). [It is of interest that NIH has been reviewed by many committees over the years: the Wolverton Committee, 1958; the Bayne-Jones Committee, 1958; the Bane Committee, 1959; the Jones Committee, 1960; the Barber Committee, 1964; the Wooldridge Committee, 1964; the Committee on Heart Disease, Cancer, and Stroke, 1964-1965; the Rogers Committee, 1966; the Ruina Committee, 1966; the Fountain Committee, 1959-1968; and others, in addition to the various Congressional Committees (e.g., the Elliott and Daddario Committees), including the examinations made annually by the Congressional Appropriations Committees.]

NCI Program Review of Clinical Studies, Collaborative Research

The NCI Scientific Directorate undertook an extensive review of cancer clinical studies at its meetings of April 7, 21, and 28, and May 12, 1964. Dr. Waalkes, Associate Director for Collaborative Research, provided a large amount of documentation for the review. This material had been discussed with the Clinical Studies Panel as part of consideration of the analysis and planning for the CCNSC. The Panel consisted of: I.S. Ravdin (University of Pennsylvania), Chairman; Emil Frei, III (NCI); Albert Segaloff (Alton Ochsner Medical Foundation); Bruce Shnider (Georgetown University); Albert Owens, Jr. (Johns Hopkins University); Anthony Curreri (University of Wisconsin); Jesse Steinfeld (University of Southern California); and Lyndon Lee (Veterans Administration). The meetings focused on improving the activities of five categories of twenty-three cooperative groups and the need for additional pharmacology studies. The five categories were: 1) Hematologic Malignancies; 2) Solid Tumors; 3) Hormone-

Dependent Tumors; 4) Surgery Adjuvant Studies; and 5) Radiation Studies. Special efforts were needed in defining protocol requirements and information flows. Some investigators objected to the requirements of uniformity imposed by NCI, but uniformity of definition and information handling was (and is) essential for drug development and for analysis and evaluation of the activities of the groups. In addition to \$5,843,000 budgeted for programmed grants, the clinical trials effort included \$1,020,816 in supporting contracts plus \$1,511,030 in transfer funds to the VA, Walter Reed Army Hospital, and the PHS Division of Hospitals. The clinical trials were financed with programmed grants because the HEW lawyers believed (erroneously, it turned out) that this course would keep the Government free of liability lawsuits.

These materials were presented to the NACC when the Chemotherapy Program was reviewed by the Council in March 1964. The NACC supported the plans for the clinical studies. Some members of the NACC were beginning to raise questions about the use of contracts. The NACC membership in 1964 consisted of: Walter Burdette (University of Utah); Lee Clark (M.D. Anderson Hospital); Philip Cohen (University of Wisconsin); George Cooper (St. Joseph College); Charles Evans (University of Washington); Sidney Farber (Harvard Medical School); Abner McGehee Harvey (Johns Hopkins University); Mary Lasker (Albert and Mary Lasker Foundation); Leo Rigler (Cedars of Lebanon Hospital); and Philippe Shubik (Chicago Medical School). Mary Lasker, supported by Sidney Farber and Leo Rigler, wanted the NACC to have the same approval requirements for contracts as for grants. Other Council members did not agree. Anticipating questions from the Council, NCI sent on May 15, 1964, to the Council a four-page document by the Associate Director for Program setting forth the nature of research contracting, the reasons for its use, and review mechanisms. The document pointed out that the NCI, in order to meet its responsibilities to further cancer research, needed to support and engage

in the full spectrum of research, with fundamental or exploratory research at one end of the spectrum and developmental research at the other. For the most part, exploratory research depended upon independent investigators conducting self-generating *projects*. Developmental research was most often part of a broader scope of multidiscipline R&D efforts integrated into a *program* consisting of many interrelated parts. Grants were most suited for funding projects and contracts for funding programs. Central control was not preferable for exploratory research (grants). The necessity of integrating the components into a program required central control, especially since the input from one contract was at times dependent on the output of other contracts. Several contracts were production contracts for defined mice and other animals, tissue culture cell lines, media, virus preparations, antibody preparations, information collecting and distribution, and so on. Programs required central planning (but not down at the project level). NCI staff conducted exploratory research on an intramural basis, administered the extensive grants activities, and managed the contract activities. The third area involved program planning and integration of science and management expertise. As an aid for planning, the Associate Director for Program created a comprehensive grid showing various scientific and administrative components making up cancer research and which contrasted with ten organismic levels (radiation; atomic; micromolecular; macromolecular; subcellular; cellular; tissue and organ; multicellular individuals; populations; and societies).

As of November 1963, the dollar distribution of contract monies was:

Chemotherapy	\$24,650,000
Leukemia Task Force	600,000
Other Leukemia Activities	325,000
Biometry	645,000

Epidemiology	389,000	
Carcinogenesis		2,023,000
<u>Viral Resources and Virus Task Force</u>	<u>2,264,000</u>	
<u>Other Virus Activities</u>	<u>2,525,000</u>	
Diagnostic Research		1,000,000
Reserve for Expenditure Adjustments	500,000	
Unallocated or Bureau of		
Budget Reserve	<u>4,045,000</u>	
TOTAL	\$38,966,000	

NACC Meeting of June 22, 1964

The NCI Director made changes in the Intramural Program and in the Grants and Training area 1963-1964 to utilize senior staff more for broad substantive cancer considerations and less for routine issues. He and the NACC agreed that analogous changes were needed in the conduct of the activities of the Council. It was also agreed that the NACC should move away from so much time spent on individual project applications and give more time and attention to cancer program considerations, including planning. To move in this direction, the Associate Director for Program sent to the Council Members a 32-page document entitled "Goals and Objectives of Cancer Research and their Implementation." This document dated June 22, 1964, was a discussion document specifically for the Planning Committee, NACC. The Associate Director also sent to the Council members the responses received from the NACC members to Dr. Endicott's request for their "*views in writing on the trends, thrusts, deficiencies and so on regarding cancer research over the next decade.*" Two responses had been received. The

contrast between the two is interesting. One, from Dr. Philip Cohen, was general and dealt with training needs (physical facilities, job opportunities, and funding support for more trained scientists), and greater dollar support for fundamental research (with less emphasis at NIH for categorical research). He warned that the gap was wide between the accumulated knowledge and the application in the clinic. He thought that all basic problems in biology, including those in cancer, were so complex that they would not be solved by merely continuing to spend more money in the same way as in the past. The other response, from Dr. Charles Evans, set forth objectives, mostly in terms of substantive scientific aspects of cancer problems. He first listed obvious objectives: cause, prevention, cures, treatment of incurable cancer, and determination of means whereby popular acceptance can be achieved for procedures that are known to prevent cancer. Next, he set forth some peripheral goals: define consequences that would follow from the controlling of cancer and make plans for use in cancer research and control of the increasing manpower pool resulting from technological advances. Next, he detailed more specific objectives related to the major goals. He also outlined some recommendations on manpower needs for cancer research and cancer control.

These two examples illustrate two very different approaches to the giving of advice. One focuses on the mechanics of funding with emphasis on basic research support. The other attempts to identify substantive scientific aspects of the problem area and project research needs based on the scientific conceptual schemes. They also illustrate very different attitudes where one view sees the problem as the glass being half-empty and the other as half-full. The former is a pessimistic view that says that we do not know enough to do more than generally support individual scientists. The other, with a more optimistic outlook, suggests that analysis of the situation can lead to selected priorities that form the basis for action. The efforts can be aimed at

solving defined problems derived from the selections of priorities. More often than not the advice given to NIH is the former.

Chapter 4. Correction of Problems, Fine Tuning Of Program Operations, and Further Expansion of Program Outputs

By mid-1964 the viral oncology activities were expanding satisfactorily. Earlier problems with the supplies of normal and tumor tissues from humans and animals and as well as those with acquiring, preserving, freezing and thawing, and transporting these tissues were solved. Virus particles seen with E.M. budding off cell membranes of animal tumor tissues were also tantalizingly observed in some human tumor biopsy specimens. With tissue culture cell lines, some problems of labeling and contamination continued until 1966.

Many additional tumor-causing viruses from animals were isolated and classified, but none clearly from man. In the hope that the biological closeness to man of non-human primates would make for sensitive test systems for finding human tumor-causing viruses, many human tumor specimens were administered to these animals, colonies of which had been developed in the resources part of the Program. Moreover, techniques developed with animal viruses for increasing the purity and concentration of virus in the preparations derived from tumor biopsies were applied to those human specimens being injected into the non-human primates. Also, as the purity of the virus preparations produced with the special centrifuges in the Program at Oak Ridge Laboratories increased, analysis could begin to determine the viral DNA (or RNA)

structure. Researchers also hoped to learn which parts of the viral DNA (or RNA) were responsible for tumor induction, for virus reproduction, and for other properties.

Participants in the SVCP discovered temperature-sensitive mutants of tumor viruses, another important tool for getting at the structure and sequences of the building blocks of the nucleic acids. Some of these Rous sarcoma virus (RSV) mutants would induce cancer transformation of tissue culture cells grown at 34 degrees C., but would lose that ability if growth was at 41 degrees C. These changes were reversible. The viruses would continue to multiply at either temperature. Further studies indicated that a single gene - called *src* - was involved in transformation. Thus the stage was set for mapping the region of the *src* gene (about 2000 nucleotides). The mutants were distributed to appropriate investigators.

The research results from the Program by mid-1964 were sufficient to warrant an NCI request to Congress for a special appropriation to fund a larger program on leukemia. For this new Program, the NCI appropriation contained an additional \$10 million.

The NCI, utilizing the "Convergence Technique," developed a systems plan for the new Special Virus Leukemia Program (SVLP). This plan provided staff and advisors a framework for decision making in the total Program perspective. It also was an aid in modifying the Program as new information was gained from the research and in projecting future activities. Once the laboratory methodologies for animal and human cancer virology were worked out (including availability of sufficient quantities of viral and immunological reagents), studies began to correlate the laboratory data with the data from population groups. These groups were constituted not only of humans and animals with different types of cancer, but also with different epidemiological categories (e.g., different age groups, different environments, contacts with different animals, and different exposures to air pollutants).

Because of the potential danger resulting from isolating and increasing the potency of several virus preparations, NCI had built a special facility for handling hazardous biological materials. [This development improved the U.S. ability to deal later with bioterrorism.] Along with the facility, the Institute developed a teaching program for handling hazardous materials that built on the excellent program of the U.S. Army. This segment of the SVLP developed improved safety measures and created the widely used red symbol warning of dangerous biological materials [Figure 3]. Later NCI developed a contractor-operated facility at Frederick, Maryland.

The number and total dollar amounts for contract-funded activities continued to increase appreciably, and the Institute continued to develop methods for improving the review of contracts and programs to achieve quality control. Numerous memoranda emanated from the NCI Office of the Director and gave detailed guidelines and instructions. These actions, supplemented by the systems plan, ensured coordination of the various components of the Program. At the NACC meetings, extensive information on these programs and contracts were supplied each year.

The Program continued to provide research materials to participants in the Program and to others including grantees. An important example of this was distribution of large amounts of *reverse transcriptase*, the enzyme that allowed the coded information in RNA viruses to be converted to DNA information. The enzyme also allowed the cloning or making copies of segments of the DNA code and the determination of sequences of building blocks in nucleic acid.

Robert Huebner and George Todaro made a major advance with the publication of their paper on the "Oncogene Theory." In this theory certain genes (*Oncogenes*) in the cell nucleus,

when turned on, can lead to cancers. Much of the time they are switched off but can be made active by radiation, certain genetic patterns where one gene may influence other genes, some chemical compounds, some hormonal agents, and ageing. The theory, supported by extensive evidence in several fields, concludes that cancer is not an infectious disease, and that cancer susceptibility is passed from one generation to the next by means of the information in the DNA. DNA information could be turned on easily or not depending on the genetic make-up and the lifetime experiences of the organism. Huebner thought that some of the coding in the cell's DNA came from tumor-causing viruses. Only later, did Bishop and Varmus discover through the application of additional tools (restriction enzyme) that oncogenes do not need to be derived from viruses and are present normally in our chromosomes. In 1972 the total number of publications emanating from the SVCP reached 604 (294 published and 310 in press).

Request for a Special \$10,000,000 Appropriation for Acute Leukemia Research

By July 1964 Dr. Endicott had reached the conclusion that the results of research on acute leukemia had advanced to a stage where additional funds should be added for this area of research. Numerous opportunities for further research existed and could be exploited if additional support were given. On July 16, 1964, the Director, NCI, sent to the Director, NIH, a memorandum headed "Need for Funds in Acute Leukemia." This memorandum, drafted by Ray Bryan, Frank ("Dick") Rauscher, and Carl Baker, and reviewed by Gordon Zubrod, provided important status summarization and justification for asking for additional funds. Dr. Endicott asked Dr. Shannon for permission to seek additional funds from the Congress for leukemia research in the amount of \$10,000,000. Requesting special funds outside the usual budget channels was highly unusual, but the NCI believed it was justified. The memorandum follows:

The pace of research in the causation of leukemia and particularly acute leukemia of childhood and comparable lesions has become very rapid, and through the improved communication lines provided by our two Task Forces, I have been made aware of a number of new observations, as yet unpublished, which when added to the evidence already at hand indicates a clear need for further intensification of this activity. It seems quite probable that a deliberate program can be successful on several critical issues that remain to be resolved to establish on a firm scientific base the viral nature of these leukemias. The objective is particularly important in light of the possibility that an agent may be isolated and that we might be able to prevent this lethal disease.

Much of the most recent work has been made possible by the diversion of funds from other areas to this one, and I feel I cannot make further diversions without serious inroads on other programs that have great importance in themselves. The resources of the National Cancer Institute as represented by the budget presented to the Congress for fiscal year 1965 are inadequate to cope with these emerging problems. I hope that it will be possible to take immediate steps to obtain a special fund with appropriate authorities in order for me to move more aggressively in the pursuit of these exciting leads.

The following is a series of specific findings that have characterized leukemia research in the past few years, most of them new observations of which many are yet to be published.

Facts

1. It is well established that leukemia in both domestic chickens and mice is caused by viruses. Extensive investigations of the disease in both species have established that virus is present and can be demonstrated by both animal tests and electron microscopy not only during clinical disease, but also prior to the onset of clinical symptoms.

Virus particles can be seen with the electron microscope in leukemic cells in the spleen, lymph nodes, bone marrow and other affected organs. What is more important, leukemia virus is produced in much larger amounts by certain cells of the body that, although they “manufacture” large quantities of virus, do not themselves undergo cancerous transformation. The cells which manufacture virus but show no ill effects of it are among those that normally produce large quantities of protein, such as the acinar cells of the pancreas, megakaryocytes of the spleen and bone marrow, and epithelial cells of the mammary glands. It therefore appears that leukemia viruses may parasitize the intracellular protein producing mechanisms of cells.

2. In 1957, Dmochowski reported the presence of virus-like particles in thin sections of lymph nodes taken from human leukemic patients. Beard (unpublished) confirmed this observation, but in only one of about a dozen cases studied.

3. Dalton and Moloney showed that virus was present in the plasma of leukemic mice, and that fractions isolated and concentrated by ultracentrifugation showed typical virus particles when examined by thin section electron microscopy. In collaboration with Porter, Frei and Mitchell they also studied over 50 plasma specimens from children with acute leukemia, and found particles resembling mouse leukemia virus particles in 8 cases.

No such particles were seen in the plasma of 86 normal humans, 36 of which were young children of the same age as the leukemic children.

Other investigators using a less critical electron microscopic method (negative staining) have reported a larger proportion of leukemia in cases showing virus-like particles (Melnick and associates; Burger and associates).

4. Fink and Malmgren succeeded in working out specific immunofluorescence methods which detect the presence of viral antigen in leukemic cells induced with certain mouse leukemia viruses. Application of the method to human leukemia, using plasma fractions shown by electron microscopy to contain virus-like particles for the production of antibodies in rabbits, has revealed a fluorescent antigen in leukemic cells in a high percentage of the human leukemia cases studied. Many of the positive cases also showed a cross reaction with specific antisera against the Rauscher mouse leukemia virus, indicating that common antigens are shared by the Rauscher virus and something (viral antigen?) in some human leukemia cells.

5. Epstein has succeeded in propagating cells from human lymphoma (Burkitt) in tissue culture, which continue to elaborate a membrane-bound virus-like particle. These tissue culture cells give a very strong immunofluorescent reaction with the human antibody reagent of Fink and Malmgren as well as with that of the Rauscher mouse leukemia virus. Mass cultivation of these cells in tissue culture could provide an abundance of virus for further studies, including vaccine development.

6. Epstein inoculated suspensions of fresh lymphoma cells from a case of Burkitt lymphoma into 4 suckling African gray monkeys. Of three that survived two years but have recently come to autopsy, two showed dilation of the marrow cavity and the resulting space filled with malignant lymphoblasts indistinguishable from those of the original Burkitt tumor. It appears that a human lymphoma has been transmitted to a sub-human primate for the first time, probably by a virus present in the inoculated cells. Of 11 monkeys inoculated with Burkitt tumor

cells that had been stored at low temperature, 5 are now showing X-ray evidence of bone marrow lesions, similar to the X-ray pictures that had been taken of the two positive monkeys, before they came to autopsy.

More recently, Epstein has reported finding myelosclerotic lesions in bone marrows of several uninoculated primates from London zoos and from an adult colony maintained in Africa. These lesions in "normal" animals apparently are indistinguishable from those which occurred in animals inoculated with Burkitt lymphoma cells. Further control studies, therefore, are obviously necessary to assess the significance of Epstein's preliminary transmission experiment in primates.

7. In NCI contract research conducted in collaboration with the Pfizer Company, a mixed mouse thymus and spleen culture was successfully inoculated with Rauscher mouse leukemia virus. For several months the cell cultures showed no evidence of producing virus, but eventually small amounts (1 or 2 particles per electron microscopic grid) were observed. Subsequently, the culture line began producing large quantities of virus and is now being used for the in vitro production of Rauscher virus.

A mixture of human embryonic thymus and spleen was established in tissue culture by the Pfizer group, and is now being used for the inoculation of human plasma concentrates in which particles are seen with the electron microscope. One such line inoculated several months ago is now showing "1 or 2 particles per grid" when culture fluid is examined under the electron microscope. Since no particles had been seen until recently, and since no such particles have yet been seen in uninoculated control culture fluids, this experiment with a human specimen containing a "candidate" virus appears to be following the same course observed with the mouse leukemia virus. Although not yet successfully established as a virus producing line of

practical significance, the results to date strongly indicate that success will be achieved in the propagation of a human leukemia virus.

8. Grace and collaborators (unpublished) have succeeded in propagating human myeloid leukemia cells in tissue culture for many months. The cultures are still in good condition and are releasing virus-like particles into tissue culture fluid. This system is now ready for mass production trials for the recovery of large amounts of the virus-like particles for further study by immunological and biological methods. Small concentrations of the materials have already been inoculated into newborn monkeys.

Leads

1. Studies on 3 “clusters” of leukemia, such as that which occurred in Niles, Illinois are under investigation. One surviving leukemic child of the Niles cluster (now in remission) has been tested on two occasions. Virus-like particles were found in her plasma on both occasions. Her mother and her sister also showed similar particles in their plasmas.

In the Green Bay, Wisconsin area there are now 5 cases of childhood leukemia within an area 1.5 miles in diameter. A sixth case just recently reported lives 11 miles away. Of these 6, 4 have been found to be positive for presence in the plasma of particles resembling mouse leukemia virus particles. The father of one case and the mother and sister of another have likewise shown virus-like particles in their plasmas. No such particles have yet been observed in normal humans unrelated to leukemics.

A third “cluster” in Osage, Iowa is also under study. Of three original cases only one is now alive. Satisfactory tests were not obtained before death of the other two, but three successive

tests on the surviving child were positive. The father of this child and the mother of one of the other children were also positive for characteristic virus-like particles in their plasmas.

A local veterinarian volunteered the information that there seemed to be an increasing incidence of lymphosarcoma in a herd of prize Holstein dairy cows in his area. This particular herd has been under close surveillance for about 15 years by the same veterinary group. The families use pasteurized milk from four different local dairies. Three of the first four leukemic children studied were bottle-fed. (Information is not yet available on the other one).

2. Three cases in which leukemia in a child has followed within a short time (2 to 3 months) a bite by a dog has come to our attention. In no case was the dog leukemic. Another case of leukemia in a young man followed shortly after the death of a pet dog with leukemia. There was no history of dog bite in this case.

Of the five cases of leukemia within a 1.5 mile diameter in the Green Bay "cluster", all families have 1 or more dogs. The dog of one of the leukemic children was clinically ill with "distemper" about 1 month before the child became symptomatic.

Virus-like particles have been observed in the plasma of 3 leukemic dogs studied by Moloney.

3. A series of papers concerned with bovine leukemias was published in Annals of the New York Academy of Sciences, 108:1149-1268,1963. Some identified herds in the United States studied by Dutcher, Coriell and Marshak have experienced multiple cases of lymphosarcoma, or leukemia, during the period of study. The most extreme case is a herd of 50 milk cows in which 20 have died of these lesions since 1956 and most of them since 1960. The course of the disease is characterized by a non-leukemic lymphocytosis followed by frank neoplasia. A pronounced drop in the lymphocytosis precedes the onset of cancer. Examination of

leukemic cell cultures and lymph nodes from affected cattle disclose particles similar to those found in mouse leukemias known to be transmitted by viruses. Milk from apparently normal individuals, those demonstrating lymphocytosis or those frankly leukemic contain racket-shaped particles, as demonstrated by negative staining under the electron microscope. Thin section specimens are being prepared.

Other herds have been identified in which leukemias and allied diseases have not been known to occur. Neither their milk nor their tissues have contained any virus-like particles on appropriate examination.

European experience suggests that bovine leukemias can be introduced into a clean herd by transfer of breeding stock from multiple case herds. More than 30,000 head of dairy cattle have been sacrificed in Denmark because of lymphocytosis.

4. Burmester has obtained evidence of antibodies against fowl leukemia virus in the serum of a few human leukemia patients.

5. Rauscher and Fink have observed three cases in which serum from leukemic patients neutralized a mouse leukemic virus.

6. Jarrett and associates have recently reported that leukemia in cats can be transmitted within the species by cell-free preparations. Virus particles similar to mouse leukemia particles were also observed. This indicates that cat leukemia is also caused by a virus.

Kenneth M. Endicott, M.D.

Dr. Endicott was authorized to present at the Appropriations Committee hearings a proposal for an expanded program for cancer virus studies. A \$10,000,000 program for these

studies was proposed in addition to the regular appropriation request. The projected expenditures of the \$10 million, as were transmitted to Herman Downey, the Clerk of the Senate Appropriations Committee, were outlined as in the following memorandum to Dr. Shannon, the Director of NIH from Carl Baker, the Acting Director of NCI, dated August 12, 1964:

Use of \$10 Million in Additional Funds.

We have previously indicated to Mr. Downey, in a budget requested through channels, that we would expend \$10 million as shown below:

(1) For research, design, mock-up and testing of special rooms, to be placed within existing or leased space to protect persons against dangerous materials

\$ 1,500,000

(2) For development and production of tissue cultures, viruses, reagents and fluorescent antibodies and other resource requirements

3,800,000

(3) Studies of viruses in animals and their relationship to human cancer

1,500,000

(4) Epidemiology and related field work including limited sampling of blood from a selected group or groups in search for causative agents

1,000,000

(5) Clinical research - strengthening of the existing NCI team, support of two additional teams for intensification

of viral and therapeutic research with patients, including maintenance of outpatients, hospital costs and related pharmacology *1,400,000*

(6) Special instrumentation and other engineering developments for virus and cell separations *800,000*

\$10,000,000

In addition, 90 additional positions should be provided for carrying out this enlarged program.

Needless to say, the number of positions authorized was nowhere near the 90 positions requested.

Planning of a New \$10 Million Viruses-Cancer-Leukemia Program

After the Appropriations Bill passed, Dr. Endicott said to Dr. Baker and Mr. Carrese, “OK, you guys have been talking about the need for program planning, plan me a \$10 million program on viruses and cancer-leukemia.” He appointed the two of them plus Dick Rauscher to form a science/management team operating from his Office to plan, develop, and manage the Program. In September 1964, the three members of the Science/Management Team isolated themselves from other contacts for a three-week period to develop a systems network depicting the Program. The planning was done in phases with each phase resulting in a more complete and refined revision. This approach set forth the Program structure based on the science and the

program logic required for moving toward Program objectives. An important addition to the network plans was the defining of key decisions (*Decision Points*) that must be made periodically to move the Program along. Spelled out for each *Decision Point* were criteria that had to be met to make the decision and the information inputs required to meet the criteria. [Systems planning for the Cancer Chemotherapy Program later led to the addition of *Monitoring Points*; these were like Decision Points except that they called for periodic decisions on whether the program structure itself must be changed. The *Monitoring Points* also required that criteria required for making the decision and the information necessary to meet the criteria be closely defined.] The illustration of the systems network (Figure 4) showed multiple inter-connections among the various parts of the Program with connecting arrows. The network consisted of two arrays or program flows: 1. Human Leukemia Etiology, Prevention and Control; and 2. Production and Quality Control of Candidate Virus(es) and Vaccines.

Systems networks provide the basis for key decisions that must be made for a program to progress operationally, i.e., through various Program phases. As a program evolves, outputs of program efforts (data or materials) move to required sites in the planned program, and flows of information and other resources move across the network. The systems approach was a great improvement over the earlier grid because inter-relationships could be shown, and Program decisions were aided by the systems network. Another advantage is that the network allows reiterative visualization of the total program, and, if changes are made, the effects on other components can be noted more easily. A systems network chart is also a great aid for presenting and communicating complex programs.

The use of a systems network for planning and operating a *research* program required modification (to accommodate the research aspects) of other systems planning efforts

(production and construction programs, e.g., the Polaris Missile Program and CPM - Critical Path Method - for major construction programs). Moreover, time and cost estimates cannot be as precise in research programs, though time is always a critical factor. In this pioneering effort by NCI, the concept of converging program efforts toward target objectives led to labeling the systems effort the “Convergence Technique.” A full presentation of this technique was later published by Lou Carrese and Carl Baker, as “The Convergence Technique. A Method for the Planning and Programming of Research Efforts,” in the April 1967 issue of *Management Science* (see vol. 13, no. 8, pp. B420-B438).

This planning activity also resulted in three historic documents, all dated September 28, 1964. They projected research efforts based on the current status of research and opportunities to exploit many leads. These documents were sent to the Scientific Directorate for a scheduled review on October 6. They were also sent to the NACC and the NCI Board of Scientific Counselors for the upcoming joint meeting to review the viruses leukemia plans on October 13 and 14. The documents were: 1. “The Special Virus-Cancer-Leukemia Program” (5 pages); 2. “Proposed Operational Plan for the Special Virus-Cancer-Leukemia Program” (3 pages); and 3. A chart titled “Gross Program Divisions, Special Virus-Cancer-Leukemia Program.” The initial Program later became known as The Special Virus Leukemia Program.

The five-page broad Program statement (1) stated:

The Special Virus-Cancer-Leukemia Program

The NCI request for a supplemental appropriation was based on the conviction that there now exists sufficient scientific knowledge and information and technical capability to plan and carry out an intensified, coordinated virus--cancer-leukemia research effort.

The program is being planned along four main lines of effort, all of which are interrelated. Concise preliminary program statements for these four program areas are given below. These broad general statements provide a convenient way to describe the total effort and, more important, serve as the basis on which the next level of more detailed plans can be formulated (see the second attachment).

I. Human Leukemia Etiology and Prevention

This major program area is the performance of integrated research and development efforts directed toward the prime objective -- prevention of human leukemia by production of an effective vaccine for human leukemia and/or other control methods of virology. An essential target in moving toward this objective is the successful growth of large quantities of human leukemia virus in tissue culture for the immunology studies requisite to vaccine development.

Following is the basic structure of the program in this area:

A. Assumption: At least one virus is an indispensable element for the induction of at least one kind of human leukemia, and the virus continues present in the individual.

B. The Main Program Objective: To develop an effective vaccine or other measures for the prevention and control of human leukemia.

C. Major Program Elements

1. *The production of large quantities of human leukemia virus (and other oncogenic viruses) necessary for requisite immunologic studies and production of an effective vaccine utilizing required cell lines.*

2. *The improved detection of specific biological activity of human candidate virus preparations for selection of specimens for additional work-up, for monitoring biohazard work, etc., by enhancing the sensitivity of present laboratory indicator systems and/or the development of new test systems.*

3. *The provision of greater capacity for screening large numbers of human leukemia for selection of the most favorable patients and materials for virus isolation and propagation studies by the further development and increased production of required reagents and increasing the number of trained personnel.*

4. *The determination of whether leukemias in certain animals are virus induced, and, if so, to establish their antigenic relationships, the mode of transmission, and attempt to determine the etiologic relationships to human leukemia.*

II. Human Leukemia Therapy [developed with Gordon Zubrod]

The second program area is concerned with the intensification and expansion of research to achieve the ultimate therapeutic objective of the complete destruction of all leukemic cells with tolerable (minimal) toxicity for the patient. Total kill of leukemic cells has been achieved in mice and approximated in a few patients. Slight improvements in therapy may make this feasible in many patients.

Following is presented the basic structure of the program plan in this area in terms of more proximate objectives:

A. Support of the patient by amelioration of drug side effects. For example, if side effects of antileukemic drugs upon bone marrow could be ignored, much larger doses could be tolerated.

1. Platelet replacement for thrombocytopenia.

a. Storage of platelets so that they can be made available to all patients.

b. Simplification of collection techniques in order to adapt them to Red Cross collection system.

c. Mass tissue culture of megakaryocytes.

2. Granulocyte replacement for agranulocytosis.

a. *Development of technique for harvesting granulocytes from 2 to 3 blood volumes of normal donor. This will require perfecting the in-line centrifuge.*

b. *Storage of granulocytes.*

c. *Mass tissue culture of precursor bone marrow cell.*

3. *Immunocyte replacement.*

Lymphocyte - plasmocyte deficiency occurs as host response to leukemia and antileukemic drugs, and is probably responsible for fungal and viral infections. Have same needs for harvesting, storage and mass culture of these plasmocyte cells and precursors.

B. Prediction from animal studies of better therapeutic ratio of drugs used in patients. It will be recalled that ultimate objective:

Greatest Efficacy

Least Toxicity = Therapeutic Ratio.

1. *Prediction of greatest efficacy.*

a. Better new drugs. These will flow from present NCI mechanisms but great need for studies on pharmacological disposition in mouse and patient.

b. Better use of current drugs.

(1) More efficacious combinations of current drugs. Studies underway but have little data on prediction systems for drug combinations or pharmacological distribution of several drugs used together.

(2) Better use of current drugs used singly. Need to validate prediction system for best route, schedule, need for maintenance, etc.

2. Prediction of least toxicity.

a. Quantitative: i.e., Prediction of safe dose. The predictive value of animal models is now understood on a dosage basis, but there is a great need to reinterpret and to refine prediction in terms of comparative blood and tissue drug concentrations. Hence need extensive increase in pharmacologic studies of all current and new drugs in animals and man.

b. Qualitative: i.e., Prediction of toxicity to specific organ systems. Same needs as under B.1.

3. Prediction of adjuvant effects of other therapies. It will be recalled that the working hypothesis is that any additional help to patient may make total destruction of

leukemic cells systematic. Thus, the destruction of the last few logs of cells might be achieved by adjuvant immunotherapy, or -- if human leukemia is due to a virus -- the production of new leukemic cells might be prevented by viricidal agents.

a. Immunotherapy. Animal studies show that Rauscher leukemia can be altered by passive immunization. Plans should be made to apply this to patients. What should be source of antibodies?

??Hyperimmunization of normal volunteer by killed vaccine.

?? In vitro antibody production.

b. Viral chemotherapy.

(1) Prediction of drugs for destroying leukemia virus.

(2) Prediction of drugs for destroying secondary viral invaders such as cytomegalic inclusion virus.

c. Fungal chemotherapy.

*Prediction of drugs for destroying secondary fungal invaders --
Histoplasma, Candida, Aspergilli, etc.*

III. Biohazards Control and Containment

The third program area is the performance of urgently needed, coordinated efforts directed toward successful containment and safe handling of oncogenic viruses – a potential biohazard to those conducting oncogenic virus investigations. The experience with animal model systems indicates that the activity of oncogenic viruses is greatly enhanced when produced in quantities and concentrations utilized in advanced study of leukemia. Also, recent developments permitting oncogenic viruses to cross species lines further emphasizes the urgency of this work.

IV. Special Animal Leukemia Ecology Studies

The fourth area is concerned with the nature of animal leukemias and their possible relationships to man. Accumulated evidence from a variety of sources suggests a relationship between the occurrence of leukemia in persons who have associated with domesticated animals and the occurrence of leukemia in these animals. Virus-like particles have been seen in cows' milk and milk products and in greater numbers from leukemic herds than from non-leukemic herds. Because of the economic, political, social, and, perhaps, health implications of these observations, it is a matter of urgent and serious obligation to clarify the nature of leukemias and associated viruses in several types of domesticated animals, their relationships with each other and with human leukemias, and to attempt determination of the significance of the virus-like particles in milk, including studies on inactivation of viruses contained in milk. The

preliminary findings suggesting the exquisite sensitivity of newborn swine to oncogenic viruses from other species should be followed up with dispatch.

In addition to the major lines of program emphasis described above, other supplementary efforts will be conducted. These efforts, although not currently judged to be critical to the achievement of the more specific objectives outlined for the major program areas, are nonetheless important for the potential basic scientific knowledge they may provide (“The Special Virus-Cancer-Leukemia Program,” Associate Director for Program to the Scientific Directorate, the Board of Scientific Counselors and the NACC, September 28, 1964).

The three-page September 28, 1964 document, *“Proposed Operational Plan for the Special Virus-Cancer-Leukemia Program”* (2) was as follows:

1. Initial Program Planning

A science/management team appointed by the Director, and operating from his Office, has developed a preliminary draft of the overall program plan. The Scientific Directorate and the National Advisory Cancer Council will review this general plan and advise the Director as to its suitability.

2. Detailed Planning Prior to Implementation

For purposes of detailed program development, it is proposed that this special research effort be divided into four major program areas: human leukemia etiology and prevention; human leukemia therapy; biohazards control and containment; and special animal leukemia ecology studies. To pinpoint working responsibility, these four areas, in turn, are divided into eight working groups representing segments of the major program areas: development; testing and monitoring; epidemiology (epizootiology); resources and logistics; production; biohazards control and containment; special animal leukemia ecology studies; and human leukemia therapy (see attached chart). A chairman for each of these working groups will be selected from NCI operating units. The chairmen will invite scientists from NCI, NIH, and outside organizations to participate as a group in the development of detailed plans for their respective program segment.

The working group chairmen (and others as required) will meet with the OD science/management team to correlate and integrate the eight separate detailed plans into one overall program plan. This more detailed plan will also be made available to the Scientific Directorate and the National Advisory Cancer Council.

3. Implementation, Monitoring and Coordination

Following the generation and review of the detailed program plans, each working group will develop individual project proposals comprising their respective program segment. These will be reviewed in the usual manner.

Once the approved projects are implemented, program monitoring and coordination will also be accomplished through the eight working groups. The chairman of each of the groups (or another member appointed by Chairman) will function as a program manager for all projects included within his particular program segment, and will have overall responsibility for monitoring and coordinating these projects regardless of the mechanism of performance. The program segment manager will monitor all projects not only from the standpoint of being generally aware of the progress and status of each project, but he will also be cognizant of problems which may be impeding the expected pace of progress toward project objectives and initiate action necessary to solve these problems. Thus, the program segment manager plays an active role in the assessment and evaluation of performance on each project and initiates action to modify the projects in close coordination with the project directors. Coordination between program segments is accomplished in two ways: through frequent "cross talk" among program segment managers and project directors; and through periodic meetings of the program segment managers with the science/management team. These meetings will take place at least quarterly, and more often if necessary, to meet the requirements of specific situations. Progress and status reports for each program segment will be presented and discussed. The OD Science/management team will integrate these reports into overall program reports and forward copies to the Director, the National Advisory Cancer Council, the Scientific Directorate, and the program segment managers. Each project director will provide a periodic, updated overview of his total program area (Proposed Operational Plan for the Special-Virus-Cancer-Leukemia Program," the Associate Directorate for Program to the Scientific Directorate, the Board of Scientific Counselors, and the NACC, September 28, 1964).

An organizational diagram was included. The Gross Program Division Chart (3) was a grid chart with the program segments down the left margin and four phases across the top:

Phase 1. Identify unknown virus agents & establish replicating capability in some system.

Phase 2. Produce large quantities of highly purified virus & reagent antibody.

Phase 3. Etiological substantiation & developmental control work: (a) substantiate leukemogenesis in man; (b) vaccine development; (c) development of other control measures.

Phase 4. Planning & execution of field trials & evaluation of control measures.

The grid chart includes additional details under each of the four Phases.

The designated program segment managers (and deputies) were: Development: Ray Bryan (Jack Dalton); Testing and Monitoring: Bob Stevenson (Mary Fink); Epidemiology (Epizootiology): Bob Miller; Production: Bob Manaker; Resources and Logistics: Bob Stevenson; Human Leukemia Therapy: Gordon Zubrod; Special Animal Leukemia Ecology Studies: John Moloney (Bob Holdenreid); Biohazards Control & Containment: Bill Payne (Robert Runkle) (Gross Program Divisions, Special Virus-Cancer-Leukemia Program,” a grid chart organizational diagram from the Associate Director for Program to the Scientific directorate, the Board of Scientific Counselors, and the NACC, September 28, 1964).

The NCI Program Review book sent to the members also contained detailed data on 283 research grants (\$13,902,772), 51 contracts (\$9,672,019), and 65 intramural research projects (about 4.4 million man years of effort) all related to virology/leukemia research projects. Also sent out was a “Report of Working Conference on Bovine Leukemia” dated September 17, 1964. Invited to this conference were 55 participants; Gordon Zubrod chaired the conference. The

Resources and Logistics Section of the Virology Research Resources Branch supplied “A Bibliography and General Reference Guide to the Bovine, Canine and Feline Leukemias”; this was a good example of the bibliographic services that the VRRB provided.

It may be noted that Bob Miller published a paper in the July 2, 1964, issue of the *New England Journal of Medicine* entitled “Radiation, Chromosomes and Viruses in the Etiology of Leukemia. Evidence from Epidemiologic Research” in which the final paragraph was as follows:

“Some viruses that produce chromosomal abnormalities are oncogenic in laboratory animals. Furthermore, unlike ionizing radiation, viruses may invoke malignant transformations in human tissue culture. Despite these impressive laboratory observations, epidemiologic research, so effective in defining other factors in leukemogenesis, has been unable to reveal convincing evidence of a virus-like spread of leukemia in man.”

With the rapid progress in animal studies, including demonstration of transmission of many animal oncogenic viruses, it may be understandable that insufficient attention was given to Bob Miller’s calling attention to the lack of epidemiologic evidence in human subjects.

Reviews of the Plans for the Special Viruses Leukemia Program

The overall Special Viruses Leukemia Program Plan was presented to the Scientific Directorate on October 6, 1964 (“The Special Virus-Cancer-Leukemia Progra,” and “Proposed Operational Plan for the Special Virus-Cancer-Leukemia Program,” from the Science Management Team to the Scientific Directorate and the NACC, September 28, 1964). Dr. Baker discussed the scientific rationale for the Program and the general administrative and operational aspects and Dr. Rauscher discussed the detailed scientific aspects. Chairmen were selected for

the eight segment working groups; the groups would function in a manner similar to existing NCI Program Review as regards review, but would have additional planning responsibilities. Following full discussion, the Plan received Scientific Directorate approval for implementation (pending approval at the joint meeting of the NACC and the Board of Scientific Councilors).

Immediately after the Scientific Directorate meeting, each Chairman was asked to review the total plan (about 160 projects) and tentatively identify those projects that he considered to be within the sphere of his particular research area. He was also asked to identify those that represented combined, coordinated responsibility of several working groups. In addition, potential investigators and their affiliations were noted after each project. A composite list was prepared for presentation at the joint meeting.

At the October 13-14, 1964, joint meeting with the NACC, essentially the same presentation was given before the Scientific Directorate. In addition to Dr. Baker's and Dr. Rauscher's presentations, Dr. Emil Frei (representing Dr. Zubrod) gave a special presentation regarding the human leukemia therapy aspects of the Program, and the role to be played by the Acute Leukemia Task Force in the effort. Following brief discussion, the total scientific and operational Plan received unanimous endorsement from the NACC (and the Board of Scientific Counselors) with the recommendation for immediate implementation.

The OD Science/Management Team and the Chairmen of the working groups spent much of the remaining time in 1964 determining the division of responsibilities and assignments of contracts to the particular working groups. Priorities were developed for each set of contracts and contracts proposals. Many meetings were held among and between the Chairmen to resolve problems. Also, firmer requirements for space and personnel were drawn up. It was clear that additional space would be necessary to carry out the Program. When the projected preliminary

totals were added up, the dollar amount was over \$13 million and the positions totaled 148. Through additional meetings focusing on priorities, the amounts for contracts were brought down to the \$7 million amount available for new contracts. Detailed allocations of the total Program funds were made into the main budget categories of contracts, other objects, travel, construction and renovation, space, equipment, payroll, and reserve for contingencies. In November, after approval by the NCI Director, potential members of the working groups were invited to serve on the working groups. Between five and ten outstanding investigators were to make up the membership of each working group. This activity under the rubric of the overall plan ensured participation of investigators within and outside the NCI in not only review of proffered projects, but in the continuing planning of needed new proposals. The first meetings of the working groups were held from mid-December 1964 to early January 1965. The eight working groups totaled 59 in memberships (27 from within NCI and 32 from outside the Institute). The OD Science/Management Team prepared for the new members of the working groups a package providing general information on the Program. The NCI staff, especially the working group Chairmen, responded very well to the sudden large increase in workload and deserve much credit for implementing quickly the new program.

The November NACC Meeting

On November 18, 1964, a main item on the agenda of the NACC meeting was a review of the total Field Studies Area. Documentation had been supplied to Council members prior to the meeting, including a listing of all contracts (“Field Studies Area Program Presentation to the National Advisory Cancer Council,” Dr. Paul Kotin to the NACC, November 18, 1964). Paul Kotin, the head of the Field Studies Area, made the presentation. Included in this review was the

program of the Viruses Research Resources Branch (headed by Bob Stevenson), which by this time had been moved into the Field Studies Area. About one-quarter of the Field Studies funds were in the VRRB. VRRB contract monies totaled about \$2.274 million; the Field Studies total was \$9.334 million. Of the VRRB funds, 53% were in Cell Culture and Tissue Materials, 30% in Laboratory Animals, 10% in Cancer Virology, and 7% in Human Cancer Virus work. Staff of the Field Studies Area would be involved in four of the eight Program Segments outlined in the presentation before the NACC at the October 12 and 13 meeting. The expanding Special Viruses Leukemia Program consisted of four parts: resources and logistics; testing and monitoring; epidemiology; and biohazards control and containment. The NACC endorsed the projected Program.

1965

By the end of 1964 the pace of research findings had picked up, and, with the new monies for the Special Virus Leukemia Program, greater progress still would be made. In addition to the techniques of virus identification by tumorigenicity and infectivity and the demonstration of type-C virus particles by electron microscopy, immunofluorescence studies and complement fixation investigations were ready for further development. These developments would require production of larger amounts of reagents, especially large amounts of better quantifying antisera of various types - and testing and monitoring procedures - and other resources such as specimens of human and animal sera and tissues, including acute leukemia specimens; tissue cultures of various cell lines; several species of animals and animal model systems; vaccines that produced protection against animal tumor viruses (polyoma, Rauscher, and Friend viruses); production of platelets and granulocytes by special centrifugation techniques

for transfusion to leukemia patients to combat bleeding and infection; and additional considerations on biohazards control and containment. Considerable confusion still existed about the relationships of the members of the four families that contained tumor-causing viruses (Papovaviruses; Adenoviruses; Poxviruses; and the Myxovirus-Like Group), partly because some viruses, like the Rous virus, were incomplete and required helper viruses for the Rous virus to reproduce. In none of these groups is every member known or suspected to be tumorigenic. Also, the animal test systems themselves were contaminated. Concerning epidemiologic patterns of tumor virus infection, there was no common denominator. Polyoma virus spreads by contact with infected urine, fowl leukosis and probably mouse leukemia viruses are transmitted transovarially, or possibly in the latter case, transuterinely; the mouse mammary agent and laboratory strains of mouse leukemia viruses are milk borne; the mammary agent can also be transmitted vertically; fibroma virus is mosquito borne; and wart viruses are probably spread by fomites (see Wally P. Rowe, "A Survey of the Tumor Virus Problems from an Epidemiological Standpoint," *Cancer Research*, vol. 25, No. 8, pp. 1277-1282, September (1965)).

Knowledge of how these viruses spread is essential for future epidemiology investigations. Some of the research findings at this stage at the molecular level would have far-reaching implications for understanding aspects of molecular biology and for the development of biotechnology. A key finding was evidence of persistence of the viral genome in virus-induced tumor cells, often with specific modification of the cells due to partial expression of the genome. Also at this stage, at the molecular level, Maurice Green at St. Louis University, an active participant in the Special Virus Leukemia Program, was demonstrating differences between the DNAs of the non-tumorigenic Types 2 and 4 adenoviruses and the tumorigenic Types 12 and 18. DNAs of types 2 and 4 have 56-57% guanine-cytosine while those of Types 12 and 18 have 48-

49% guanine-cytosine. These findings suggest that the tumorigenic adenoviruses may have evolved from the nontumorigenic viruses through loss of a piece of DNA rich in guanine-cytosine. It is also possible that tumorigenic and nontumorigenic adenoviruses, although possessing in common certain properties which lead to their classification as a family, may be genetically unrelated. Green also observed that the four DNA-containing viruses that produce tumors in mammals, *viz.*, adenovirus Types 12 and 18, the polyoma virus, and the papilloma virus, have similar base compositions. It also seemed possible that the tumorigenic potential of a virus might depend on the existence in its DNA of a region homologous in structure to a region of DNA of the host cell. If such a segment of host cell DNA combines with, or is replaced by, the tumor virus DNA, the functions controlled by this region of host cell DNA would come under the control of the tumor virus DNA; i.e., the end result might be expressed as a take-over of the control of cell division (See Ed Lennette, "Formal Discussion of a Survey of the Tumor Virus Problem from an Epidemiological Standpoint," *Cancer Research*, Vol. 25, No. 5, pp. 1286-1288, September (1965)). [These investigations were the forerunners of the identifications of gene sequences of oncogenes - 1969, and proto-oncogenes - 1973]. Also by 1965 important advances in chemotherapy of leukemic children had been achieved. Combination of four drugs (vincristine, amethopterin, 6-mercaptopurine, and prednisone) given simultaneously was producing long-term remissions or possibly cures. With these four drugs the desired chemotherapeutic effects were cumulative while the adverse toxic effects were not, thus allowing increased doses for treatment without increased toxicity. The transfusion of platelets and granulocytes and the placement of patients in a "life island" with a controlled "germ-free" environment reduced deaths from bacterial and fungal infections, a serious problem for patients

whose bone marrows and immune systems were damaged by the chemotherapeutic drugs. Money from the Special Virus Leukemia Program helped fund therapy parts of the Program.

Working Group Meetings

Many meetings were held during the first half of 1965 with the working groups. Also many meetings were held with the Chairmen of the working groups with the OD Science/Management Team and among the Chairmen. Within dollar limits, priorities were hammered out, existing projects were modified, and new projects were proposed. Thus, these committees were not just reviewing proposals, but they were also engaged in planning new efforts in research and in the production of needed resources. In May, proposals were presented before the Scientific Directorate for approval or modification. Preliminary estimates were developed for additional Program efforts for Fiscal Year 1966. These actions were taken to meet the objectives in the Special Virus Leukemia Program. Attention was given to requirements of data flows and reporting, as well as scientific information and administrative and accounting requirements. By June 30, 1965, all planned projects were officially executed as research contracts. The NCI staff put forth unusual efforts to meet these tight deadlines.

Emergency High Hazard Facility

On February 1, 1965, a memorandum was sent to the Director, NIH, from Dr. Endicott requesting special construction authority to build an emergency high hazard facility on the NIH campus. This request was made because the various viruses being worked on were potentially dangerous to those investigators working with these viruses, and immediate action was needed to protect them. The Office of the Secretary, HEW, approved the request on April 12, 1965. The

designation of the building as a temporary, emergency structure, which at that time was an appropriate designation, allowed progress on the actual construction to proceed at a much more rapid schedule than was usual to move through the morass of construction authorities and approvals. An amount of \$2.8 million was reserved for construction in Fiscal Year 1966. Gordon Zubrod, Director of Intramural Research, and Bill Payne, Chairman of the Biohazards Control and Containment working group, developed the coordination of activities for this contract. Dr. Payne, other NCI scientists, and the Biohazards Control and Containment working group also developed requirements for a research and development contract in biohazards control and containment (to include the design, mockup, testing, fabrication, and installation of new equipment, instrumentation, procedures, etc.). After a meeting with potential contractors where the Program and the requirements of the contract were explained and questions were answered, the working group reviewed proposals from five potential contractors. On approval April 27, 1965, a contract was awarded for the first of five phases with a ceiling of \$990,000 from 1965 funds. On authorization of the U.S. Congress for special construction, NCI contracts were awarded to universities for the construction of three buildings for studies of bovine leukemia and one building for studies of cat leukemia.

Special Virus Leukemia Program -- End of F. Y. 1965

With the end of Fiscal Year 1965 on June 30, 1965, the Science/Management Group sent on August 3 a summarizing memorandum to members of the working groups. Part of this memorandum follows:

In a span of approximately eight months, the chairmen and working group members have developed detailed program plans for their respective areas, and accomplished the difficult task

of developing and reviewing numerous research projects which have been officially executed as 48 research contracts. As of the close of the books for fiscal year 1965, \$9,932,000 of the \$10,000,000 appropriated has been obligated. It is realized that the fast pace of activities required for this accomplishment has left insufficient time for working group members to acquire a detailed knowledge of the individual contracts developed by working groups other than their own.

Attachment I presents key information on each contract developed and implemented during the year. The contracts are listed by working groups to stay within the program structure of fiscal year 1965. It is hoped that this material will provide you with the necessary background information so that the tasks of developing new projects and modifying existing program elements can be performed against a complete knowledge of the total program.

There will be some attempt to establish a better distribution of contract renewal dates by fiscal year quarters so as to reduce the heavy concentration of contract reviews that usually takes place in the third and fourth quarters. If this can be practically accomplished, you will receive an updated list of contracts reflecting any changes in renewal date.

Attachment II presents a summary breakdown of the number of contracts and the amount of funds obligated by the working groups.

Attachment III is a summary report of both the scientific and administrative activities accomplished in the program for the time period September 1964 through June 1965.

Attachment IV presents a reiteration and discussion of the main underlying program assumption.

It became increasingly apparent during the year that areas of overlap between the functions of the working groups on Developmental Research, Production, and Resources and

Logistics were resulting in an uneven degree of participation by these groups in the program and in confusion as to which group had the responsibility of soliciting, developing, reviewing, and requisite monitoring of various production type contracts. After several discussions with the chairmen of these groups, it seems desirable to effect the following changes:

Eliminate the working group of Production at this time and re-align its membership with the Developmental Research and Resources and Logistics group as follows:

ORIGINAL MEMBERSHIP OF

PRODUCTION GROUP

NEW ALIGNMENT

Dr. Robert Manaker, NCI (Chairman) Developmental Research

Dr. Robert Couch, NIAID Resources & Logistics

Dr. Paul Gerber, DBS Developmental Research

Dr. Leonard Hayflick, Wistar Institute Testing & Monitoring

Dr. Alice Moore, Sloan-Kettering Inst. Developmental Research

Dr. Timothy O'Conner, NCI Developmental Research

Dr. Alan Rabson, NCI Developmental Research

With the end of the activities of the Special Virus Leukemia Program within fiscal year 1965, Dr. Ray Bryan has resigned as Chairman of the Developmental Research Working Group,

in order to devote full time to his heavy responsibilities as a senior program leader in the NCI.

Dr. Robert Manaker has agreed to succeed Dr. Bryan as Chairman of the Developmental

Research Working Group -- effective July 1, 1965. Dr. A.J. Dalton has agreed to continue as

Vice-Chairman.

Attachment V presents a new list of the members of each working group and includes the above changes.

The memorandum concludes with the reassignment of four contracts to Resources & Logistics and one to Developmental Research. The 48 contracts were distributed among the Program Segments as follows: 11 (\$2,163,724) -- Developmental Research; 5 (\$1,547,847) -- Production; 10 (\$2,279,165) -- Special Animal Leukemia Ecology Studies; 8 (\$1,115,595) -- Human Leukemia Therapy; 5 (\$812,936) -- Testing & Monitoring; 4 (\$357,129) -- Resources & Logistics; 1 (\$31,000) -- Epidemiology; and 4 (\$1,161,851) -- Biohazards Control & Containment. For Direct Operations (Personnel, Travel, Equipment, etc.), \$462,741 was obligated ("Program Materials," OD Science/Management Team to Members of Working Groups of the Special-Virus Leukemia, August 3, 1965).

August 13-14, 1965 NACC Meeting

In July 1965 systems planning (the "Convergence Technique") was applied to the Cancer Chemotherapy Program. *Monitoring Points* were added to the *Decision Points* on the systems networking chart for the Chemotherapy Program. It may be recalled that *Decision Points* require decisions that move the Program forward operationally toward the *Objectives* while the *Monitoring Points* require periodic considerations of whether the program itself needs modification. *Monitoring Points* were added to the systems network chart for viral oncology (SVLP).

At the August NACC meeting, an in depth review of the Cancer Chemotherapy Program was made; extensive information had been supplied to the Council members prior to the meeting. Dr. Endicott reviewed the history of the Program. Dr. Baker presented an extensive assessment

of current scientific data in the cancer chemotherapy field and discussed the dynamics of the Program's drug development activities through the various steps from acquisition of materials to use of drugs in the treatment of cancer patients. Dr. Zubrod presented program plans for a modified Chemotherapy Program, utilizing the systems planning chart developed with the "Convergence Technique." He stressed the opportunities available for future improvements from the data and the management apparatus developed over the past decade. He discussed in detail the conceptual basis and theories underlying screening and clinical trials and described plans to incorporate cell kinetics into the Program base. From the minutes of the Council meeting: *The Council expressed approval of the material presented and recommended that it be made available to the scientific community as a published monograph.* [The material was published as: Zubrod, G., Schapartz, S., Leiter, J., Endicott, K., Carrese, L., and Baker, C., "The Chemotherapy Program of the National Cancer Institute: History, Analysis, and Plans" - *Cancer Chemotherapy Reports*, vol. 50, No. 7, pp. 348-540, (1966).] The Council also noted that this in-depth review was part of the regular, scheduled program review already planned before the action of the Wooldrige Committee. *The Council then adopted the following motion:*

"That the Council supports the general approach to cancer chemotherapy as outlined in the presentation of new program, including the lymphomas, leukemias, and breast cancers, with the recognition that a) this will have some impact on other parts of the program because of the need to maintain during the current year the total program at roughly the current level and b) as the program evolves during the coming year and as significant shifts of dollars are made between segments of the program, the Council would expect these shifts to be reported to it for such advisory inputs as it would wish to make in the evolution of the program during the coming and subsequent years." Members of the Council at the meeting were: Walter J. Burdette, Salt

Lake General Hospital; R. Lee Clark, M.D. Anderson Hospital and Tumor Institute; Philip P. Cohen, University of Wisconsin; Charles A. Evans, University of Washington; Sidney Farber, Harvard Medical School; Leo G. Rigler, University of California at Los Angeles; Philippe Shubik, The Chicago Medical School; Howard E. Skipper, Southern Research Institute; Joseph L. Melnick, Baylor University College of Medicine; Rubin H. Flocks, University of Iowa; and Lyndon E. Lee, Jr. (Ex Officio), Veterans Administration.

Considerable discussion was held on the role of the Council with respect to contracts and the Collaborative Research Programs. There was general agreement that the Council could not spend time reviewing every grant application, nor every contract. However, by law no grant could be awarded without approval of the Council; such was not the case with contracts. Some believed Council approval should be required for each contract as well. If this approval were instituted, it would have run in the face of general Government contracting policies and practices. One Council member considered the role of the Council in review of Collaborative Programs and the corresponding contracts “confusing” and “a vexatious and disturbing issue,” “an issue only because it was misunderstood.” He moved, and the Council agreed, *“that the Director work out a simple system at every Council meeting, special or regular, of having a short review of the contracts which have been awarded since the last meeting, the areas in which they are, and any other information that would be important for the Council to know, so that the Council could then advise the Director in a better informed manner on planning and on the overall missions of the Cancer Institute.”* The Director agreed to the motion and suggested that the motion be amended to *“include not only a report of contracts which have been let in the intervening period but plans for invitations for proposals.”* The amended motion was accepted.

On September 1, 1965, Dr. Shannon sent to Mr. Herman Downey, the Clerk of the Subcommittee of the Senate Committee on Appropriations, the material in the verbatim transcript and the minutes of the NACC meeting of August 13-14, 1965 [excerpted in the above two paragraphs]. This was done because Senator Hill, Chairman of the Senate Committee, had been told that the Chemotherapy Program was spending too much money and was not getting results and that the NCI was not providing the NACC information on the Chemotherapy Program or on contracts. The memorandum and the attachments were sent to Senator Hill to refute the charges.

Hearings Before Congressman Rogers Subcommittee

On September 1, 1965, Dr. Endicott, Dr. Baker and Mr. Learmouth appeared before the Rogers Subcommittee (2-6:15 p.m.) and were queried on a wide range of subjects. The Subcommittee staff displayed a lively interest in the evolution of the organization and programs of the NCI and particularly in those areas of applied and developmental research which were funded by contracts. They were especially interested in the planning functions and the charting techniques used for the Virus-Leukemia and Chemotherapy Programs. The Congressman expressed the view that support for free roving research through the grants activities was overdone and that expansion of applied and developmental research through contracts would provide society with practical answers to urgent problems at an earlier date. NCI was commended for consolidating the administration of grants and contracts. There were questions about the working relationships with the Bureau of State Services in cancer control and environmental carcinogenesis and about pros and cons of an annual authorization in lieu of the current open ended enabling legislation. Mr. Rogers seemed to favor annual authorization. An

interesting set of questions were: (1) Would NCI be better off if it were an independent agency? (2) Would NIH be more effective if it were not a part of the Public Health Service? (3) Should the health function be given an independent departmental status? and (4) If the present department is maintained, should there be Under Secretaries for Health, for Education, and for Welfare? The following materials were supplied to the Subcommittee:

A. A list of accomplishments of the Cancer Chemotherapy Program.

B. A list of key research developments in carcinogenesis.

C. A general statement on cancer research developments since 1937.

D. A list of research grants and contracts for Fiscal Year 1964 classified in areas of cancer research.

E. A progress report on the first year's operation of the Special Virus-Leukemia Program.

F. A memorandum dated November 5, 1965 to the NACC from the Associate Director for Program entitled "External Contract Research Centers," which outlined a plan for a major, multipurpose research and development, contractor operated facility (Appearance before the Rogers Subcommittee, September 1, 1965," Director, NCI, to Director, NIH, September 2, 1965).

Organization of NCI Extramural Research

As a follow-up to Dr. Endicott's memorandum of July 15, 1965, on the reorganization of NCI, Dr. Phillip Waalkes, who succeeded Dr. Ralph Meader as Associate Director for Grants and Training, sent on October 25, 1965, a memorandum to the Staff, Extramural Research, NCI.

Dr. Meader retired after over 17 years service in NCI as head of the Grants and Training activities. Excerpts of the memorandum follow:

Although still awaiting final approval, it is planned to proceed as rapidly as possible to operate in accordance with the proposed new organization for Extramural Research which includes the Office of the Associate Director and five operating areas. Under this arrangement, within the Office of the Associate Director, Dr. Samuel Herman will act as Deputy Chief for Extramural Research. Mr. George Brandner, while retaining his position as Chief of the Grants and Research Contracts Operations Branch, is now part of the Office of the Associate Director.

The remaining four areas of Extramural Research, the individuals acting as heads, and the professional staff are as follows:

1. Program Review and Evaluation - Dr. Robert Greenfield.

Working with Dr. Greenfield, the professional staff includes Dr. Nadkarni and Dr. Lauri Luoto.

2. Special Programs Branch - Dr. William Walter.

Tentatively, Dr. Carl Hansen, Jr. has been assigned to work in this branch.

3. Awards Review and Technical Administration Branch - Dr. O. Malcolm Ray.

Professional staff assignments include Dr. Arthur Skipper and Dr. Ruth Lyman.

4. Cancer Therapy Evaluation Center - Dr. Margaret Sloan.

Working with Dr. Sloan will be all the professional staff who were members of the Clinical Branch of Collaborative Research (“Organization of the Extramural Research Division of NCI,” Associate Director for Grants and Training, NCI, to Staff, Extramural Research, NCI, October 25, 1965).

Ethical and Moral Aspects of Clinical Investigations

NIH began a new review of ethical and moral issues related to clinical investigation in the Fall of 1965, well before the subject became prominent with the laity. When the Clinical Center was established in 1955, guidelines were formulated that aimed at ensuring the safety and welfare of patients participating in clinical investigations. Dr. Jack Masur, the first Director of the Center, always insisted that the patient's welfare should always take precedence over the needs of the research. A committee chaired by Dr. Nathaniel Berlin, the NCI Clinical Director, was appointed to review the experience at NIH in this area and suggest any needed changes. The committee met thirteen times, mostly with the Clinical Directors of each Institute. The Executive Secretary of the NACC Subcommittee on Diagnosis and Treatment, Dr. Margaret Edwards, reviewed the ethical standards of 21 professional societies and the committee provided information on their practices regarding ethics policies.

The committee suggested a number of changes, mostly to clarify and elaborate the existing definitions, policies and practices. For example, the definitions of classes of patients were enlarged and the details of informed consent were expanded. The use of group actions was clarified. A review of the Outpatient Department was recommended. As before, the Clinical Director of an Institute has the ultimate responsibility for patient care in that Institute. He is the senior physician in that Institute ("Ad Hoc Committee," Dr. Berlin, Chairman, Ad Hoc Committee, to Members of the Ad Hoc Committee, September 9, 1965).

It is of interest that at about this same time this subject was looked at by Mr. Edward Rourke, Assistant General Counsel, Office of the PHS Surgeon General. In an astute memorandum dated October 26, 1965, to Surgeon General William Stewart, he pointed out that very little had been done anywhere to bring to bear on the subject attention from outside the

medical and scientific research fields, including the law. He predicted that the public was very likely to want to have a greater say about how clinical investigations would be carried out. He stated:

The judgements that will in the long run have the significant impact on clinical research will be those of the courts, Congressmen, trustees, and other “lay” representatives of the public. What I feel is overdue is recognition by the medical scientist that he will not ultimately make the rules that will govern his work in this area and that he can at best hope that those who will make them will have an adequate understanding of his problems and of the values he serves with such dedication.

If this be so, the time has long since come to move out of the medical-scientific context with its preoccupation with morals and ethics, and at least for the scientist to share the problem and, if he be allowed, the responsibility for its solution with others. The risks of doing so are obvious, but to continue in an isolation that has been largely characteristic to date only postpones an inevitable accounting with, I think, greater risks to the total research effort.

I say “preoccupation” with morals and ethics partly in sympathy with the scientist who, when faced with a problem not subject to the scientific discipline, apparently can think of nowhere else to turn, and partly with impatience for the almost pathological urge to ignore or minimize the basic, operative mechanism of society that sets the standards for the conduct of all of us -- the law. The scientist may not like the judgements the law is likely to make, but he can hardly ignore them for long and flourish.

This brings me to my second point. The law to date is hardly as vague and uncertain as it is sometimes made to appear, if attention is paid to it at all. Certainly how far it will go in the future to provide a secure basis for clinical research is not clear, and at present it provides no

such basis for manipulative research on children or the mentally incompetent. But it begins firmly with the competent patient's or subject's free right to control the use of his person whether the purpose be diagnostic, therapeutic, or research. Only the individual, with all his ignorance, superstitions and foibles, can make the important choice and, being fully informed as possible, he is free to make it for particular reasons or for no reasons at all. While I do not mean to exclude other considerations, the basic proposition is that the decision to be a subject of research is not one to be made by the physician or scientists but one to be made by the subject.

It is the failure to observe scrupulously this one principle that will cause lay or public outrage and lawsuits that may threaten the whole field of clinical research. And I suspect that it is the scientist's awareness that this principle is not always observed that disturbs him deeply and sends him groping for moral and ethical guides. I also suggest that scrupulous observance of this principle will reduce the problem to where it might be left largely to the scientific community to measure, as only an expert can, whether the potential scientific gain is worth the risks the patient or subject knowingly is asked to take. Granted the principle may need refinement and that, even so, it may in application prevent certain research from being conducted. But in general the use of human beings for research without their informed consent is not likely in my judgement to be accepted by our law or other aspects of our "lay" society however important to society that research may be.

More sophisticated statements of such a principle and of "codes" of conduct are possible, and several are available. Although none are beyond some criticism, both from the legal and other points of view, they fairly represent a consensus appropriate for utilization. I thus suggest a major problem is not to develop another formulation. Instead, it seems to me the

greater need for the PHS is to define to what extent it has responsibility in the application and enforcement of the principles that are generally accepted.

Rourke suggested that the Public Health Service make a broadly based effort to delineate the PHS responsibility expressly in the grant area so that harm that arises beyond the reach of this delineation can fairly be said, in any quarter, to be the responsibility of others -- those who will and should remain in control of the situation -- the investigators and their institutions. [These observations of Mr. Rourke showed great prescience as can be seen from later developments in gene cloning, gene therapy, gene modification, and other advances in molecular biology and biotechnology.] (“Clinical Research,” Edward J. Rourke, Assistant General Counsel, to Surgeon General, PHS, October 26, 1965.)

Heart Disease, Cancer, and Stroke Amendments of 1965

The Heart Disease, Cancer, and Stroke Amendments of 1965, Public Law 89-239, 89th Congress, was signed into law by President Lyndon Johnson on October 6, 1965. President Johnson had established a Commission on Heart Disease, Cancer, and Stroke on February 10, 1964 with Michael DeBakey as Chairman; Sidney Farber, Lee Clark, and Frank Horsfall constituted the Subcommittee on Cancer. The Commission recommended the creation of “a national network for patient care, research and teaching in heart disease, cancer, and stroke.” At the apex of the network, 20 cancer centers were to be established within 5 years; at the base, 200 diagnostic and therapeutic stations were to be established. Each center would be distributed geographically to serve about 10 million in population. The cost for cancer activities was estimated to be \$2.98 billion over 5 years (\$357 million the first year). In the 1950’s Lee Clark, with support by Sidney Farber and the NCI, established the American Association of Cancer

Institutes. Dr. Clark visualized this group as eventually forming the base for the network recommended by the Commission. Farber and Clark and Mary Lasker wanted a network of cancer centers each like the existing comprehensive centers (Memorial Sloan-Kettering Cancer Institute, M.D. Anderson Hospital and Tumor Institute, Roswell Park Memorial Institute, and the National Cancer Institute). Ten other centers of less comprehensive scope, including Dr. Farber's Children's Cancer Research Foundation, were functioning. They wanted the centers to be independent from the medical schools and closely tied to NCI. They were thwarted in the first instance by the legislative process and in the second by the Administration. The contents of the Bill as finally signed by the President on October 6, 1965, bore little resemblance to the recommendations of the Commission. The concept was weakened, e.g., "complexes" became "programs"; "coordination" became "cooperation"; and the categorical emphasis was lessened. Cancer received only 8% of the money of the Regional Medical Program, the program at NIH established to administer the Heart Disease, Cancer, And Stroke effort. This proposed extension of medical care with government support failed. Mary Lasker was very disappointed ("A National Program to Conquer Heart Disease, Cancer and Stroke," President's Commission on Heart Disease, Cancer and Stroke, February 1965, pp. 105-128).

The November, 1965 NACC Meeting

At the NACC November meeting, members focused on a presentation given on the e Field Studies Area Program on November 15, 1965. Included in this review was the program of the Virology Research Resources Branch. Material was provided to members of the Council prior to the meeting (28 pages of the 82 pages of total text were for the VRRB Program, and all contracts for Field Studies were listed). This material described how the with the added appropriation for the Special Virus Leukemia Program, the viruses-cancer activities had moved

into high gear, especially in the production, certification, distribution and use of supporting resources. Some of the highlights of the program's activities included the following: over 300 serologically distinct viruses had been recovered from humans. In order to maintain this success, it was projected that homotypic diagnostic reagents were needed in larger quantities, including those for the simian viruses. There had also been increased production on avian tumor viruses, antigens, antisera, and control sera; 400 sera per month were being used to make a diagnostic survey of breeding colonies. Fluorescent antibody procedures had been refined and several population surveys were planned for the future. Dr. John Bader was producing sufficient amounts of Rous associated viruses (discovered by Dr. Harry Rubin) to distribute samples to other investigators. A tissue culture of myeloblasts had been established, and herpes-like virus particles had been seen on electron microscopy in the cultures. In the CCNSC Program, 12 additional characterized cell lines were established (these added to the American Type Culture Collection make a total of 37 certified cell lines). Standardization had been imposed on cell culture media and serum supplements; fetal calf serum for tissue culture media had also been standardized. Diploid cell lines were being distributed to requesting investigators. Improvements were continuing to be made in the design, fabrication and use of special high speed zonal ultracentrifugation rotors, permitting greater purification of virus preparations for further studies on tumor-causing and other virus preparations (in other fields, better vaccines had already been produced by this new technology). Developmental research had been applied to produce new and improved laboratory animals, including the marmoset, bushbabies, and tree shrews; diseases and lack of knowledge of norms of physiology plagued the use of imported monkeys, but these problems were corrected to allow not only clean animals, but adequate supplies of newborns in captivity. A battery of diagnostic reagents for detecting latent mouse viruses had been applied to

a surveillance program for mouse production colonies; a symposium and training courses on the use of the reagents were established. RIF-free chicken eggs (eggs free of resistance-inducing factor needed for virus assays) were sent out to investigators and breeders (170 dozen eggs sent). A mycoplasma screening service had been established and a problem with contamination of tissue culture cell lines had been corrected. Developmental research was being applied to determine optimal freezing and thawing parameters for cells and cell lines. A contract to produce germ-free hamsters had not been successful. A major effort was being made to establish a tissue procurement system that would overcome the difficulty of individuals to obtain human embryonic tissues and specimens from cancer patients, especially leukemia specimens. During 1965, about 730 sterile autopsies were performed; from these, 14,000 vials (1 gram of tissue per vial) were collected and 10,000 vials were delivered to 75 investigators. Of 500 requests for tissues, about 95% were met. Screening of known oncogenic viruses was being made in monkeys and baboons. Dr. Maurice Hilleman of Merck Sharp & Dohme had been a grantee for years; however, a ruling from the Surgeon General no longer allowed staff of commercial organizations to have grants. NCI quickly awarded a contract for Dr. Hilleman because of his outstanding research, especially on vaccines. He had demonstrated that Adenovirus Type 7 and SV40 viruses were oncogenic. He had also showed that protection against large doses of infectious oncogenic virus could be achieved by subsequent immunization with irradiated, killed tumor cells transformed by the same virus type. At this time the only method for determining the sizes of viruses was filtration through “gradacol” membranes. The VRRB extended their production from England with a small contract without which these membranes would not have been available. Also at this time virus preparations were beginning to be highly purified, and new physicochemical procedures, including use of the special ultracentrifugation rotors, were being

refined as resources that could help determine the detailed structure of oncogenic viruses. Thus, the stage was set to determine which parts of the smaller oncogenic virus molecules were actually producing oncogenic changes in cells, which parts were necessary for replication of virus, and which parts were for other functions.

The total dollars for viruses-cancer studies in the Field Studies area for Fiscal Year 1965 was \$6,028,300 and budgeted for Fiscal Year 1966 \$7,511,700. As a result of reorganization, transferred two groups from the Intramural part of NCI to the Field Studies area: 1) the Viral Oncology Section (from the Laboratory of Viral Oncology) to become the Viral Leukemia & Lymphoma Branch (Dr. Rauscher); and 2) the Laboratory of Viral Carcinogenesis to become the Viral Biology Branch (Dr. Dalton). Dr. Stevenson's VRRB would be designated the Viral Carcinogenesis Branch. With these changes, the total amount budgeted for viruses-cancer work in Field Studies would be about \$11.5 million and would add 65 positions; \$3.5 million was budgeted for the new special hazard building ("Field Studies Area Program Presentation to the National Advisory Cancer Council," Program Review Book, November 15, 1965, pp. 55-78).

External Contract Research Centers

At the October 1965 NACC meeting there was a general discussion on the desirability of creating for biomedical research organizations similar to those sponsored by other Federal agencies (e.g., IDA, RAND Corporation, MIT Lincoln Laboratory, etc.) for the performance of evaluative, analytical, planning and other functions.

The Council asked NCI staff to prepare a brief statement on these organizations and some typical assignments might be given to such organizations. On November 1965 the Associate Director for Program sent to the NACC a ten-page document identifying 61 such center, an

analysis of the types of activities performed, working agreements with sponsoring agencies, etc. Ten tasks were outlined to illustrate some of the assignments NCI might make if External Contract Research Center were in operation. Following discussion no clear recommendation was made (“External Contract Research Centers,” to the Members, National Advisory Cancer Council from the Associate Director for the Program, November 5, 1965).

Scientific Directorate Functions

On November 29, 1965, Dr. Endicott sent to members of the Scientific Directorate a detailed set of instructions for operations of the Directorate, including program and contract reviews. The NCI had completed its reorganization and had received approval from the Surgeon General. The reorganization effort extended over three years (see Scientific Directorate minutes for August 21 and September 4, 1962; April 2, June 28, July 2, and July 15, 1963; June 30 and July 14, 1964; and March 9, October 5, and October 19, 1965; these informative documents reveal recurring problems, a variety of proposals, and absence of clear consensus on the best manner in which the Directorate is to conduct its evaluative role). Dr. Endicott’s November 29 memorandum listed six roles for the Scientific Directorate:

- 1. Broad policy development and formulation.*
- 2. Evaluation of programs and program plans.*
- 3. Coordination of programs.*
- 4. Resolution of differences between a Scientific Director and a Program Review Committee or a Contract Review Committee.*
- 5. Primary review of contracts of critical program significance for which review by established committees would be inappropriate.*

6. *Review of proposals for promotion of senior professional staff.*

The memorandum goes on:

Evaluation of programs and program plans (item 2.) has repeatedly engaged the attention of the Directorate. The major decisions are decisions on programs (i.e., in comparison with decisions on individual contracts) since these decisions broadly determine whole series of far-reaching subsequent actions and additional decision-making frameworks. For example, such program decisions should be made prior to the invitation of new project proposals (contracts or grants). Moreover, major program decisions need to be made within the full perspective of the total NCI program if the appropriated funds and other resources are to be most effectively allocated and used for cancer research. Because the NCI is a public agency, our reviews of programs (including contracts) must not only be sound, but visible, and soundly documented. Recent actions of Congressional committees (Senate Appropriations Committee Report on the 1966 Supplemental Appropriation, pages 32-33; see also the Conference Report, pages 7-8), and of the National Advisory Cancer Council (minutes of the August 1965 meeting), emphasize this need for the Scientific Directorate to review all NCI programs within the overall Institute perspective.

The Directorate must assure itself that individual contracts are reviewed well for intrinsic merit. But, as it has agreed in the past, this does not mean that it must review each contract proposal individually. Once a system of satisfactory program review has been developed, the Directorate may feel it can depend primarily upon program quality to reflect, in summation, the quality of an area's contract reviews. It does have the responsibility for assuring the Director that contract proposals are receiving sound review. (See below, CONTRACT REVIEWS.)

PROGRAM REVIEWS

The outline below of review of program plans for the four newly organized major program operating areas (General Laboratories and Clinics; Extramural Activities; Etiology; and Chemotherapy) is based on recent discussions of the Directorate. Each program leader will annually present a description of his program and program plans. Major objectives of the area, program logic with consideration of optional approaches, and program plans extending beyond the following year will be presented, but emphases, selection of detailed items for discussion, and the format of presentation may vary with the program area.

Programs of the Etiology and Chemotherapy areas will be described in broad strokes, showing program philosophy, logic, objectives and relationships. Charts showing integration of program elements will be used as appropriate. Emphasis will be given to contract-supported efforts. The presentation should include plans for shifts in contractual activities when needed, to bring ongoing efforts into line with program objectives and plans. Summaries and progress statements of individual contracts (see below) should be included. From time to time program leaders may bring before the Directorate general and specific problems concerning contracts or, with respect to internal operations, plans for major changes involving space, positions, dollars, and other resource needs. Efforts that may have substantial impact on other program areas will be specifically identified.

In the area of General Laboratories and Clinics the Scientific Director will present a program review with the following elements: (1) broad philosophy, hopes, aspirations and objectives; (2) program plans of major scope and direction with an indication of changes contemplated involving substantial space, dollar and other resource needs and contract

demands; (3) work undertaken that will have a substantial impact on other program areas, particularly when it involves contracts; and (4) issues on which he would like advice from the directorate.

In the Extramural Activities area the Associate Director will present, in very broad strokes, objectives in the grants area with some assessment of the scientific content, deficiencies and plans for new areas in which the grants staff will make special efforts. Emphasis will be on: (1) selected information he judges to be valuable for the Directorate, including periodic assessment of a system of contracts and grants review; (2) cross-impacts upon other areas, e.g., programmed grants in chemotherapy, centers grants, single instrument support, etc.; and (3) items on which he would like advice from the Directorate.

The primary benefits of program reviews result from the program leaders and their staffs pulling together in an integrated manner the various activities within the program, juxtaposed against program objectives in such a way that priorities can be more easily established by them. The requirement for written statements, which are necessary as part of the annual review for the Council and for other purposes, further aids in sharpening up program activities. Such written material should also form the basis for required NIH annual reports and for budget development. In these presentations special efforts must be made continually to include plans on a longer-range basis (in the perspective of at least three years). With such reviews and documentation the Scientific Directorate will be in a better position to carry out its role of evaluation of programs and program plans.

The next sections of the memorandum set forth detailed requirements for CONTRACT REVIEWS and INFORMATION FOR NACC (based on motions of the Council at its recent meeting). The final part of the memorandum is:

IMPLEMENTATION OF THESE POLICIES

All NCI staff are responsible for carrying out the duties indicated for them in this memorandum; the focal point for implementation, however, is the Associate Director for Extramural Activities. He will issue the required detailed procedures in writing and establish the new contract review committees (Etiology Contract Review Committee; Drug Development Contract Review Committee; Drug Evaluation Contract Review Committee; Endocrine Contract Review Committee).

The various Scientific Directors should now send their nominations for membership on the appropriate contract review committees and program review committees for the Etiology and Chemotherapy areas to me through the Associate Director for Extramural Activities.

The Personnel Officer will prepare the necessary instructions for implementing the promotion reviews (see minutes of the Directorate, October 19, 1965. Promotion reviews will be conducted by the Core Members of the Scientific Directorate (see attached membership list of the Directorate).

I look forward to having this new system in full operation by the end of this calendar year.

The attachment to the memorandum:

Membership of the NCI

Scientific Directorate

Members (Voting):

Core Members:

C. Gordon Zubrod, Chairman

Paul Kotin, Vice-Chairman

Carl G. Baker, Executive Secretary

Nathaniel I. Berlin

Robert E. Learmouth

Eugene J. Van Scott

T. Philip Waalkes

Other Members:

W. Ray Bryan

William M. Haenszel

Samuel S. Herman

Seymour Perry

David P. Rall

Saul A. Schepartz

Margaret H. Sloan

Associate Members (Non-Voting):

George A. Brandner

James F. Kieley

Deputy Scientific Directors may substitute for Core

Members when absent (no other substitutions).

Attendance by others will be by invitation only (“Scientific Directorate

Functions (including Program and Contract Reviews,” to the Members of the Scientific Directorate, National Cancer Institute from the Director, National Cancer Institute, November 29, 1965).

1966

Completion of the NCI Reorganization

In a memorandum dated February 1, 1966, Dr. Endicott announced the approval of the Surgeon General of the NCI reorganization. The main changes in addition to those listed above were: Dr. Eugene Van Scott would become Scientific Director for General Laboratories and Clinics; and Dr. T. Philip Waalkes would become Associate Director for Extramural Activities. Dr. Samuel S. Herman would be the Deputy Associate Director for Extramural Activities and there would be four Branches: Special Programs Branch (Dr. William A. Walter); Awards Review and Technical Administration Branch (Open); Cancer Therapy Evaluation Branch (Dr. Margaret H. Sloan); and Grants and Research Contracts Branch (George A. Brandner). As indicated above transferred from the Intramural Area were: Dr. Ray Bryan and two Branch Chiefs and their staffs (Dr. Dalton and Dr. Rauscher). Dr. Stevenson's VRRB became the Viral Carcinogenesis Branch.

Meeting on February 5-6, 1966 of the NACC Subcommittee on Heart Disease, Cancer and Stroke

On February 5, 1966 the Council Policy Subcommittee on Heart Disease, Cancer and Stroke (Drs. Sidney Farber, Chairman; Philip Cohen; Roger Egeberg; and Ruben Flocks) met with members of the Association of Cancer Institute Directors for discussion of the Heart Disease, Cancer and Stroke regional program developments. This joint meeting, followed by a day's meeting of the Subcommittee itself, would bring the participants up to date on activities in

the Heart Disease, Cancer and Stroke area and enable the Subcommittee to discuss implications for the NCI programs for the purpose of informing the Council at the March, 1966 meeting. The agenda for the February 6 NACC meeting included:

- 1) Report of trips to research organizations.....Dr. Endicott*
- 2) Review of Heart Disease, Cancer and Stroke.....Dr. Farber*
- 3) Discussion of ACID meeting.*
- 4) Implications of Heart Disease, Cancer and Stroke*

Activities for NCI programs.

- a) clinical training grants.*
- b) clinical research center grants.*
- c) radiation therapy.*
- d) chemotherapy.*
- e) cancer detection.*
- f) support of cancer institutes.*

The first issues discussed at the meeting was the reduction of NCI funds and the cutback of Collaborative Research monies as a result of the Wooldridge Committee recommendation. The amounts awarded for recommended competing continuation grants would be held to no more than the current amounts plus 5% increase. The Heart Disease, Cancer and Stroke Bill would possibly be a factor in reducing the funds made available to NCI.

Dr. Farber again raised the issue of the relationship between the NACC and the NCI staff, emphasizing the need to make it clear that the Council and staff work together in common toward the same goals. He stated that the staff should feel that Council meetings are useful and that the Council members must feel that they are useful. He thought the Council should not be

only an advisory group. The paper work prepared by NCI for the Council should be done only for a purpose and in less volume. (The large volume of paper work prepared by NCI had been in response to the Council's requests for more information).

Dr. Endicott reported on his visits to various organizations around the country and listed the places where programs in cancer could be developed if NCI received an increase in appropriated funds. These places included: University of Washington; University of Minnesota; a grouping of cancer organizations in the Detroit area; University of Iowa; at Houston at the M.D. Anderson Hospital and Tumor Institute and the Baylor College of Medicine; Tulane University; the University of Southern California; University of Pennsylvania; and Johns Hopkins University. San Francisco, he indicated, might be ready in two years. LSU had no interest. Dr. Farber thought Dr. Endicott gave a good recital of current possibilities. In Dr. Meader's visits around the country he found interest in cell biology in only one instance (Dr. Saul Kit at Baylor).

NCI already had received 40 applications for training grants totaling about \$5 million, though only \$3.4 million was available in the budget. It was expected that about an additional 100 training grant applications would be received in the fiscal year (totaling about \$5-6 million). In training grants in radiotherapy, additional equipment would be needed. Funds from the Heart Disease, Cancer and Stroke program should result in more support for additional service and educational programs in institutes, and NCI could come along behind them with research planning dollars followed by research dollars. There could be fluid institutional and regional funds within the regional framework of the new program (the Regional Medical Program). It was not clear in early 1966 how the Program would develop.

A Coordinated Research Program in Breast Cancer

In Fiscal Year 1966 the Congress provided an additional 1.650 million dollars to NCI for a more intensified effort in breast cancer research, The NCI Director appointed a special study group of experts to formulate a general plan to include basic, applied and developmental research on the etiology, diagnosis and treatment of breast cancer. The plan was developed with the use of the “Convergence Technique,” a systems planning scheme for research developed at NCI. The plan included a systems flow chart.

The study group concluded that sufficient information and research leads exist, and the techniques are available so that a productive research effort can be planned and implemented in three major areas of research in breast cancer: a) the development of effective programs for early case findings; b) the development of useful prognostic indicators; and c) the devising of improved therapeutic strategies based on the utilization of such prognostic factors. The recommendations included a proposed Breast Cancer Task Force that would serve as the operating mechanism for further detailed planning and implementation of a coordinated program. The Task Force approach represented an integrated, multi-disciplinary, problem solving endeavor, and this philosophy provided the general frame of reference for the planning efforts of the Group. Further detailed planning was judged to be the proper responsibility of the Breast Cancer Task Force General Plan for a Coordinated research Group (“a Program in Breast Cancer,” Dr. Mortimer Lipsett, Chairman Special Study Group and the Breast Cancer Task Force, April 13, 1966).

May 17, 1966 Meeting of the NACC *Ad Hoc* Group Concerned with the Information to the Council for Program Reviews

Still continuing to search for a satisfactory way to compile information considered the optimal content and amount of information judged necessary for program reviews by the NACC, Dr. Endicott had appointed at the March Council meeting an *ad hoc* group of NACC members to meet with NCI staff. The purpose of the meeting was to develop plans for providing the Council with requisite program information and its organization. The *ad hoc* group consisted of: Philip Cohen, University of Wisconsin, Chairman; Joseph L. Melnick, Baylor University College of Medicine; and Philippe Shubik, Chicago Medical School. Staff of the NCI in attendance were Drs. Endicott, Baker, and Waalkes and Mr. Brandner. The following account of the May 17, 1966, meeting is based on the minutes of this NACC *Ad Hoc* Group meeting. As a point of departure, Dr. Baker thought it would be helpful if the group was clear on the definitions of project reviews and program reviews, the latter of which, unlike review of grants, requires the concept of integrating each program and its review within the total scope of cancer research. He noted that the NCI Scientific Directorate, by devoting considerable time and effort on a continuing basis, had made progress in the complex task of reviewing broad programs and in the context of the total NCI framework. He indicated that there are diverse opinions as to whether programs can be reviewed adequately without project detail. Dr. Baker said he gathered that the Ruina Committee, the HEW Secretary's Advisory Committee on the Management of NIH Research Contracts and Grants, had been given the impression by some Council members that they received little or no program information on the Cancer Chemotherapy Program from the Institute. He recalled that the Council had been through three cycles of program reviews and referred to the extensive documentation on programs supplied to the Council in conjunction with program reviews. He asked for comments on the values and deficiencies of this type of

documentation and for specific indications of what information on programs was wanted by the Council. This request was not answered.

Dr. Cohen questioned whether the NCI had what it could call an evaluation basis of what was obtained for the contract monies over a period of time. He stated that in spite of the program information which had been made available to the Council each year, he had not seen what had been actually accomplished and how fifty million dollars had been spent. Dr. Baker indicated that the type of documentation in the green books for the Chemotherapy Program that had been presented to the Council (published in Chemotherapy Reports - see above) came closer to answering this question than anything else, certainly more than for an equivalent amount of money in the regular grants area. In the Program Review Documents presented annually to the NACC, dollar figures are displayed for each contract, for organizational groupings (sections and Divisions), and for various scientific areas. Progress reports are made annually for research advances.

Dr. Endicott reviewed the history of the three major program areas in which NCI had contract efforts: Chemotherapy; Carcinogenesis; and Virology. The Special Viruses Leukemia Program was funding work with contracts to many of the outstanding investigators who were receiving grant support, including those who made significant contributions to the polio research area.

In referring to some of the organizations participating in the contracts area, Dr. Cohen felt that the same level of assured competence may not exist as in the grants operation. He said that he was amazed at the number of organizations that were “rigged up” overnight and were participating in the contracts program. He indicated he had the feeling that with the contracts mechanism, NCI was spending a large amount of money on lesser odds of quality turnout than

with the grants mechanism. Dr. Baker pointed out that the objectives in the grants area differed from those in programmatic research and therefore questioned whether the criteria and procedures used for assessing competence and quality in the system employed for review of individual research grants were suitable for review of programmatic research efforts. To illustrate, he suggested applying a frequent question asked of the CCNSC effort to the regular research chemotherapy grants: “For all the money spent since 1955, what effective drugs have been discovered?” He stated he knew of none. But, he said, perhaps this was an inappropriate question to ask of the grants area just as some of the questions appropriate for the grants area may not be appropriate for programmatic research. It depended, he thought, on the objectives and the degree of integration of projects within a total program framework.

Dr. Cohen singled out one of the current CCNSC contractors receiving large contract support and did not think that this organization was geared to scientific knowledge commensurate to other scientific organizations. He wanted to know what the return was from the millions of dollars poured into organizations of this type. Dr. Endicott reported that at the time of establishment of the contracts in CCNSC, this particular laboratory was the only one in the country that was headed by an individual who was sufficiently competent in the biology of cancer to set up quantitatively reproducible screens on the scale required. The universities were not interested in undertaking this screening work so NCI persuaded this contractor to do it. Since this contractor was also receiving large grant support from NCI at that time, a decision had to be made whether to have grants and contracts money both mixed into the same research. A decision was made that research carried out there to implement needed program efforts would be funded through the contracts mechanism.

Dr. Shubik asked who should make the fundamental decision as to the scientific soundness of a program and decide whether or not a particular program is right for emphasis. Dr. Endicott said that he, representing the Surgeon General, in cooperation with the NACC, had the responsibility to make this decision, and that he did make many such decisions. However, oftentimes the decisions were made by Congress. Many forces affected the decisions and their implementation. Dr. Cohen did not believe that the scientific talent on the Council was such that at any given time the Council could give better scientific advice than could a study section or some special review group. Additional discussion followed on the different requirements for formulating and making decisions in broad program areas of cancer research compared to those in specialized disciplines for deciding on individual projects.

Dr. Melnick made reference to the first box on Flow Chart A in the Gray Book (Contract Program Review Procedures) which indicated that program area scientists originate projects. The procedures subsequent to that point in the flow, he thought, were handled very well by Mr. Brandner's office. Dr. Endicott pointed out that the ideas underlying the origination of projects could be obtained from scientists in the field -- whether program area scientists or scientists elsewhere. Indeed, responsible program management demanded it. Therefore, the program chief should seek whatever consultation he needed. Dr. Endicott was asked who determined which people were to be considered competent in a particular field. He replied that this decision was made at the Institute level by the same people deciding who was competent to serve as a Council or Study Section member [for the Council, lay members might be nominated by NCI but were generally appointed by levels above the NCI; sometimes non-lay members were also appointed above the NCI level]. He added that all nominees selected for advisory functions must carry his approval so far as NCI is concerned. He said there was little difficulty in deciding who the

leaders were in a particular field. Dr. Endicott mentioned that there might be more than one school of thought in a field, such as the virus field. It was expressed by Dr. Cohen that it should be the responsibility of the Council to identify major areas of interest and spell out what kind of program should be mounted.

Dr. Melnick referred to the informational material included in the Red Book regarding Microbiological Associates, Inc. He was concerned about the size of the program in dollars and the salaries received by the two Ph.D.'s involved in the contract. Dr. Endicott explained that this contract was additional NCI backup for Dr. Huebner's program and that the reason only two Ph.D.'s were listed was that most of the Ph.D.'s involved in this contract were located in Dr. Huebner's laboratory. Dr. Huebner and his staff exercised close and frequent scientific management over this contract. Dr. Melnick suggested that the documentation should indicate this and stated that he favored providing as much support to Dr. Huebner as he could utilize. Dr. Endicott spoke of the limited resources available to Dr. Huebner in the National Institute of Allergy and Infectious Diseases. He said that the Cancer Institute had taken advantage of Dr. Huebner's skills in the field of virology by allowing him to expand his capabilities within the framework of local contractors. Viral diagnostic reagents were also provided from this contract to qualified investigators.

Dr. Endicott suggested three alternatives for reviewing programs: (1) a device utilizing the staff with consultants; (2) Council subcommittee with NCI supporting staff; or (3) create an outside organization which is done to some extent by the Department of Defense. The *ad hoc* group was in favor of the second alternative. It was recommended that the following Council members be appointed to serve on the program planning subcommittee: Dr. Philip Cohen, Chairman; Dr. Emanuel Farber; Dr. Joseph Melnick; and Dr. Leo Rigler.

Mr. Brandner inquired about what contracts material would be presented to the Council at the June meeting. It was agreed that he should continue to present the same kinds of material as he had done in the past (Minutes of the NACC AD Hoc Group Concerned with the Information to the Council for Program Reviews,” June 8, 1966).

NACC Meeting of June 26-28, 1966 - The Ruina Report

The Wooldridge Committee called for yet another review of the Cancer Chemotherapy Collaboration Program by experts in the field. They were appointed to a committee chaired by Dr. Arthur Richardson (the Richardson Committee). The review and the Committee’s Report were excellent. The Report was generally supportive. Some managerial changes and additional pharmacology efforts were recommended. The Report was sent to the NACC prior to the June 1966 Council meeting (“Report of the Cancer Chemotherapy Collaborative Program,” a.k.a. “the Richardson Committee Report”, June 1966).

In addition to the reports of the Subcommittee on the Heart Disease, Cancer and Stroke Program and the Ad Hoc Group Concerned with the Information to the Council on the agenda, Dr. Endicott would present for discussion the Ruina Report (Report of the Secretary’s Advisory Committee on the Management of National Institutes Health Research Contracts and Grants). Dr. Shannon was also present for the presentation. Much of the discussion at the meeting of the ad hoc group was again covered at the Council meeting. The Ruina Report was very germane to the items discussed by the ad hoc group and the Council. More than anyone at NIH, Dr. Endicott and the NCI people were more attuned to planning, directed research, and application of research advances as soon as they became available. Nevertheless, Mary Lasker and Sidney Farber, both again on the NACC, used the criticism of the Collaborative Research areas by the Wooldridge

Committee to urge the Congress to require Cancer Council approval of each NCI contract. In the Fall of 1965 they went to see Senator Lister Hill, Chairman of the Senate Appropriations Committee, and asked that this requirement be mandated by the Congress. Mary Lasker claimed that the NCI had not given the Cancer Council any information on the Cancer Chemotherapy Program. However, as is evident from the material already presented in this history, many reviews of the Program had been held, each one accompanied by extensive documentation. Several were before the NACC; on August 13-14, 1965, the Council approved the comprehensive systems plan for the Chemotherapy Program (developed with use of the Convergence Technique). The October 19, 1965, Report of the Senate Appropriations Subcommittee on the Supplementary Appropriation Bill, 1966 contained the mandate urged by Mrs. Lasker and Dr. Farber. Not only would such a requirement reduce the capabilities of the NCI to manage the complex programs requiring integration of component parts, but such a mandate would also alter the pattern of governmental contracting in general. Dr. Endicott appealed to Dr. Shannon who in turn went to see Representative John Fogarty, Chairman of the House Appropriations Committee. Fogarty said he would need a letter from the Secretary of Health, Education and Welfare, John Gardner, if he were to intervene. On October 20 Secretary Gardner wrote to Representative Fogarty stating that such a fundamental change in policy called for should not be considered without a thorough study. He promised to initiate immediately such a study. The restrictive language was removed from the Senate Bill by the joint House-Senate conference committee with the expectation that a Report of the study would be available by the end of February, 1966. This activity led to the appointment of the Secretary's Advisory Committee on the Management of National Institutes of Health Research Contracts and Grants, chaired by Dr. Jack P. Ruina, President of the Institute for Defense Analysis (the Ruina

Committee). The main finding of the Ruina Report was that not only were the Advisory Councils not required by law to pass on contracts, but that they should not be required to do so. The Report also stated that the grants approach was inappropriate for directed research or development programs, and the contract should be used for such programs. Furthermore, programs for directed research - including objectives, justification, expected funding levels, management plans, and types of contractors should be submitted to the appropriate advisory council for review and approval prior to initiation, termination, or substantial change in scale or direction of effort; once initiated, execution of such a program should be the full responsibility of a program manager. The Report also suggested that the NIH needed to take significant steps to make career opportunities and status for program managers more attractive; a strong management structure for directed research should be established independent of the intramural or extramural research efforts. NCI was in agreement with the Report except that recruitment difficulties with government salary levels made it necessary to blend Intramural and Collaborative Program staff functions. While the NCI agreed, as stated in the Report, that there were too few staff of NCI who had the necessary skills for managing large scientific programs, there were a number of staff in the Chemotherapy Program and in the Special Virus Leukemia Program who had become very competent in managing large, complex biomedical R & D programs. A good example was Robert Stevenson, Head of the Viruses Research Resources Branch, who later was the head of the Frederick, Maryland, contractor-operator facility by Litton Industries, and still later the Director of the American Type Culture Collection.

The Council discussed the Ruina Report a second day. Dr. Endicott summarized the results of the Report for the NACC. The Report upheld the position of Dr. Endicott and Dr. Shannon. Mrs. Lasker was very upset, and a heated session took place (Minutes and Verbatim

Transcripts of the June 26-28, 1966, Council Meeting, July 1966). An excellent account of these activities and subsequent ones that led to The National Cancer Act of 1971 can be found in the book *Cancer Crusade* by Richard A. Rettig (Princeton University Press, Princeton, New Jersey, 1977). Another excellent book on these activities, but on a broader front of medical research and not just cancer, is *Politics, Science, and Dread Disease* by Stephen P. Strickland (Harvard University Press, Cambridge, Massachusetts, 1972). Based on an interview on January 13, 1970, with Mary Lasker, Strickland wrote, "*In Mrs. Lasker's judgement, Dr. Shannon's inherent conservatism and his ego, which caused him to be increasingly unreceptive to ideas of others, are factors in what she believes is a recent period of disappointing progress. She does not claim to have possessed over-riding power; she confesses, sadly, that in those several struggles in which she represented one point of view and Shannon the opposite - struggles over pace and direction, she insists, not over control of internal management - she almost always lost*" (p. 228). Mrs. Lasker had lost this battle, but she won the war later when The National Cancer Act of 1971 was signed. It made delivery of cancer care part of the research responsibilities of NCI; in addition, the enlarged Board that replaced the Council gained greater power, and the appointment of the Director of NCI (and the Director of NIH) became an action of the President. The Board would no longer be chaired by the Surgeon General or the NCI Director. In the ensuing Council discussion, views *pro* and *con* on the issue of grants philosophy *versus* directed or targeted research were aired.

Planning of Research Programs; Grants vs. Contracts

The extent and manner in which science can or should be planned nationally is an old issue. Two divergent views on this subject are presented by 1) J. D. Bernal, in his book *The*

Social Function of Science (New York: Macmillan (1939), who holds to the Marxist view that the role of science is not to understand nature, but to change and that centralized planning and control were appropriated) and 2) M. Polanyi, "The Planning of Science," *Pol. Quart.*, 16, No. 4, 324-325 (1945) who argues for the necessity of giving freedom to the investigator in his conduct of research. Vanavar Bush, in his *Science - The Endless Frontier: A Report to the President*, Washington, D.C.: U.S. Government Printing Office (1945), also noted the underlying conflict between independence of the individual scientist and the centrally planned programs in biomedical research. A related issue is the level at which planning is considered. D.C. Marquis discussed research planning at three levels - experimental design, program design, and policy design in "Research Planning at the Frontiers of Science," *The American Psychologist*," Oct. 1948, p.431. In 1953, Charles V. Kidd, head of the NIH Office of Program Planning, published a very significant paper in *Science*, 118, no. 3058, August 7(1953), pp.147-152, entitled "Research Planning and Research Policy. Scientists and Administrators." The opening two sentences in this paper are:

"One of the central dilemmas of research is reconciliation of the intellectual freedom required for effective exploration of the unknown with the selection and direction of effort implicit in the functioning of any organization with defined functions or limited resources. The concept of "research planning" is one aspect of this dilemma."

In the paper Kidd explores some aspects of the problem, some ways in which untoward consequences of the dilemma can be minimized, the meanings assigned to research planning by different groups, the kinds of planning appropriately done by these groups, and the interrelationships among various kinds of research planning.

Even at the first meeting of the Cancer Chemotherapy Committee on November 10, 1953, the degree of “direction” or “engineering” that should be incorporated into policy governing an expanded program of chemotherapy of cancer was debated. Committee members were Walsh McDermott, Chairman; S. Farber; W.U. Gardner; A. Gellhorn; C.P. Rhoads; L.H. Schmidt; and M.J. Shear (J. M. Buchanan was absent). NIH staff present were: J.A. Shannon; J.R. Heller; G.B. Mider; R.G. Meader; K.M. Endicott; C.D. Larson, Executive Secretary; L.W. Law; F.W. Appel; E.M. Allen; and R.O. Barney. Mr. J.E. Spike represented the American Cancer Society. The conclusions and recommendations in the Committee Report were:

1. Leads developed in recent years warrant initiation of an expanded program at this time.

2. Prior to a grant becoming operable, agreement will be reached between the Committee, its panels and the investigator, that the major emphasis of the research done under this particular support will be on enterprises recommended by the Committee. It appeared to be the general feeling of the Committee that a highly directed program was not feasible in peacetime.

3. The Committee saw need for expansion in six areas:

A. Development of improved criteria for measurement of effectiveness of chemotherapeutic agents.

B. Need of studies of the nature and mechanism of the development of resistance of tumors to chemotherapeutic agents.

C. Need of expanded and broadened evaluation of currently available and promising agents.

D. Need for work aimed at improving the methods of clinical verification of the efficacy of animal screening methods.

E. Need of study of the chemical nature of currently active compounds as a basis of determining where new syntheses should be encouraged.

F. Need for a survey of activities of all potentials of personnel, laboratories, and clinical material for an expanded program. What are the resources that might be put at the disposal of the chemotherapy program?

The Congress decided that the program as outlined and implemented was of insufficient scope and aggressiveness; Congressional action led to the establishment of the Cancer Chemotherapy National Service Center.

Albert Sabin, in an article in the June 23, 1967, issue of *Science*, called for more planning of coordinated, collaborative programs aimed at solving important disease problems. Administrators also needed to consider planning for implementation; in the past most reviews of a problem area, though providing sound analysis of the problem area, had not followed through on implementation. Ad hoc groups made up of leading experts in the field should participate in the planning, and Institute Directors, with help from the appropriate Advisory Councils, should determine the priorities.

Rettig, in his book *Cancer Crusade* (pp. 14-17), has also discussed the key issues: “*The conflict between the fundamental research strategy and the categorical disease strategy, then, actually masks five closely related issues. What kind of research is to be supported or favored - basic or clinical? What instrument of support is to be used - the grant or contract? Who is to make the authoritative decisions allocating support - the external scientific community, the professional staff of an institute, or the advisory council to an institute? Who is to be supported -*

university scientists or industrial researchers? What is to be the extent of formal research planning - limited, significant, or very extensive? This potpourri of issues was basically rolled into one in the debate over The National Cancer Act of 1971. The overarching issue concerned the most appropriate strategy of research management for conducting the war against cancer.”

And further:

“Were there major scientific or clinical advances in our knowledge of cancer that justified the establishment of a national cancer program?”

And further:

“How persuasive was the case that money, management, and organization could influence the pace, and direction of scientific and clinical progress related to cancer?”

Continuation of the NACC Meeting of June 26-28, 1966

Members of the NACC had varied views on the issues of 1) the extent to which the science can and should be planned and managed nationally; and 2) the strategy of research management (see Rettig, *Cancer Crusade*, pp. 68-69). The spirited discussion following presentation of the Ruina Report and Dr. Shannon’s response to each of the twelve Recommendations in the Report attested to the high interest in the matter. The official response of the NIH was general agreement to the twelve Ruina Report Recommendations except for Recommendations 9 & 10 (“Report of the Secretary’s Advisory Committee on the Management of NIH Research Contract and Grants (The Ruina Committee Report),” Director, NIH, to the Institute Directors/Division Chiefs, June 9, 1966). These two Recommendations dealt with chairing the Council and with Council meetings in the absence of NCI personnel. Dr. Shannon thought it impractical to implement these Recommendations. The Ruina Report also made seven

significant Findings, two of which were: 1) *“An Advisory Council, though required by law to approve individual grants, is not required by law to approve individual contracts, and should not be required to do so.”*; and 2) *“Programs of directed research or development as distinct from undirected research should use the contract as the instrument for obtaining information, materials, and services; conversely, individual research or training projects (or local accumulations of these) should be supported, as in the past, by grants. The distinction NIH makes between contracts and grants, though it is a distinction not uniformly made within the Government, is useful for NIH and should be preserved.”*

Most of the discussion related to the role of the Council and the kind of information that should be provided to the Council. Little time was spent on what the nature of the Council’s advice should be except as regards review of contracts. In discussion of documentation that should be supplied to the Council, some views expressed made it seem like past program reviews before the Council had never taken place. This included the Viral Oncology and the Cancer Chemotherapy Programs which included details of goals, on-going work, and future projected efforts, including plans with the convergence technique. Plans for implementing the SVLP were presented to the Council as soon as possible after Congress voted to add \$10 million to initiate the Program. Considering the extensive information supplied in the documents that accompanied each annual Program review, the NCI staff believed they were giving the Council more than enough needed information. With respect to the complaints of some that the material (in addition to that supplied for grants reviews) was too voluminous, the staff documents had the general summary information up front with increasing detail supplied as the reader went deeper into the document. Thus, the reader could read only the front sections if he or she wanted not to read additional detail. Individual contracts were listed at the end sections. The large volume of

material was prepared in response to the requests from the Council for more information. Also, it is especially difficult to deal with the complex issues when the considerations are addressed only three times a year for a few days each.

Admittedly, program reviews and accompanying materials across such a complex subject as cancer research are difficult to assimilate, but the staff did not feel that the advice they received was commensurate with the content of the NCI review documents nor the effort required to produce them. The Council was not satisfied with the material supplied, though what else was wanted was not made clear. Some Council members felt that the staff Program review documents spelled out the operations and plans in too finished a form so that the Council could not say yes or no on the presented material. The staff thought when presentations were made that ample opportunities for questions and advice were available. Moreover, the staff was available to answer any questions that might be raised and to supply additional material if requested. Thus, though the overall goals of the staff and Council were congruent, an air of dissatisfaction existed. The attempt of Mary Lasker and Sidney Farber at this meeting to get the Council to vote to require the yes or no votes on each contract, particularly in view of the Ruina Report findings, did not help resolve differences. Dr. Farber did provide a helpful discussion of the importance of advisory groups (especially with advisors drawn from outside the NCI), to communicate with the scientific community and the public, and to represent them. Perhaps the NCI did not make clear the large numbers of outside advisors on NCI advisory committees (see Working Group memberships shown below).

A June 30, 1966, letter from one Council member to Dr. Endicott may give some of the flavor of the meeting:

Dear Ken:

Once again I marvel at your self control.

I still don't know what we voted on in the Sunday afternoon Donnybrook. Dr. - X - made a thirty-minute motion. The first 15 minutes I interpreted to say-the contracts should be brought before the Council in the manner of the "Red Books" as this past meeting; that is, to say, for information, not approval or disapproval. This 15-minute motion I quickly seconded because it seemed to me a reasonable and workable arrangement or compromise. Then there was another 15-minute addition to the motion that slowly changed from what I had seconded to "the Council will or may approve or disapprove the contracts and perhaps the NCI's in-house program as well-but of course with no intent of interference, etc. etc." This change, as far as I know, was never seconded but was voted on assuming my second of the first 15 minutes applied to the about-face in the second 15 minutes. In my mind, it didn't, but in the hysteria of the moment and the demand for "a vote, I have to leave in 5 minutes". I couldn't get a word in edgewise and the chair didn't recognize my hand raised high in the air. For this simple reason I voted against the motion I had seconded-it just was no longer the same motion. Oh well, maybe it'll all go away one of these days.

I had a speech all prepared for the executive session for Tuesday afternoon that included dramatic political suicide (sort of like the Buddhist's setting himself on fire). It started out with a semi-public spanking of the vendetta specialists, then a veiled threat to begin exposure of the greediness of those who want all the funds appropriated by Congress (to work on control of the neoplastic diseases in our life time) for their own pet fun-projects regardless of unequivocal pertinence and with no allowable effort by anyone toward coordination and focusing on a goal.

The last part of “my never-given speech” was an attack on Dr. - Y’s - “when-are-you-going-to-stop-beating-your-wife” report on your contract program.

I never gave my speech because things were going relatively well Tuesday afternoon and it would only have caused another Donnybrook (but with the other side taking a few lumps as well as you). I have long felt that you should quit when you are ahead or not rock the boat when virtue seems to be triumphing.

The research goes well, but I don’t know how much more of this sort of business I can stand. I know you must feel the same.

Best regards.

Yours sincerely,

Members of the National Advisory Cancer Council in 1966 were:

Mr. John Mack Carter

Editor, Ladies Home Journal

Dr. Murray Copeland

M.D. Anderson Hospital and
Tumor Institute

Dr. Charles Evans

University of Washington

Dr. Philip Cohen

University of Wisconsin

Dr. Roger O. Egeberg

University of Southern
California

Dr. Sidney Farber

Children’s Cancer Research

Foundation

Dr. Rubin Flocks
University of Iowa

Mrs. Albert Lasker
Albert & Mary Lasker
Foundation

Dr. Joseph L. Melnick
Baylor University

Dr. Leo G. Rigler
University of California,
Los Angeles

Dr. Philippe Shubik
Chicago Medical School

Dr. Howard Skipper
Southern Research Institute

EX OFFICIO MEMBERS:

Dr. Martin Engle
Veterans Administration
Alternate: Dr. Lyndon Lee

Dr. Shirley Fisk
Department of Defense
Alternate: Gen. Joe

Blumberg

Dr. William Stewart
Surgeon General, USPHS

Submittal of Information to the Rogers Committee and to the President

Paul Rogers, Chairman, Special Subcommittee on HEW Investigation, House Committee on Interstate and Foreign Commerce, in a letter to the Secretary, HEW, dated June 9, 1966, asked for additional information from NIH and the Department on their response to the harsh criticism by the Wooldridge Committee of NIH regarding planning activities of the NIH. NCI's part of the NIH response (drafted by Lou Carrese) demonstrated the various planning activities of the Institute that had been developed over the previous five years. The reorganization of the NCI was aimed at increasing the Institute planning functions. The key role of the Scientific Directorate was emphasized. The Office of the Associate Director for Program (and the Executive Secretary of the Scientific Directorate function) provided a focal point for Institute-wide planning, but this Office worked closely with the senior program leaders in developing plans. Systems plans for the Chemotherapy Program, the Special Virus Leukemia Program, the Carcinogenesis Program, and the Breast Cancer Task Force were examples of extensive planning efforts in NCI. Two Subcommittees of the NACC, Carcinogenesis and Prevention and Diagnosis and Treatment, and the newly established Council Planning Committee were created to move toward engaging the Council in greater planning efforts.

Meeting with the President

On June 27, 1966, President Lyndon Johnson met with Dr. Shannon, the directors of several Institutes, and others, to discuss the further effort needed to reduce disease, disabilities, and premature deaths through research and related federal health action. The meeting provided a direct insight in the President's views in the health and medical research area. In turn, it was possible for NIH staff to convey major program developments as well as problems that needed further action. A resume of the meeting was prepared by NIH ("Report of the Meeting with the

President and Further Plans,” Director, NIH, to the Secretary, HEW, and the Surgeon General, July 13, 1966).

In August 1966, President Johnson, on advice from the President’s Science Advisory Committee, requested a report on total activities of the NIH. Apparently this request stemmed from the criticism from the Wooldridge Committee. The NIH again submitted extensive information on the activities of the Institutes. The NCI submittal included a report on the Special Virus Leukemia Program. It included projected research program budgets of \$16.5 million for Fiscal Year 1967, rising to \$30 million by Fiscal Year 1971. Programs of sufficient scope to justify these budgets were in the plans (“The Advancement of Knowledge for the Nation’s Health, A Report to the President on the Research Progress of the National Institutes of Health,” DHEW, Public Health Services, July, 1967).

The September 25-27, 1966 NACC Meeting

Program reviews for the Grants and Training area, the Intramural area, and the Etiology area were on the agenda for the September meeting. Extensive information for each of these areas was prepared and sent to the Council members prior to the meeting (23 pages for the Grants and Training area; 101 pages for the Intramural area; and 97 pages for the Etiology area; existing contracts were listed). Of the 97 pages from Etiology, 56 dealt with viruses-cancer work; of 23 pages of bibliographic listings by the NCI staff, 16 pages were for viruses-cancer work in Etiology.

At the November 1965 meeting, the NACC Subcommittee on Carcinogenesis and Prevention had endorsed the plans of the NCI Extramural Activities staff to develop new approaches for evaluating the effectiveness of the grants activities in terms of the goals and

objectives of cancer research. As part of the presentation of the Grants and Training area (Dr. Philip Waalkes, Associate Director for Grants and Training), a preliminary report on the subject was presented at the September 25-27, 1966, Council meeting. An outline of the goals and objectives of research on cancer was developed by a group of staff detached from other duties: Dr. Abraham Cantarow; Dr. Robert Greenfield; Dr. LeMar Remmert; and Dr. Michel Klein. They worked with the Associate Director for Program and Mr. Carrese in biweekly sessions. The mission of the grants and training programs was divided into four goals: 1) Prevention of cancer in man; 2) Detection and diagnosis of cancer in man; 3) Treatment of cancer in man; and 4) Prognosis of cancer in man, including which individuals will develop cancer and what would be the courses of the diseases under different conditions. The goals were subdivided into more specific objective areas that were further subdivided. Charts in a goal-oriented framework were prepared for each of the four goals. This arrangement allowed for identifying relationships, gap areas, areas of over-emphasis, etc., and, when the grants were put into the appropriate areas on the charts, the relative investment, resource and manpower requirements, and dollar projections for each area could be estimated. Discipline-oriented projects supported by grants could be fitted to the goal-oriented framework. As an example of an area for analysis, the group presented the topic of Chemical Carcinogenesis. Grants classified as chemical carcinogenesis totaled \$3.615 million. For future analysis, thirteen topics and seven program areas were proposed for development. The Council endorsed the new effort of analysis and encouraged the staff to continue the development along the lines displayed at the meeting.

Summaries of the research results from the Laboratories and the Clinical Branches of the Intramural Area (Dr. Eugene Van Scott, Scientific Director for General Laboratories and Clinics) were sent to the Council before the meeting, and the programs were presented to the Council for

discussion. The Laboratories were Biology, Pathology, Pathologic Anatomy, and Physiology; the Clinical Branches were Dermatology, Metabolism, Surgery, and Immunology. There was general discussion, and a number of questions were raised on details of the research.

The Etiology Area also sent to Council members before the meeting extensive informational material on its programs. This included the overall report by the Scientific Director for Etiology (Dr. Paul Kotin), and the summary reports of the Associate Scientific Directors for Carcinogenesis, Demography, and Viral Oncology. Included with the reports of the Associate Director for Viral Oncology (Dr. Ray Bryan) were summary reports from the Viral Carcinogenesis Branch (Dr. Robert Stevenson), from the Viral Leukemia & Lymphoma Branch and the Special Virus Leukemia Program (Dr. Frank Rauscher), and the Viral Biology Branch (Dr. A. J. Dalton).

In the Appendix were more detailed reports that also included projected plans for the future. Selected *examples* are given below.

The Viral Carcinogenesis Branch:

One of the most significant projections was the plan to increase work on DNA viruses when the new NCI building 37 was completed and would provide more space. The special viral biohazards building was expected to be completed in early 1968, providing additional space and safe handling of biohazardous materials. As the viruses-cancer work enlarged, more attention would be given to information needs and services, data flows, and conferences, insuring sound linkages between intramural and extramural investigators. A target of 100 liters of characterized calf serum per month was set, and increased production was underway of animal virus reagents (simian, bovine, feline, and canine virus diagnostic agents). Production of additional human

embryo kidney cells from additional sources of supply was being achieved, and improved freezing of primary trypsinized cell suspensions was permitting storage and shipping of various cell types. Contracts for the preparation of reagents needed for the search for neoantigens were being developed (oncogenic adenoviruses, varicella, herpes, cytomegaloviruses, and others). Collection, processing, and storage of serum from patients with advanced metastatic cancers plus control specimens were activities that were progressing well. A feasibility study of a facility to house primates had been completed. Long term holding of over 2000 primates would be needed by 1968. A variety of pro-simians, monkeys, and baboons were being inoculated with human clinical material, cell lines derived from Burkitt lymphoma, known oncogenic viruses, etc.

The Viral Biology Branch:

Work aimed at clarifying the significance of particles seen with electron microscopy would continue. In collaboration with the NCI clinical staff, 141 plasma specimens from 120 cases of leukemia had yielded 13% positive for type C particles, about the same proportion of positives found in previous studies. The results were consistent with those obtained in neoplastic diseases of animals induced with low doses of RNA tumor viruses or in the naturally occurring animal diseases. Membrane-bound virus particles of the “herpes” type had also been seen in 8 of the 9 Burkitt lymphoma cell lines recently established, and 5 of 12 cell lines of human leukemia; the particle could not be propagated in any cell line, and it showed no antigenic relationship to other members of the herpes group or any other known virus compared up to that point. The crossing of species barriers had been demonstrated following intracranial inoculation of high titer Rous sarcoma virus into rabbits, guinea pigs hamsters, cats and dogs; the tumors were mostly

gliomas and meningiomas. The viral agent isolated from Sarcoma-37 is closely related to the Moloney leukemia agent.

The Viral Leukemia and Lymphoma Branch:

Animal work with C type RNA viruses and “herpes-like” viruses associated with naturally prevalent and transmissible neoplasms continued to form a basis for work in man. To move ahead with human leukemia and lymphoma, two new highly sensitive immunological techniques were developed for the detection of specific, leukemia associated antigens and/or antibodies that could be of viral derivation (formerly demonstrated with the fluorescent antibody technique). The new, more sensitive techniques were the Ouchterlony precipitin reaction and specific hemagglutination of antigen-coated tanned erythrocytes. These techniques could be used not only to detect murine leukemia viruses, but also to quantitate the amount of virus present in various systems and to differentiate the various murine leukemia viruses. These *in vitro* monitoring techniques were of paramount importance to the human leukemia problem because it had not yet been possible to develop a sensitive laboratory animal system (including primates) that would support replication of, and/or disease induction by, candidate human leukemia viruses. Density gradient centrifugation was being applied to quality control in commercial laboratories engaged in the production of large quantities of murine leukemia virus under contract. Members of the Branch were serving as Project Officers on 9 contracts, funded at about \$3.7 million. One of the contracts deserves special mention because it was providing a critical resource and unique technical competence to the research activities of the Branch as well as the entire Special Virus Leukemia Program. The objectives of this contract with Bionetics Research Laboratories, Inc. were: (a) to determine whether newborn, mother-deprived primates of various

species are susceptible to the oncogenic and/or leukemogenic effects of known viruses and of candidate viruses recovered directly from man; and (b) to test available means and develop new means to enhance the susceptibility of primates to virus replication and/or disease induction. Pursuant to these objectives, the contractor had provided, largely from his own breeding colony, over 700 newborn viable primates suitable for inoculation. These animals had been inoculated with high priority materials received from over 50 different investigators from 40 different laboratories throughout the country and abroad.

The Special Virus Leukemia Program:

During Fiscal Year 1966, the overall management of the Special Virus Leukemia Program (SVLP) was placed in the Office of the Chief, Viral Leukemia and Lymphoma Branch (Dr. Rauscher). After the initial plan of the Program, further details were added following numerous discussions with key program leaders and research leaders of NCI as well as with university, cancer institute, and industrial personnel expert in virology, oncology, immunology, biology, chemotherapy, etc. As listed above, the Program operationally had been divided into seven program segments or working groups: Developmental Research; Testing and Monitoring; Resources and Logistics; Epidemiology; Special Animal Leukemia Ecology Studies; Human Leukemia Therapy; and Biohazards Control and Containment. Membership of the working groups consisted of investigators from inside and outside NCI, selected for their expertise in the subject matter brought before the respective working groups. They were being asked to review projects for scientific excellence and relevance to the planned Program, but they were also being asked to suggest additional work that needed to be done. Dr. Bob Huebner later pointed out that this third function was difficult for most investigators to get used to because in the past their

thinking was restricted by resource constraints. Of the 180 projects then making up the Program plan, 70 were being conducted by investigators in government laboratories and clinical facilities, universities, cancer institutes, non-profit laboratories, and commercial facilities.

The extensive material on the SVLP presented to the NACC was a synopsis of progress highlights of the Fiscal Year 1966. Each reported item was accompanied with an explanation of its significance. Projected plans for future work were also presented. Selected examples are given here. The successful culturing in large amounts of tumor cells from 21 patients with leukemia or lymphoma was yielding large amounts of type C or herpes viruses. These greater amounts would be used for characterization of the viruses, for comparison studies of ability to cross species lines in producing malignancies, and for immunology and epidemiology investigations. An epidemiologic survey on Burkitt lymphoma in Africa was planned. Follow-up would be made on the capability to immunize mice against three classes of 14 viruses causing leukemia in mice and rats; live or killed virus vaccines had been prepared that prevented the leukemia. It had been shown that a chicken tumor virus could induce cancers in mice, rats, guinea pigs, rabbits, sheep, goats, dogs, and monkeys; steps had already been taken to improve safety procedures, facilities, and equipment which were in the process of fabrication. Herpes type virus particles were found in a tissue culture cell line derived from tissues of a monkey treated with a chemical compound known to induce cancer in laboratory mice and rats; the monkey later developed leukemia, and this finding would be explored further.

Projected efforts also included work by NCI staff to determine the biological, chemical, and physical properties of murine leukemia and other viruses, to devise and evaluate methods for the controlled degradation of the animal leukemia viruses into their subviral component parts including nucleic acid, protein and lipid, and to determine the mechanisms by which tumor

viruses transform cells at the molecular level. As improvements in biohazards control and containment were made the results would be widely distributed to the scientific community, and the information would be utilized in the planning for a major biohazards facility. Longer range plans called for a nationwide monitoring system for the surveillance of laboratory personnel working with oncogenic viruses, including a system for collecting sera from these workers at regular intervals, and for development of standardized specifications for biohazard operations. Many additional findings and planned efforts were reported to the Council. As the Ruina Committee stated, the Program reviews with the NACC seemed over-elaborate. The NCI staff agreed, but the NCI was trying to respond to the call from the Council for more information.

1967

Dr. Robert Huebner's Memorandum to the Surgeon General

On January 24, 1967, Dr. Huebner (Chief, Laboratory of Infectious Diseases, NIAID), as a follow-up of discussions, sent a memorandum to William H. Stewart, Surgeon General, U.S.P.H.S., in response to questions raised in the discussions. Excerpts from the memorandum follow:

“The unprecedented support to basic research by the NIH in recent years depended more than anything else on the missions described and/or implied in the programs of our categorical institutes. Mission-oriented research does not compete with or threaten basic research, as articles in recent medical and scientific journals suggest. They are mutually dependent, one for justification, the other for sustenance. Whatever is really excellent in scientific achievement is almost always both basic and mission-oriented.”

“One important point regarding funds for science brought out by Weinberg (Basic Research and National Goals, National Academy of Sciences, March (1965) is that one must distinguish not only basic but mission-oriented science from political and social action programs in which scientific discoveries are merely applied; all too often our political leaders fail to make this distinction.”

“In order to really solve many of the complex human disease problems, we have no choice but to adopt the ‘big science’ approach.”

“If the NIH is to achieve its ambitious goals, its Director and the rest of its leadership must periodically redefine and fully accept its mission. Well-planned national research programs cannot be mounted and carried out within the framework of conventional academic type structures. What is needed are structures tailored to serve well planned scientific missions (See appendix). The recent reorganization of the National Cancer Institute represents a major step in this direction.”

“Perhaps many of the suggested candidates for the job [Director, NIH] can meet these and other specifications required by his peers in the PHS and DHEW, but the only one known to me who has actually conceived and operated mission-oriented programs such as I have described and who has successfully handled great responsibilities is Ken Endicott. Despite enormous pressures and frustrations, both within and without NIH, he has mobilized every research resource available, including diverse scientific talents, in the battle against cancer.

Scientists in the cancer field, both here and elsewhere, are full of enthusiasm and hope for the future precisely because they can identify with a well defined and well organized still developing research mission at the NIH. The NIH needs more programs which are as well planned as several of those in NCI.”

“NIH is still a young organization with a promise for improving the future of man that may equal or exceed any of man’s existing institutions. We must keep it from hardening into an organization that merely perpetuates itself for purely institutional reasons. The promise of the 1940’s gave rise to the 20-fold growth of NIH in the 50’s. Now with much greater potential, the institutes require a leadership whose horizons are limitless yet realistic. Our goals are ambitious because there is so much to do, and Dr. Endicott I believe has the perspective, the courage and the experience to give the impetus and direction needed to achieve most if not all of these goals.”

“Appendix”

“It seems to me the organizational structure of much of the intramural side of the NIH is not well adopted to serve mission-oriented programs. Institute, laboratory, section and unit structures created without relevance to a specific mission are best designed to preserve the organizational status quo if only because they provide few mechanisms for launching new programs and disbanding others. The present structures, like academic departments, provide security and tenure which has definite advantages, but also provide minimum impetus for change even when an investigator’s own results clearly indicate such a change.”

“One of the best conceived and best organized mission-directed programs at the NIH is NCI’s Special Virus Leukemia Program. Although this program has been underway only for

several years, it is functioning well and has excellent direction. In its first year or two, the rather large amounts of money allocated were put on all available horses; some of them naturally will not prove out. With the elimination of false leads and unproductive efforts, funds are now being redirected into programs with top-flight research talent and definitive programs. When the major breakthroughs come in leukemia etiology the Special Virus Leukemia Program will not only have diminished the time lag required for application, but will be poised to immediately apply new discoveries to the control and prevention of leukemia and related cancers.”

“Structural reform should not be contemplated merely for convenience; what it must do is to make possible or greatly facilitate desirable changes and growth within productive existing programs; it should eliminate redundant efforts, time wasted in duplicate efforts and pave the way for setting up new programs. Organizational reform is bound to meet with opposition, but few changes in government operations, no matter how necessary, have ever been welcomed by all. Finally, I should point out that Ken Endicott achieved his reorganization with a minimum of psychological trauma to his staff.”

Etiology Annual Report, July 1, 1966 - June 30, 1967

Of the 756 pages of the 1966-1967 Annual Report for Etiology, 334 pages discussed the Viruses-Cancer activities. Dr. Paul Kotin, Scientific Director for Etiology, accepted the offer of Director, National Institute of Environmental Sciences in July 1966, but agreed to also continue as Scientific Director until a successor could be found. Several investigators expert in cancer causation turned down the invitation to head the NCI Etiology Area. Dr. Carl Baker, Associate Director for Program, agreed to become Scientific Director for Etiology in April, 1967. In late Fiscal Year 1967 Dr. Robert Stevenson left the NCI to join the headquarters staff of Union

Carbide. At the same time Dr. Ian Mitchell, Associate Director for Planning and Analysis, Etiology, moved to the Regional Medical Program, NIH. Dr. Ray Bryan asked to be relieved of his responsibilities as Associate Scientific Director for Viral Oncology, with which heavy administrative duties were associated, to concentrate on scientific aspects of important research opportunities, particularly in the elucidation of the Type C particle and “helper” areas. Dr. Frank Rauscher succeeded Dr. Bryan. Dr. Hans Falk, Deputy Scientific Director and Associate Scientific Director for Carcinogenesis, was expected to join Dr. Kotin in North Carolina in Fiscal Year, 1968.

In October 1965 Dr. Stevenson had constituted a small working committee made up of Albert Sabin, Bob Huebner, Ed Lennette, Joe Melnick, and Stevenson to advise on the isolation of neoantigens from virus infected cell cultures. The neoantigens were to be tested against sera of patients with advanced metastatic lesions from a wide variety of tumor types. A contract with Dr. Maurice Hilleman (at Merck) was awarded to evaluate the opposite approach of testing human tumor specimens with high titer sera developed in hamsters against specific virus transformed tumor cells. Investigators, including Dr. Sabin, were having difficulties getting the reagents of sufficient purity to conduct these studies. It was anticipated (correctly) that purification procedures with the new zonal centrifugation rotors would correct this difficulty. The working group did not think the state of the art at that time would allow conducting sero-epidemiology field studies, but would expect that such studies could be conducted short time later.

Dr. Maurice Green and colleagues had found that messenger RNA (mRNA) coded by viral DNA (and specifically complementary to that of the particular virus involved in oncogenesis) is present in tumor cells of hamsters induced with various oncogenic human adenoviruses. A contract was awarded to investigate this system in human tumors. These tumors

would be studied to determine the presence of viral specific RNA by pulse labeling human tumors grown in tissue culture followed by isolation and hybridization of the cell RNA with specific viral DNA's. Largely to expand the area of DNA-RNA hybridization investigation and the general area of solid tumor virology, a conference was held at the Airlie House Conference Center, Warrenton, Virginia, September 18-29, 1966, to which 60 Investigators were invited. The Directors of NCI and NIAID and the NACC called for enlarged program on solid tumors. In line with this development, the NCI, though short on space and inhibited by position ceilings, provided additional support to Dr. Huebner and his Laboratory staff by transfer of \$153,000 and by funding 7 contracts totaling \$2.159 million.

At the June 20, 1967, Scientific Directorate meeting, Dr. Morrison presented the Proposed SVLP Medical Monitoring Program. With the possible hazards to those who work with materials in the SVLP, the need for a medical monitoring program was clear, especially for those who would be working in the new Emergency Virus Isolation Facility (Building 41). Based on a report from the Biohazards Control and Containment Working Group, the Joint Chairmen, SVLP, passed the following resolution:

“Be it resolved that the Director, NCI, with the concurrence of the Scientific Directorate, request the NIH Employee Health Service with the cooperation of the NCI Medicine Branch, the NCI Epidemiology Branch, and the Clinical Pathology Department of the Clinical Center to devise and initiate a medical monitoring program for employees of the Special Virus Leukemia Program (“Resolution of the Joint Working Group Chairmen, June 1967).

The Scientific Directorate endorsed the resolution. The Program was initiated and supported with SVLP funds. The Biohazards Control and Containment Working Group was responsible for the now widespread warning symbol of biohazards danger. This symbol became

generally accepted to indicate possible danger from biological materials. A small contract had been let to recommend a symbol that would serve as such a warning. Thirty potential symbols were field tested for recognition of the symbol and for remembering the meaning of the symbol. The winning symbol of the field-testing is now the accepted biohazards warning icon (see Figure 1).

Annual Program Review, Scientific Directorate Meeting, August 8, 1967

On August 8, 1967, the Annual Program Review of the Viral Oncology Program was presented by Dr. Rauscher to the Scientific Directorate. A 131 page report was sent to the members prior to the meeting. A new program component, the Solid Tumor-Virus Program Segment, was planned late in Fiscal Year 1967, and the plans, including the establishment of a new Working Group, were presented at the meeting. The main initial thrust of this new program area was to produce large quantities of T antigens (antigens associated with tumor initiation and growth). They had to be free of virus particle antigens and produced in quantities sufficient to test for T antibodies in sera from human cancer patients and matched controls. The human sera were currently being collected according to the specifications of the DNA Cancer Virus Working Group. Various methods of purification of T antigens were underway. Although most of the effort was focused on the adenoviruses, other viruses were under study. Tumor-inducing polyoma virus and SV40 virus were being investigated because of their small size. The DNA of these viruses contains sufficient genetic information for the synthesis of only 5-8 proteins of average size. The Report went on to say: *“If each of these proteins synthesized by these small viruses could be identified, reasonable mechanisms for viral carcinogenesis could be proposed. Studies of conditional lethal mutants can provide unequivocal identification of each of these 5-8 viral proteins, and can identify which proteins within this group are required to accomplish*

malignant transformation. This is the reason for the importance of these studies for mechanisms of carcinogenesis.”

“Conditional lethal mutants have been used with notable success to identify viral functions. When infection is carried out under non-permissive conditions (e.g., elevated temperature) the protein synthesized by a mutated viral gene is non-functional; when infection is carried out under permissive conditions, the protein is functional. By comparing the events occurring in a cell infected by a conditional lethal mutant under permissive and non-permissive conditions, those proteins whose synthesis is controlled by viral genes can be identified.”

In the report, Dr. Rauscher presented 16 highlights of progress, listed terminated projects, and projected main new directions for the future. Examples of projects curtailed or stopped were on mycoplasma, Reo Viruses and Cytomegalovirus. The report listed 13 reasons for considering Herpes Type Virus (HTV) an important candidate for consideration as an etiologic agent for human cancer. Among other reasons, it was the most commonly isolated virus from leukemia and lymphoma materials. During the past year it had been found that a HTV was the cause of Marek's Disease. Ray Bryan's section of the Report discussed the status and future directions of the C-Type viruses. From the Report: *“More recently a strain of mouse sarcoma virus, the Moloney strain, has been found to be “defective” and also dependent upon co-infection with a leukemia virus for its replication in infectious form. As in the avian system, pseudotypes having different envelop properties corresponding to those of the helper viruses employed can be produced both in vivo and in vitro, and the defective virus can be used as an indicator agent for the detection of leukemia viruses, through their helper actions.”* And further in the Report:

“Two recent fundamental discoveries of far reaching significance to the search for tumor viruses are: (1) that the viral genome, or some noninfective form of the virus, persists in cells

that have been transformed to malignancy by avian and murine sarcoma viruses; and (2) that the functional gnomes, or noninfective forms, can pass between cells in close physical contact, in vivo and in vitro, in the absence of an infectious process.”

“Cells of tumors induced in foreign hosts by several of the known strains of avian and murine sarcoma viruses usually do not show replication of the virus in infectious form, probably due to a lack of some enzymatic or other biochemical capability. However, when such foreign, noninfective, cells are transplanted back into natural hosts, or placed in close physical contact with natural host cells in tissue culture, the viral genetic information passes into the natural host cells with the result that the latter biochemically competent cells produce and release infectious virus. If the oncogenic viral genome is the defective type, the addition of a helper virus is required for the virus production.”

Dr. Rauscher next discussed key scientific and managerial problems faced by the SVLP:

Scientific Problems: 1) Scaling up virus production to large scale; 2) Availability of leukemia tissue specimens and reagents in large amounts required for large scale sero-epidemiologic field studies (due to the relative rarity of leukemia, the time required for the field investigations is large - 5-7 years); 3) An important question is whether enough antibodies would be produced to confer immunity following introduction of a vaccine (also a question of whether tolerance to the virus introduced at an early age would occur); 4) There was not available at the time a sufficiently sensitive animal or tissue culture indicator for determination of infectivity and disease induction capabilities (Type C or Herpes Type); and 5) There might be difficulty in having an effective vaccine if tumors are induced by combinations of common ubiquitous viruses plus environmental, physical or chemical carcinogens.

Managerial Problems: 1) There was a shortage of time to provide intellectual and technical motivation, guidance and thrust for the program, and to accomplish all the tasks required to manage 61 contract laboratories, the SVLP, and the other activities including research by program managers and project officers; some staff were project officers on 5 to 15 contracts; 2) There was a shortage of staff capable of handling the combined scientific and managerial requirements; 3) It took 1 to 3 years before a new recruit became an effective science administrator; 4) Considerable time was required in meetings for coordination of various aspects of the Program (once a month for Joint Chairmen meetings; once a month for Core Group meetings; and meetings once a month for updating of scientific progress and problems); 5) Much time was spent on trips to contractor facilities; and 6) The time spent on preparation of reports for reviews was excessive. The solutions to some of these problems were helped by the capable contract specialists and by the selfless dedication and skill of the Segment Chairmen, Vice-Chairmen and Members, and the Scientific Coordinator in Virology, Dr. Ray Bryan. Space to be made available in the new Building 37 (Biohazards Building) would allow additional recruitment. However, the need was to recruit knowledgeable, objective, energetic and thick-skinned professionals willing to perform as full-time program managers, a resource in short supply in the biomedical field. Training programs were initiated for NCI staff and for contractor personnel. Another significant help in dealing with some of the problems was the output of the Program Analysis and Communications Section (PAC), headed by Dr. Deward Waggoner, in the Office of the Scientific Director for Viral Oncology. In addition to the regular Cancer Alerting and Bibliographic Services and correlation of clinical data with laboratory data, the Section maintained an inventory of specimens from leukemia patients and conducted Special Studies on tissue cell line inventories. With Dr. Mary Fink, studies were underway on development of

methodology and protocols for a differential comparison of serological virus testing by eight different scientists, on the same specimens, using four known cell lines as antigens. These service activities were in the process of being converted to computer based systems.

Three major management functions are communications, coordination and monitoring. Since the operating basis for the SVLP was a nation-wide network of coordinated research involving the cooperative efforts of scientists at the NIH with other scientists located in numerous institutions worldwide, an active communications system embracing more than the conventional aspects of data retrieval, analysis and dissemination was deemed essential. A complex data system had evolved. Since the beginning of the SVLP to mid-1967, information concerning its management and scientific activities had been presented to the scientific and lay communities principally through the following outlets: at least (a) 76 lectures and 60 publications by NCI personnel, (b) 50 lectures and 35 publications by contract scientists, (c) 60 publications by scientists (predominantly U.S. grantees) not directly funded by SVLP but who had been provided SVLP resources necessary for their studies, (d) 4 overall SVLP progress reports (also containing unpublished data) each of which had been distributed to about 250 persons in the U.S. and abroad, and (e) 25 articles in lay news media through efforts originating entirely with these media. The SVLP sponsored the Second Joint Working Conference held in Williamsburg, Virginia. It was a three day meeting attended by 200 people who were participants in or were related to the Program. The attained purpose of this meeting and subsequent meetings was to critically assess the current status of progress, problems and projections of ongoing efforts within or relevant to the Program. Informal exchange of ideas and information, much of which was still unpublished, was especially productive.

Coordination and monitoring functions were done at all levels, but the main labor for this was done by the Working Groups, which also conducted the initial reviews of individual contracts.

These Groups in 1967-1968 were:

DEVELOPMENTAL RESEARCH

TESTING & MONITORING

R.A. Manaker, NCI

M. Fink, NCI

A.J. Dalton, NCI

J. Duff, NCI

T. O'Connor, NCI

A.J. Dalton, NCI

A. Rabson, NCI

R. Malmgren, NCI

S. Stewart, NCI

J. Sever, NINDB

P. Gerber, DBS

T. Borsos, NCI

W. Ashe, NIDR

M. Schneiderman, NCI

G. Foley, CCRF, Boston

L. Hayflick, Wistar Inst.

B. Roizman, U. of Chicago

A. Brown, Ft. Detrick

D. Walker, U. of Wisconsin

N. Schmidt, Calif. PHS Labs.

W. Henle, Children's Hosp.,

Philadelphia.

A. Howatson, U. of Toronto

RESOURCES & LOGISTICS

EPIDEMIOLOGY

R. Holdenreid, NCI

R. Miller, NCI

H. Steinman, NCI

B. MacMahon, Harvard U.

V. Evans, NCI

N. Mantel, NCI

W. Heston NCI	R. Seltser, Johns Hopkins
W. Rowe, NIAID	R. Tjalma, U. of Michigan
A. Webb, NIAID	
H. Morgan, U. Rochester	
R. Yoder, Tulane U.	
R. Atcheson, UPH	
T. Berge, ATCC	

HUMAN LEUKEMIA THERAPY

SOLID TUMOR-VIRUS SEGMENT

S. Perry, NCI	R. Huebner, NIAID
E. Henderson, NCI	J. Duff, NCI
D. Rall, NCI	C. Boone, NCI
S. Schepartz, NCI	H. Rapp, NCI
A. Serpick, NCI, Baltimore	W. Rowe, NIAID
E. Frei, M.D. Anderson	J. Melnick, Baylor U.
J. Burchenal, Sloan-Kettering	A. Sabin, U. Cincina.
J. Holland, Roswell Park	R. Dulbecco, Salk Ins.
S. Farber, CCRF, Boston	E. Lennette, Cal. DPH.
M. Green, St. Louis U.	

Coordination of the activities became more significant as the Program enlarged. Of the 180 projects that made up the Program systems plan, 100 were being conducted. Dr. Dalton was assigned coordination tasks for Electron Microscopy studies. Dr. Fink was assigned responsibilities for Immunology, Serology Testing, and Standardization of Antisera (Two

important meetings of the Immunology Subgroup were held: one on Immunology Methods and Vaccine Considerations on December 12, 1966; and the other on Comparative Serology on May 22, 1967). Dr. O'Connor was assigned coordination of activities on Biophysical Aspects of Viruses, and Purification, Concentration and Characterization of Viruses. Dr. Chirigos was to coordinate Production, Bioassay, Certification, Storage, Distribution, and Use of Animal Viruses (and Model Systems).

Coordination was required not only between these functions and the Working Group activities, but also with the four major areas of effort on the systems plan and the major objectives. The four areas were: 1) Human Leukemia Etiology and Prevention (Drs. Manaker and Dalton); 2) Special Animal Leukemia Ecology Studies (Drs. Moloney and Glynn); 3) Biohazards Control and Containment (Drs. Payne and Runkle); and 4) Human Leukemia Therapy (Drs. Perry and Henderson). A fifth area was added: Solid Tumor-Virus Program Area (Drs. Huebner and Duff). Dr. Huebner prepared an excellent twelve-page proposal for Program expansion for solid tumor virology efforts in Fiscal Year 1968, with projections into 1969-1972. Coordination was also required with the activities of the research conducted by the in-house laboratories. The staff of the Viral Oncology Division conducted these activities. The Branches making up Viral Oncology were: a) Viral Leukemia and Lymphoma Branch (John Moloney; Tim O'Connor, Associate Chief); b) Viral Biology Branch (A.J. Dalton; Associate Chief, Bob Manaker); c) Viral Carcinogenesis Branch (Jim Duff, Acting). In addition there were important Sections in the Office of the Associate Scientific Director for Viral Oncology supervised by an Assistant for Laboratories (R. Reisinger): 1. Biohazards Control and Containment Section (Al Hellman); 2. Program Resources and Logistics Section (Bob Holdenreid); 3. Research Support

Section (J. Kvedar). Also there was the Program Analysis and Communication Section (Deward Waggoner).

Included in the Report was the monthly listing of the status of every contract. The 90 active contracts totaled \$16.496 million. The in-house was at the level of \$2.713 million. Viral oncology grants (296 projects) totaled \$28.323 million. Thus, the total level for viral oncology work was \$47.532 million. Of the funds for Viral Oncology in the Etiology area, 33% were in Human Leukemia Etiology and Prevention; 21% in Program Resources; 14% in Special Animal Ecology Studies; 12% in Solid Tumor-Virus; 6% in Biohazards Control and Containment; and 14% in Direct Operations. Viral Oncology funds accounted for 64% of the funds for Etiology. These figures are for Fiscal Year 1967.

The NACC Meeting in October, 1967

On October 9, 1967, Dr. Carl Baker, who succeeded Dr. Paul Kotin as Scientific Director for Etiology, introduced the Annual Program Review for Etiology. Sent to the Council members prior to the meeting was a 407 page Report on the programs in Etiology. The front parts of the Report were condensed general summaries; further into the Report more specific details were included; in the back of the Report were summary paragraphs on individual contracts. The first 41 pages of the Report was a broad analysis on cancer, cancer research and the Etiology Program by the Scientific Director for Etiology. A preliminary systems planning chart for chemical carcinogenesis was included.

Program leaders next presented reviews of their respective areas: Marvin Schneiderman, Biometry Branch; Bob Miller, Epidemiology; Hans Falk, Carcinogenesis; and Dick Rauscher,

Viral Oncology; plus Ray Bryan, The “C” type effort - Old & New Approaches; and Jim Duff, The Solid Tumor-Virus Program.

Much of the material in the Report was the same as that in the Report presented to the NCI Scientific Directorate in August (see above). The greatest concerns were in recruitment difficulties, especially in the chemical carcinogenesis area. Projected NIH budget cuts and position ceilings and funds held in reserve were also of concern. A cost reduction program at the time called for a budget reduction for NCI of \$2.492 million and personnel cuts of 42 positions. Costs for partial outfitting the new Emergency Virus Biohazards Facility at the time exceeded the funds available by about \$600,000.

The above subjects were discussed at the Council meeting. The Carcinogenesis Area received special attention since the need for greater research efforts in the area, especially for screening methodology and capacity, was clearly warranted. A number of questions were raised about particular contracts, and the staff provided answers.

Dr. Huebner and several members of his staff transferred to NCI in late 1967.

1968

The Third Joint Working Conference of the SVLP, March 11-13, 1968

The Third Working Conference of the Special Virus Leukemia Program was held March 11-13, 1968, at the Airlie Conference Center in Warrenton, Virginia. Sixty-four invited participants attended the meeting. Dr. Rauscher presented the overall progress of the SVLP and the Solid Tumor-Virus Program Segment. He discussed both the scientific and managerial developments. Because of the growing significance of the Solid Tumor-Virus Program Segment, the SVLP was changed to the SVCP (Special Virus Cancer Program). The Working Group

Chairmen discussed the progress, current activities, and projected plans for their respective areas of responsibilities. During these presentations, discussion was invited from the participants, including the current status of their work. In an informal environment, unpublished work was presented to the group, and extensive open discussion ensued. This pattern of free revealing of unpublished work and give and take discussion of new information and current thinking set the agenda for subsequent annual meetings of the SVCP. Dr. Maurice Hilleman (of Merck) stated that the main reason he joined in the activities of the SVCP was to be at the annual meetings where exchange of current information and ideas were freely exchanged well before the information was published. It appeared that an esprit de corps was developing (that did grow with each subsequent SVCP meeting) “Special Virus-Leukemia Program Overall Summary,” SVLP Program Report, no. 5).

Among many highlights reported by Dr. Rauscher were the following:

1. Tissue culture cell lines had been established from tumor cells from 200 leukemia patients; a herpes type virus was identified in 80 of these cultures.

2. A herpes type virus (the Epstein-Barr Virus), which causes infectious mononucleosis under some conditions, was found in 29 of 30 African children afflicted with Burkitt’s lymphoma; 100% of children with this disease had high titers of antibody to this virus, whereas less than 50% of normal children living in the same area had antibodies to this virus.

3. The Epstein-Barr virus was also found to be associated with Hodgkin’s disease and cancers of the postnasal space.

4. The herpes type virus was not found to be associated with acute leukemia of children.

5. Herpes simplex virus type 2 was found to be associated with cervical cancers; it is mediated through sexual contacts.

6. A C-type virus was found to be responsible for producing lymphosarcoma in cats; a cross reaction was shown between this cat lymphosarcoma virus and mouse leukemia viruses; this virus also induced lymphosarcoma in a beagle dog from which C-type virus was recovered (“Progress Highlights,” SVCP, 1969 Congressional Budget Hearings, Spring, 1961).

Report on the Tissue Procurement Program

In conjunction with the 1968 Working Conference, Drs. Robert Holdenreid and Robert Depue of the Program Resources & Logistics Section prepared a Report on the Tissue Procurement Program. This effort was initiated by Harvey Scudder and developed by Bob Stevenson as part of the provision of needed resources in the face of the almost entire absence of a mechanism for providing resources required for the viral oncology development. Making available sufficient amounts of tissues, especially from humans, and in particular, enough leukemia specimens, was crucial to the expanded research effort. The Report follows:

“When the Human Tissue Procurement Program was begun there were a number of identifiable problems which needed solutions. The object of the program is to supply useful tissue specimens for cancer and virus research. Several general requirements for these tissues were developed:

- 1. Rapid processing of tissue and information.*
- 2. The avoidance of extraneous contamination of tissue during collection and processing, and identification of inherent contaminants.*
- 3. The ability to obtain and maintain viable human tissue.*

4. The provision for rapid and accurate histologic diagnosis.

A wide variety of tissue types were called for, including human embryonic material, prenatal tissue, malignant material from adults and children as well as nonneoplastic control tissues from all age groups. In order to meet these requirements, solutions had to be found to the following problems:

1. Development of a sterile autopsy method that would prevent extraneous contamination of tissues during collection.

2. A bacteriologic and mycologic survey of postmortem tissues to act as a control on problem 1 and to identify the inherent contaminants of such tissue.

3. The viability of autopsy and surgical material when freshly obtained and the allowable postmortem period for collection of viable tissue.

4. Development of equipment for the freezing of tissues in liquid nitrogen, and for the shipping of these tissues to conform with postal regulations.

5. The viability of tumor slices frozen in liquid nitrogen.

6. The viability of trypsinized frozen cell suspensions.

7. Possible methods of separation of tumor cells from normal stroma to provide uniform tumor cell suspensions.

8. The establishment of a data processing system to aid in the rapid processing and dissemination of information associated with tissue specimens.

Of these problems the sterile autopsy method, the bacteriologic survey, and the freezing equipment designed have been successfully completed to this date. The survey of the viability of

fresh tissue is essentially complete and the compilation of the data produced in this study is now under way. Each of the remaining problems is discussed individually below, along with program objectives in these areas.

VIABILITY OF AUTOPSY AND SURGICAL MATERIALS

A pilot study of the viability of adult human tissues was completed at the Navy Tissue Bank. This study indicated the feasibility of collection of viable surgical and autopsy material. A one and one-half year study of the viability of surgical and autopsy tissue is under way at Roswell Park and Georgetown. These data are now being compiled and will be analyzed to establish viability estimates for various tumors and normal adult tissues.

The perinatal tissues obtained in the program have undergone tests to establish the degree of viability of this type of tissue. All tests have indicated a high degree of viability.

Under the Milwaukee contract, methods of cultivation of human trophoblast and choriocarcinomas have been investigated. Normal trophoblast has been successfully grown in explant culture to date. Specimens of trophoblast have also been trypsinized at Melpar and have been distributed for evaluation as to growth potential and suitability for virus transformation studies. The investigation of culture techniques for trophoblastic tissue will continue under Dr. Pattillo. The total program cost for this phase is estimated to be approximately \$60,000. Approximately 40% of this money has been expended to date.

VIABILITY OF TISSUE SLICES FROZEN IN DIMETHYLSUFOXIDE (DMSO)

Limited studies have been performed at Roswell Park and Georgetown Medical School on the viability of frozen tumors. These studies have indicated that this type of material is useful for explant or organ culture. Successful use has been made of it at the University of Washington and at the University of Maryland, as well as at NCI. We have also had an equal number of reports of failure of this kind of material. The data at hand are not sufficient for proper evaluation. Therefore, a study of the viability of frozen tumor slices presently in storage at Roswell Park and Georgetown University was started in July 1967. Two hundred samples of representative tumors and normal tissues will be selected from the bank. These will be examined for content of malignant cells by frozen section. They will then be explanted to tissue culture and observed for the presence of cellular outgrowth and the type of cell that is propagated. The remaining sample will then be trypsinized and examined for viability by a vital staining technique. The study should be complete in one year and is estimated to require \$25,000 and one man-year of work. This project is part of a contract let in June 1967 to Medical Research Consultants.

It is not anticipated that perinatal tissue be stored by this method; therefore, no study is to be undertaken in this area.

No trophoblastic or embryonic tissue has been viable frozen in liquid nitrogen in our program to date. We expect to utilize the results of the tumor and adult normal tissue study at Melpar to guide future work in freezing trophoblast tissue. Freezing equipment is included in the Marquette budget for fiscal year 1968. We expect preliminary studies begun in December 1967 will be completed by August 1968. The cost of this study is estimated to be approximately \$10,000.

VIABILITY OF FROZEN CELL SUSPENSIONS

It is planned to trypsinize fresh tumors which have been demonstrated to contain a high percentage of malignant cells. Conventional trypsinization procedures will be employed. Under this program fresh human tumors would be surveyed by frozen section, and suitable specimens trypsinized and tested for viability before trypsinization and after rate-controlled freezing. This project will then serve as a source of material for the planned production of homogeneous cell suspensions. If trypsinized tumor cell suspensions prove to have a greater viable capacity than whole frozen tumors, they could be added as a standard item to the tumor bank starting in 1967. Medical Research Consultants will also accomplish this work.

The Tissue Procurement Program has extensive experience with the production of viable frozen cell suspensions of perinatal tissues. Suspensions of kidney and lung cells have been standardized and are distributed on a regular basis. In addition, perinatal thymus and spleen have been tested for suitability; however, these tissues have shown little promise to date. It is hoped that information gained in other studies may permit the resumption of the studies on thymus and spleen in 1968. It is estimated that it will require \$25,000 and one man-year of work to develop these two tissues to a standard product.

Trypsinized trophoblast suspensions have been produced in pilot quantity. Samples of these specimens have been distributed for evaluation as to growth. These cells are difficult to handle and require more work on culture methods.

PRODUCTION OF HOMOGENEOUS CELL SUSPENSIONS

It is planned to use the zonal centrifuge and other methods as applicable in a development study to separate tumor cells from normal stroma cells. Fibroblastic cells are always present in any tumor or normal tissue preparation. These cells tend to outgrow and replace in culture the tumor cells that are of prime interest. Therefore, it would be an immense aid to research on cancer if the cells of interest could be isolated in quantity, free of other cells. It is estimated that such a project would take approximately two years, starting July, 1967. The total cost would be \$120,000 and involve four to six man-years effort. By the beginning of 1969 we should be in a position to decide on the desirability of routine production and distribution of trypsinized homogeneous tumor cell suspensions. At this time no estimate can be made as to the potential cost of production of this material, since neither the demand nor the probable cell yield can be estimated at this time.

REVISION OF DATA PROCESSING SYSTEM

The variety of operations now in being was not anticipated when the first data system was designed for the Tissue Procurement Program. Therefore, it was determined in July 1966 to rewrite the computer programs to provide more flexibility for operation and ease in data processing. An analyst and a programmer of the NIH Computer Division have completed a program that is under testing. The routine computer runs will then be made at NIH and the terminal equipment will no longer be required in the Health Research Contract.”

The Report also discussed with brief paragraphs each of the 12 contracts totaling \$481,300. Three of the contracts were for obtaining tissues from patients in Africa with Burkitt's lymphoma and control subjects (Korle Bu Hospital, University of Ibadan, and Makerere University).

Dr. Depue also prepared a status Report (August 20, 1968) on the Inbred Populations Project. At the suggestion of Dr. Albert Sabin, who was Chairman of the Herpes Virus Working Group advising on the Solid Tumor Virus Working Group, this Project would develop tissue culture cell lines derived from inbred populations. In addition to other uses, the different cell lines would be used to investigate their different susceptibilities to different viruses. Ten to twelve inbred or ethnic groups would be sought, and six to twelve cell lines established from individuals in each population. The clinical materials would be obtained from circumcisions or skin

biopsies. At this time (August, 1968), 21 different inbred or ethnic populations had been identified. They were:

1. Amish people in Lancaster, Pennsylvania.
2. Pima and Papago Indian Tribes.
3. Navajo Tribes.
4. Nomadic Eskimo Tribes.
5. Pure Hawaiian People.
6. Japanese in Hawaii.
7. The Hutterites (a Mennonite group in North Dakota).
8. The Lumbees (a group of people in the mountains of North Carolina).

9. The Gulla (people residing on islands off the coast of Georgia).
10. Vinalhaven Island (in Penobscot Bay).
11. A German group in Mexico.
12. French People in St. Thomas.
13. Tangier Island, Virginia.
14. Incestuous Births.
15. Chinese People in San Francisco.
16. Germanic People in Northern Italy.
17. Dutch People on Saba, Netherlands Antillies.
18. Samaritans.
19. French Canadian People (on islands in the St. Lawrence River).
20. Parses (in Bombay).
21. African Tribes.

After initial processing the materials would be shipped to a central laboratory for further culture. [This project was soon discontinued when it was learned that the cell lines showed no differences in virus reactivity.] (Robert Holdenreid and Robert Depue, "Five Year Program Projections for the Tissue Procurement Program," July 1963; Robert Depue, "Interim Report on Inbred Populations Project (Albert Sabin)" August 20, 1968).

Answers to NCI Organization Task Force Questions

On September 10, 1968, the NCI Organization Task Force (chaired by Jesse Steinfeld, Associate Director for Program) sent to senior staff members of the NCI a series of questions.

These were organized as follows:

A. Questions concerning the conceptual and philosophical strategy for carrying out the mission [of NCI].

1. Should the NCI have intramural research programs?
2. Should the NCI have non-programmed research?
3. Should the NCI programs provide “in-house” training activities for professional personnel?

B. Questions concerning the organization and conduct of research.

1. If the NCI is to engage in non-programmed research activities, how should these relate administratively and organizationally to other NCI programs (Etiology-Chemotherapy)?
2. What are the criteria that determine when a scientific area is ripe for organized or targeted efforts?
3. Should targeted NCI programs (Etiology-Therapy) contain a non-programmed or non-targeted component?
4. Should non-programmed research areas have programmed research components and, if so, how do these relate to the programmed areas?
5. Should a non-targeted research area be organized along disciplinary or “problem solving” lines?
6. Should line and staff research supervisory positions be permanent, rotating, or finite in duration?

C. Questions concerning the management and administration of research.

1. What criteria should determine apportionment of resources between targeted and non-targeted research programs in:

(a) The non-targeted area alone vs. the targeted areas?;

(b) The Chemotherapy and Etiology programs themselves?

2. What criteria should be used to identify “gap areas” in non-targeted research areas?

3. What criteria should determine magnitude of programs in non-targeted research areas?

4. What proportion of scientists in a section, lab or branch should have permanent or temporary employment?

5. Should NCI have a formal but optional program for “self renewal” type of educational experience similar to sabbatical years for tenured university professors?

6. How can scientists managers be identified, groomed, tested, rewarded, and ultimately retired in the NCI environment?

7. Should NCI have a formal mechanism with a specified committee structure for review of national scientific competencies prior to selection of senior scientists managers?

D. How can scientific collaboration be facilitated between scientists in different organizational components (a) within NCI and (b) between NCI and NIH, other government agencies, universities, and private foundations?

The September 15, 1968, response of the Scientific Director for Etiology is given here because it illustrates consideration of several philosophic and policy issues germane to management of large scale biomedical research programs.

“SUBJECT: Answers to questions posed to the NCI Organization Task

Force.

A.1. Yes. It appears to me that the total in-house activities of NCI cannot be totally subsumed under the chemotherapy and etiology programs as effectively as having in addition a third component covering aspects not encompassed within the mission of these two programs (While it is conceivable to distribute the third component activities into the other two areas (or even to combine all three into a monolithic pyramid), I do not see that this would provide as strong an NCI program as we now have). While some aspects of etiology and prevention research and therapeutic research overlap each other, there are several additional important areas of research: the nature of cancer; interactions between the cancer and hosts; modifications of the subjects when cancer develops and progresses; and several areas involving longer range objectives, many of which are oriented more to scientific disciplines [e.g., developmental biology] than to specific tightly defined cancer problems.

Since longer range problems are involved, the degree of coordination of research programs should be less tight compared with the shorter range, well spelled out, integrated research program efforts. Therefore, considerable leeway in problem selection and use of research time should exist for those investigators engaged in the longer range, probing efforts. We must not fall into the trap, however, of thinking that the conduct of research in the long-range efforts and the short-range efforts are as neatly separable into black and white as our discussion might imply. Actually these efforts form a continuum. Thus, all program segment areas in in-house research should contain some elements of tightly integrated program efforts plus looser, more probing and varied approaches. It appears appropriate to maintain a

somewhat greater emphasis on the more loosely coordinated approaches in the GL&C area than in the other areas, because of a higher proportion of longer range efforts.

There are three reasons for having in-house effort along the lines of GL&C in addition to the above factors:

a) the senior staff of the Institute must make many decisions affecting the conduct of research both on in-house and outside programs. This staff will be much more capable of making appropriate judgments even on outside activities if their responsibilities include the management of large complex in-house research operations, encompassing both the GL&C and the more highly programmed types of research efforts.

b) infrequent intermittent consultation, particularly in the form of outside committees, is insufficient to meet the needs for expert knowledge and advice to the senior management staff of the Cancer Institute. Therefore, it is very important that in-house staff consisting of experts in the many disciplines and specialties of the cancer field be on the staff and available immediately on call and for continuing participation in many activities of the Institute important for sustained programs.

c) the question has sometimes been asked, "Why should research that can be done in the university be done at NIH?" The reverse question makes as much sense as this question. It is very difficult to build and maintain, though easy to destroy, a sizable, effective research organization. All of the reviews of NIH to date have led to the conclusion that the in-house research program of NIH generally is very sound. Thus, the third reason for maintaining this type of research is the fact that a sound research operation is already in existence. This is not easy to come by and should be carefully nurtured rather than even entertaining questions that imply it should perhaps not exist.

The main point here is the need for both planned integrated programmatic research plus more loosely coordinated research, some of which will have long-term objectives and some of which will have heavier discipline or specialty flavor. For key high-priority problems in cancer that can be definitively stated, a serious hard-hitting attack on the problems can be achieved only with a sizable, multi-discipline integrated programmatic research effort. These key problems more generally will have ends-oriented objectives associated with the selected problems that are of anticipated solution within about a decade. However, not all areas of cancer can be so definitively laid out, nor can all long-range objectives be so clearly specified. Therefore, in addition to the programmatic research efforts, it is also essential to have major segments engaged in more loosely coordinated research efforts. A balance between the two types must be striven for, and it is a main management task of the Institute Director to continually adjust the various elements required to maintain an effective, productive (and a not too inharmonious) balance.

It is my conviction that the style of management employed by the present NCI Director is the best one for achieving productive Institute output, i.e., progress toward achieving ends-oriented objectives. Strong reliance is placed on line channel program leaders with both responsibilities and authorities of considerable scope given to them. Control appropriate at the Institute Director level is maintained, however, by the timely making of key decisions on major items of program substance and the large block allocations of resources required to implement approved program elements (without waste of his and the program leaders' time on minor items). Appropriate control is also maintained by a willingness to change leadership and/or organization whenever the output of a major area is not productive. Coordination and balance are maintained by this kind of decision-making within the total NCI framework of the four major

segments: Grants, GL&C, Chemotherapy, and Etiology, and with Executive Officer activities within this framework. Other devices include: the Scientific Directorate; use of information from the staff activities of budget, planning and analysis, personnel, grants and contracts management; and numerous periodic and ad hoc reviews of various types (both of the committee type and reviews up several echelons in line and over a score of “staff” channels).

Many of our problems and much diversion of our time, energies and efforts from program substance have resulted from over-emphasis on these latter three activities, particularly in meeting demands imposed from outside the Institute. Coupled with the problems resulting from decisions being made through the many “staff” channels with counter-parts at several echelons, often without reference to program substance and often resulting in conflicting rules and decisions, is making of decisions on relatively minor items, e.g., an Assistant Secretary of the second largest Department passing on a \$25 expenditure at seven echelons below the Secretary’s level, at echelons well above the level at which the function is to be performed (at least four “staff” channels have been ruling on travel requests: budget, administration, international activities, and the NIH Office of the Director of Laboratories and Clinics, in addition to line channels). This latter mode of operation is especially pernicious since in toto it consumes large amounts of time, energies and efforts (plus vast quantities of paper) and diverts them from higher priority items appropriate for the respective higher echelons. Since the decision-maker is so far removed from the substance of the work and how it is being performed, he is ill equipped to deal with the issue (e.g., on what basis was a decision being made by Personnel staff at the levels of the Office of the Surgeon General, Office of the Secretary, and Civil Service Commission on the promotion to GS-16 of a mathematical statistician whose promotion was based on the quality of some 150 papers on complex mathematics and statistics

and their application to biomedical problems?). In the attempt to communicate from the lower echelons to higher levels time-consuming memoranda are generated in large numbers (and with a heavy weight of copies). The number of steps often involved also produce unreasonable delays (e.g., Institute plans for Building 37 were completed in four months and the building was completed in slightly over two years, but clearances of the detailed plans took six years!).

Accumulation and retention of philosophies, rules, regulations, procedures, and clearances generated when NIH was much smaller and had less complex program responsibilities account for many of the difficulties. Updating and modifications for appropriateness of these elements have not kept pace with growth of NIH over the past twelve years (perhaps many of us have not adequately perceived the meaning of this growth nor appreciated what it means when we note such comparisons as the following:

1. The NCI budget is currently larger than the total NIH budget of only twelve years ago;

2. The budgets of the Chemotherapy and Etiology Programs of NCI are each larger than the total NIH budget of only twenty years ago, each is of the size of the current total NIDR budget, and each is larger than the budgets of each of the Divisions at NIH except DRFR).

Clearly an over-hauling is needed, not merely struggles to “speed-up” the decisions at each step or tinkering in the older framework. I believe the key to dealing with these problems lies in making changes in the system that accomplish two things: (1) we must drive the decision-making back into the line channels (this also includes a drastic curbing of our mania for committees) and drastically reduce the decision-making taking place in the various “staff” channels; and (2) we must drive detailed decision-making down to lower and lower echelons.

These comments and suggestions apply to the whole of DHEW, but we can do much in our own areas at NIH. I urge an examination of NIH operations in the light of the above considerations and suggest that we greatly strengthen the roles of the Institute Directors (with some exceptions I do not mean to include the Division Chiefs). This can be done by translating the above two principles into actuality.

This brings us to the relationships between NCI and other Institutes and the staff of the Office of the Director, NIH and certain related Divisions. The need to apply the two principles is very strong here, I believe. Too many detailed decisions have been being made in too many channels outside line channels. The frequent direct dealing between the NIH Associate Directors for Extramural Programs and the Institute Associate Directors for Extramural Programs and between the NIH Director of Laboratories and Clinics and the Institute Scientific Directors, often with decision-making occurring in the process (and often on items more appropriately settled at lower echelons) has weakened the role of Institute Directors and results in confusion for the Scientific Directors as to whom they are responsible. The situation in NCI is more complicated because of the existence of two large complex programmatic areas involving in-house and outside activities under Scientific Directors in addition to the older "intramural" area under another Scientific Director who attends the meetings of "the" Scientific Directors.

There is considerable agreement that the present arrangement is not entirely satisfactory. What should be done? I shall propose some options (in order of priority):

1. If the two principles mentioned above are actuated, many of the problems disappear. Therefore, I propose that the style of managing NIH be altered to drastically reduce the decisions made outside the line channel between the Director, NIH and the Institute Directors, that these decisions deal only with major items, and that major policy discussions be

held in the forum of a greatly strengthened Institute Directors meeting. The senior staff of the Director, NIH, would become staff and help formulate appropriate issues, objectives and options for decision-making within the line channel framework. Obviously, under this proposal much of the detailed decision-making formerly or currently made at the NIH level would henceforth be made below that level (e.g., ruling on individual promotions below the GS-16 level). With this proposal the Scientific Directors meetings could be abolished and the issue of proper representation of the NCI would not exist, or the Scientific Directors, including more than one per Institute, could deal with research program substance, objectives, evaluation and projected needs instead of administrative detail.

2. If option 1 is not acceptable, appoint a third NIH Associate Director for programmatic research (or developmental research. Please can't we get rid of that label, "Collaborative Programs"?) and drastically reduce the details of decision-making at the NIH level. The Institute Director should not be excluded from the channels of decision-making flows. If it still seems necessary to have meetings of the Scientific Directors, then the two NIH associate directors (general labs and clinics and programmatic research) could each meet with their own Institute counterparts, hopefully to cover research program substance rather than administrative detail (It is anticipated that the type of organization current in NCI will become the pattern in the other Institutes over the next decade).

3. Leave the organization at the NIH level as it is presently constituted, but drastically reduce the details of decision-making at the NIH level (including not passing on individual promotions below the GS-16 level). If the Scientific Directors meetings would still be held, research programs could be presented and those Institute program leaders having

responsibilities outside the general labs and clinics or “intramural” area could be invited on an ad hoc basis.

4. Leave it as it is (I do not consider this a satisfactory option).

A.2. Yes. As indicated in the answers to question A.1., for longer range, probing research efforts a variety of concepts, ideas, approaches, methodologies and techniques are desired and the chances of opening up new directions are greater if central coordination is low. Therefore, for these kinds of research efforts non-programmed research is desirable.

A.3. Yes. The in-house activities of NIH have always had a heavy element of on-the-job training; this will continue. Again a formalized teaching program is not necessary to provide such training; however, liberal support of course work should continue. Obviously the large number of seminars and talks held at NIH also provide a great deal of training in-house. It is doubtful whether a more formalized training program for professional personnel should be instituted, though for semi-professional a more formalized effort might have considerable merit, particularly for technicians in certain areas.

B.1. Along the same general lines as in the past, i.e., with the program leaders of GL&C, etiology and chemotherapy reporting directly to the Director, NCI, with subsidiary coordination conducted through the Scientific Directorate, joint meetings of the program leaders when necessary, and encouragement of collaboration among the individual scientists in the three areas (see A.1. answer).

B.2. A number of books have been written on this subject without particularly answering the question. I doubt if satisfactory criteria can be formulated that allow determination of the timing, or of making an organized or targeted research effort for a given area. With more time and thought perhaps some general criteria might be developed of possible usefulness, but this

type of decision is not made by formally setting down criteria. Rather, it is made by enterprising senior program managers who perceive the possibilities of developing an area, lay out a proposal or plan, energetically seek support and funding for the work with success, and drive to implement the efforts. Rarely if ever are criteria set down underlining such decisions. While we attempted to develop the rationale for an expanded integrated program in viral oncology in requesting support for the SVLP, just as important if not more so was the attitude on the part of senior staff to move in this direction.

B.3. Yes. See answer to question A.1.

B.4. Yes. The present attempt to develop an integrated program in immunology is an example of a programmatic effort in the general area of GL&C and also illustrates the possibility of programming research efforts in a given discipline. Whenever serious, hard-hitting attacks are to be made on defined problems, programmatic efforts generally will provide a more relevant program, and if well planned will provide the additional needed basis for determining priority judgments as to relevancy in addition to the usual determination of project excellence. It appears appropriate to consider developing programmatic efforts in GL&C also around key problems of cancer such as: prevention of metastases; how tumor tissues can compete more successfully for metabolic building blocks than non-tumorous host tissues; the understanding of cachexia and its prevention; a diagnostic research program; etc.

B.5. Both. See above.

B.6. Long term, but removal at the discretion of supervisory line channels, e.g., if the decision to remove is made by the immediate supervisor, the action should stand. This reply, however, supposes a reasonable personnel system which we do not have. Therefore, if we are going to continue to have impracticable means for removing those in supervisory positions even

when the functions of the particular group are below par, then I suppose appointments of finite duration or even as the less desirable rotating appointments should be instituted as second best alternative.

C.1. Again I doubt if criteria can be developed which provide the basis for deciding apportionment of resources between targeted and non-targeted research programs or the levels of either. I do not believe these decisions are made in this manner. Decisions are made in resolving competing budget requests, position ceilings, space allocations, etc. against proposed program substance. Thus, the amounts in the various areas evolve over time, rather than being determined on the basis of some pre-determined criteria. I do not believe development of criteria would improve the actual distribution of resources compared with the present system.

C.2. I do not believe gap areas are identified by developing criteria unless criteria in this case means establishment of several goals and objectives placed in a priority perspective. Once these definitive goals and objectives are hammered out, then the ongoing work is assessed against the higher priority objectives; one may then find gap areas and indeed one may also find that much work going on is of lesser priority and cannot be afforded with the total budget restrictions.

C.3. I believe this question has been answered above, but I would also add that setting objectives and introduction of programmatic efforts in the GL&C area would assist in making decisions on the magnitude of efforts. In real life, of course, space allocations set limits on in-house work. I do not know how large the effort in non-programmatic work should be; however, I think further discussion of pros and cons of the need for work in several disciplines in relation to long-range objectives in cancer research, plus an assessment of the chance of obtaining higher

quality manpower in the particular disciplines, might further aid in the continual decision-making on the magnitude of non-targeted research efforts.

C.6. This question is answered in practice as part of the main duties of senior management in an organization. Observation of several characteristics of young research individuals while they are performing on the job provides inputs helpful for selecting individuals as research program managers. These characteristics include sound knowledge of a scientific area which probably ought to extend beyond a very narrow specialization expertise. Indications of interest in objectives appropriate for the organization beyond their immediate work area are also important. The ability to work well with many different individuals is probably essential and should be looked for. Something harder to define but often labeled as “common sense” is also essential. If the individuals have participated in a number of group activities, particularly in the area of scientific expertise or on important problems of the organization and have done well at this, this may be an important indicator. When an organization is in an unfavorable competitive position to recruit senior program managers, it has no choice but to gamble on younger men to assume larger spheres of responsibility.

This is by no means unfortunate since a younger person who can perform effectively as a program leader is more likely to develop program effectively and in line with forefront trends of concepts and efforts. The grooming and testing can best be done on the job, with appropriate guidance from a more senior program leader, but with delegation of full responsibility and authority for the program area rather than requiring approval on detailed items at higher levels. For those who do well as program leaders, particularly the younger man in both non-programmed and programmed research areas, it is essential that they receive recognition and rewards such as promotions and other honors and perquisites. It is still much more difficult to

provide this to the young program leaders in a programmatic area at NIH than in the non-programmed area. This policy if continued will be disastrous for the full development of NIH over the next decade. No organization has solved adequately the problem of what to do with the older senior staff person whose productivity has for one reason or another fallen off. Senior management often attempts to develop assignments that might utilize the extensive background experience of such individuals, but often this is not highly successful. One possibility is providing a means for such individuals to write broad historical reviews in the area in which they did significant work; but if the steam is still not there it is difficult to make this a fruitful operation. Perhaps the other approach needed is a more liberal retirement policy at the option of the Government at younger ages than is presently the case.

C.7. No. I do not believe committees necessarily make better judgments than capable senior program managers, who after all have the responsibility for selecting staff. Rather than thinking of additional committees, we should be thinking of reducing committee activities and strengthen the hands of line officials who have been asked to assume responsibility for program management. I believe the over-extensive use of committees has weakened this proper function of line executives and should be reversed.

D. I do not believe this is a problem when extensive resources are not required for the collaboration if the investigator is as vigorous as he should be. When major resources are required, the collaborative effort should be well planned so that decision on allocation of these resources can be considered in proper perspective for allocation of other resources. There are a few silly rules about non-Government investigators (from commercial organizations) not working in Government facilities and about Government investigators not working in commercial organization facilities that could be changed to facilitate collaboration.

I find that after writing all the above in response to the questions, the question of what to do about GL&C has not been dealt with explicitly. Therefore, let me state simply what I believe to be the best course of action. Immediately appoint Dr. Jesse Steinfeld to the position of Scientific Director for Laboratories and Clinics, NCI. He can set to work on strengthening the soft spots, which will require some reorganization. (See answers to A.1, A.2, B.4, and C.6).

These items may seem petty compared with the mission of NIH and the outstanding research accomplishments made by the NIH staff, but the operational administrative requirements need to advance as NIH grows and increases in complexity.

The Task Force on NCI Organization reported to Dr. Endicott on October 15, 1968. In addition to the Chairman, Dr. Jesse Steinfeld, other members of the Task Force were:

Dr. Carl Baker, Scientific Director for Etiology, NCI

Dr. Nathaniel Berlin, Clinical Director, NCI

Dr. John Fahey, Chief, Immunology Branch, NCI

Dr. Donald Fredrickson, Scientific Director, NHI

Dr. Paul Kotin, Director, Division of Environmental
Heath Sciences

Dr. Seymour Kreshover, Director, NIDR

Dr. G. Burroughs Mider, Special Assistant to the Director
for Program development and Evaluation, NLM

Dr. Gerald Mueller, Professor of Oncology, U. of Wisconsin

Mr. Richard Seggel, Executive Officer, NIH

Dr. Howard Skipper, Vice President and Director, Southern
Research Institute

Dr. Gordon Zubrod, Scientific Director for Chemotherapy, NCI

Mr. Louis Carrese, Deputy Associate Director for Program, NCI,

Executive Secretary.

The Conclusions and Recommendations of the Committee Report largely followed the content of the September 15, 1968, response to the Committee questions by the Scientific Director for Etiology (*q.v.*) (“NCI Organization Task Force,” September 10, 1968; Report of the Task Force on NCI Organizations,” October 15, 1968).

Dr. Miller’s Memorandum on the Coming Need for All-Purpose Biostatisticians

On October 1, 1968, Dr. Robert Miller, Chief of the Epidemiology Branch, Etiology, wrote to Dr. Endicott pointing out the shortage of biostatisticians and the increasing need for their expertise as many more biomedical research studies are expected to take place. He pointed out that NIH had been fortunate to have leaders in applying their talents to practical problems (while also making fundamental advances in mathematical statistics), but that many would soon be retiring. This group, largely self taught, included Jerry Cornfield, Sam Greenhouse, Bill Haenszel, Nathan Mantel, Felix Moore, Sid Cutler, and Marvin Schneiderman. He suggested that the requirement for military service might be used to attract appropriate talents into the field with the offer of training, on-the-job and in school (“A Coming Desperate Need for All-Purpose Biostatisticians,” Robert Miller, Chief, Epidemiology, NCI, to the Director, NCI, October 1, 1968). A clear need for a training program in epidemiology and biomedical statistics was evident.

Dr. Bill Haenszel, the Scientific Director for Etiology, asked to put together a proposal for training additional biostatisticians. He sent his proposal to the Scientific Director for Etiology

on October 15, 1968. It was an extension of a 1966 proposal to Drs. Kotin and Endicott from Bill Haenszel to develop a training program between the University of Pittsburgh Graduate School of Public Health and the NCI. Position ceilings limited what could be done, but NCI gave new emphasis to biostatistics and epidemiology that gradually overcame the shortages in these two areas. The number of epidemiologists increased markedly over the next several years.

Unfortunately too many in the field often seemed to think that cause and effect was established when only a correlation is found. Even when the epidemiologists call for caution in interpreting the data and warning that correlation does not always mean causation, the media often exaggerate the possible significance (“Outline of Proposal for NCI (NIH) Training Program for Biostatisticians (and Epidemiologists),” Chief, Biometry Branch to the Scientific Director, Etiology, October 15, 1968).

The October 7-9, 1968 NACC Meeting

At the 1967 fall meeting of the NACC, the Etiology Area Program presentation emphasized the Viral Oncology area. At the 1968 meeting, the Etiology presentation emphasized the chemical carcinogenesis area. The presentation of the Scientific Director for Etiology was similar to the one presented by him at Wood’s Hole in July, 1968 (see “Revised Remarks at the Wood’s Hole Informal Meeting in Carcinogenesis-Genetics,” July 1968). He and Dr. Umberto Saffiotti presented an enlarged carcinogenesis program with a convergence chart displaying the defined goals and objectives and the program components. Included was a list of factors that needed to be taken into account to determine priorities for order of screening for carcinogenicity. With over 3 million [then] known chemical compounds, screening capacity would be able to

screen only a minor portion; hence, priority determinations were important. Two factors not previously given much attention were the total amounts of a compound produced and amounts exposed to human subjects.

A number of recent organizational changes had taken place: Dr. Umberto Saffiotti, who had been with Dr. Philippe Shubik, succeeded Dr. Hans Falk; Dr. Falk had joined Dr. Kotin in North Carolina. Dr. Gio Gori joined the NCI staff in the Office of the Scientific Director for Etiology. Dr. Robert Huebner had joined the staff of NCI and was to be Chief of the NCI Viral Carcinogenesis Branch and the Chairman of the Solid Tumor Virus Program, NCI Special Virus Cancer Program. Dr. Huebner appointed three advisory groups for the Solid Tumor Virus Studies: 1. Herpes Virus Working Group (Dr. Sabin, Chairman); 2. Adenovirus-Papova Virus Working Group (Dr. Huebner, Chairman); and 3. Transplantation Antigen Working Group (Dr. Habel, Chairman). An Etiology Program Advisory Committee was appointed by Dr. Baker. Its members were: Richard Mason, Chairman; Michael Shimkin; Karl Habel; Charles Evans; Maureen Henderson; Harold Rusch; and Jerry Cornfield. The Committee's first meeting would be held at the end of the calendar year.

Anticipated budget reductions, position restrictions, and new program requirements required cut backs in some areas. Levels of contracting aiming at a reduction average of 15 to 20 percent and cutbacks in internal operations were initiated. A freeze on new hiring was in effect. Nevertheless, plans were being formulated for a complex program designed to produce a less hazardous cigarette, and plans for a larger carcinogenesis screening effort had been formulated. The Third National Cancer Survey, which was discussed at a previous Council meeting, would need to be continued over the subsequent four or five years. As anticipated in the 1967 Annual

Report, reductions of production of lesser priority virology resources had been effected. Some enlargement of the carcinogenesis screening efforts had been initiated.

Dr. Rauscher presented the annual Program Review Report for the Viral Oncology area. This submitted Report made up 200 pages of the 375 page Etiology Report (of which 212 pages were Appendix items on contract numbers and dollar amounts and on brief summaries of specific contracts). Some of the highlights were:

1. Under the leadership of Dr. Robert Miller, a registry of childhood cancer deaths since 1960 (22,000 through 1964) had been established. Analysis of the data revealed that (1) no cancers occurred in 7000 Maryland children immunized against measles in 1961 with a vaccine which was later found to be contaminated with a virus capable of inducing cancer in lower animals; (2) when an identical twin develops leukemia under six years of age, there is a high probability (1 in 5) that the co-twin will develop the disease soon thereafter; (3) various aspects of the occurrence of brain tumors in children suggest that a virus or other environmental factor may be related to its causation; and (4) certain cancers occur excessively in children with specific congenital defects.

2. Seventy new patients had been seen in the projects funded for the collection of clinical specimens and epidemiologic information from children suffering from Burkitt's lymphoma in Ghana, Nigeria, and Uganda. Immunologic and tissue culture studies were being conducted. Correlations of data suggested that the Burkitt lymphoma is related to socio-economic status.

3. Various species of crawling and flying insects, including mosquitoes, can transmit animal leukemia and sarcoma viruses from one animal to another with resulting tumor induction.

4. The same virus which appeared to cause infectious mononucleosis in the United States was isolated from 25 of 26 African children afflicted with Burkitt lymphoma. Also, 100% of African children with this disease were found to have high titers of antibody to this virus, whereas less than 50% of normal children living in the same area had antibodies to this virus.

5. During the previous year, 5 new and highly sensitive methods have been developed for the detection and recovery of tumor viruses from animal cancers (helper viruses; co-cultivation of cancer cells with normal cells; DNA-RNA homology; T-antigen and other serological techniques; and centrifugal concentration).

6. During the previous year, 6 new animal tumor viruses were discovered. Over 60 viruses had been found that cause virtually all kinds of cancer in every major group of animals, including sub-human primates.

7. The responsibility for virus production and distribution was centralized, allowing coordination of all steps from virus production, monitoring, storage, and issue, thus insuring that output could be closely geared to demand. Uniform issue procedures and quality control of products had been established. These steps made possible efficient provision of resources to research laboratories.

8. New concepts in containment facilities were developed. Sophisticated laboratory units and containment equipment had been evaluated by both physical and biological techniques. Environmental factors that influence the laboratory environment were being elucidated. The mechanisms of cross-contamination and the hazard of potential laboratory exposure to man by some candidate tumor agents were demonstrated. Advice on this subject was continuing to be given to SVCP participants.

9. It was demonstrated that animal tumor viruses would be killed by pasteurization.

10. Since production in quantity of purified T and tumor antigens had been achieved in several of the NCI-supported research contract laboratories (supervised by the staff of the Viral Carcinogenesis Branch and the Solid Tumor-Virus Working Segment), a large-scale sero-epidemiologic study could be undertaken. With coordination by Dr. Huebner, a dozen expert investigators worked together in the study. The results on the 390 sera collected (Dr. Robert Depue, Project Officer on contract with M.D. Anderson Hospital and Tumor Institute) were in agreement and unequivocal. Less than 4% of all the sera showed reactions to the various representative antigens in CF, and were fewer in the FA tests. Thus, there was complete agreement that 96% of the cancer patients and controls contained no antibodies to the virus specific T, tumor and virion antigens of the oncogenic adenoviruses. Thus, a well controlled large-scale serological-epidemiological study has shown that human cancer patients do not show significant antibody responses to the T or tumor antigens representative of the known oncogenic human adenoviruses.

The Viral Oncology area in 1967 had 133 contracts totaling \$19,207,982.

The NACC members asked many questions, especially about the contracts. Some members still were not comfortable with targeted research and contracts and would have preferred to see much of the contract funds go for grants. Nevertheless the Council generally endorsed the presented programs. The proposed enlargement of the carcinogenesis area and the Third National Cancer Survey were seen as very significant components of the NCI efforts.

The membership of the Council was:

Dr. Hugh Butt, Mayo Clinic.

Dr. Murray Copeland, M.D. Anderson Hospital and Tumor
Institute.

Dr. Juan del Regato, Penrose Cancer Hospital.

Dr. Emmanuel Farber, University of Pittsburgh School of
Medicine.

Dr. Sidney Farber, Harvard Medical School.

Dr. Rubin Flocks, University Hospitals, State University of
Iowa.

Dr. Leon Jacobson, University of Chicago & Argonne Cancer
Research Hospital.

Dr. Joseph Melnick, Baylor College of Medicine.

Dr. Paul Talalay, Johns Hopkins School of Medicine.

Dr. Jane Wright, New York Medical College (see Minutes of the NACC Meeting.

October 7-9, 1968)..

The Etiology Program Management Group

In October 1968 the Scientific Director for Etiology established the Etiology Program Management Group (EPMG) made up of senior staff of the Etiology area. Its function would be to review areas of cancer research significant to cancer causation and prevention, including biometry and epidemiology and other related methodologies. Sometimes the review subject would be on on-going work; at other times the review might cover areas not covered (or inadequately covered). The following document laid out a proposed schedule of agenda items for several meetings of the EPMG:

October 28, 1968

PROPOSED SCHEDULING OF AGENDA ITEMS FOR THE
NEXT SEVERAL EPMG MEETINGS

<u>Mtgs.</u>	<u>Subjects</u>	<u>Presenters</u>
1	<i>Plans for an expanded chemical carcinogenesis and cancer prevention program.</i>	<i>Saffiotti & Baker</i>
	<i>Interrelationships among demographic, epidemiologic, laboratory and preventive measures.</i>	
2	<i>A. General aspects</i>	<i>Baker & Schneiderman</i>
	<i>&</i>	
3	<i>B. The National Death Index, the Third National Cancer Survey, and the End Results Program: implications of data from these efforts to the Chemical Carcinogenesis and Viral Oncology Programs (What special groups, e.g., industrial or other exposure groups, should be matched against the National Death Index? What are the implications of end results data and demographic</i>	<i>Miller, Haenszel, Cutler, Bailer, Saffiotti, Rauscher, Schneiderman, Berg</i>

trends for cancer etiology and prevention activities?

What are the needs in these areas of the Chemical Carcinogenesis and Viral Oncology Programs? Clues for cancer laboratory studies from the epidemiology of congenital disorders?).

4&5 C. Laboratory Studies and Groups at Different

Risks to Cancers.

1) Identification of the groups and logistics required for laboratory studies (including question of serum storage). Miller, Haenszel, Schneiderman, Newell, Gori

2) Priority laboratory studies on the environments of the groups at risk. Saffiotti, Lloyd, Gori, Rauscher, Haenszel, Huebner, Weisburger

3) Priority laboratory studies on specimens derived from or directly with members constituting groups at different risks. Miller, Rauscher, Saffiotti

4) Pathology aspects. Berg

6. D. Malignant Transformation Studies on Specimens from High Cancer Risk Miller, Rauscher, Saffiotti

Populations.

7., *Identification of Carcinogenic Agents*

8. & *(Viral and Chemical) for Man.*

9. *A. Viral agents.*

1) *Herpes-type particles and Burkitt's lymphoma (e.g., what information is required for a decision on whether to proceed with vaccination or to reduce present efforts pending development of a definitive animal model?)* Rauscher, Huebner, Miller, Schneiderman

2) *Herpes Type 2 and cervical cancer.* Rauscher, Haenszel, Miller

B. Chemical agents.

1) *Review of history.* Saffiotti, Peters

2) *Identification of chemical carcinogens in animal systems (including end-points used).* Saffiotti, Berg, Bates, Weisburger

3) *Information required in man.* Miller, Schneiderman, Saffiotti

4) *Possible preventive actions.* Saffiotti, Gori,

Miller

- 5) Possible short-cuts to carcinogen screening (including validation of proposed screening systems). *Saffiotti, DiPaolo, Weisburger,*

Bates

10. Tobacco and Health. *Saffiotti,*

Baker

11. Review of the Status of Human Adenoviruses and Cancer; Future Course. *Rauscher, Huebner, Duff*

12. Etiology Activities and Computer, Systems Design and Programming.

A. Utilization of computer resources. *Weiss, Gori,*

B. Degree of centralization? *Schneiderman,*

C. Projected needs of the Chemical Carcinogenesis & Viral Oncology *Rauscher, Saffiotti*

13. Infectious Mononucleosis and Leukemia and/or Lymphoma. *Miller, Rauscher*

This schedule was based in part on responses from the Etiology staff to a request from the Scientific Director for Etiology for suggested agenda items for EPMG meetings. A summary of these items is given below:

SUGGESTED FUTURE AGENDA ITEMS FOR EPMG MEETINGS

The following items have been suggested by various staff members as possible future agenda items for the EPMG meetings. Some overlap and suggest very similar topics, but they are presented as received.

1. Laboratory studies in special population groups with varying risks to cancers (inherent population characteristics and/or environmental characteristics).

2. In vitro malignant transformation of tissues from high cancer risk populations: Discussion of current status of this problem (EPMG, and various investigators involved).

3. Viral or biochemical transformation of tissues from persons at exceptionally high risk of neoplasia.

Leukemia - Twins, Down's Syndrome, Klinefelter's syndrome, polycythemia vera, etc.

Lymphoma - Genetically induced immune deficiency diseases, Sjogren's syndrome.

Wilms', liver visceral cytomegaly (liver cells, for example) or adrenocortical neoplasia.

4. a) Chemical Carcinogenesis and Cancer Prevention Program.

b) Relationships between Viral and Chemical Carcinogenesis (and Biometry and Epidemiology).

5. Tobacco and Health (Reports of Subgroups).

6. Future needs for consultation service in systems design and programming for the Etiology area.

7. Utilization of Computer Resources in Etiology.

Mr. Weiss and his staff have been discussing a large variety of

Etiology programs with program leaders. When his findings and recommendations have crystallized somewhat, I (Dr. Fish) suggest that he present them to the EPMG.

8. *Carcinogenesis studies in animals: Should the most basic studies involve completely virus-free animals for both viral and chemical carcinogenesis research? If so, should a greater effort be made, now, for their development? (EMPG and various investigators involved).*
9. *How can neoplasia in domestic animals be more effectively studied at NCI?*
10. *A National Death Index may soon be established. From our knowledge of chemical or viral oncogenesis, what special exposure groups, industrial or otherwise, should be matched against this list to learn of altered cancer experience in man attributable to specific environmental agents?*
11. *Ten-city surveys: potential application in collection of data bearing on virology and pathology program interests.*
12. *Studies of herpes and cervical cancer: epidemiology, virology, pathology, and animal experimentation aspects.*
13. *Herpes-type particles in Burkitt's lymphoma: What additional information is needed for the decision to be made whether to:
(a) Move toward developing a vaccine on a large scale for determining whether it will reduce frequency of disease*

(evidence of etiological role); or

(b) Reduce present effort pending definitive proof that some herpes-viruses can induce neoplasia in some animal systems (e.g., frog tumors; Marek's disease; EB virus in animal systems)? (EPMG plus other program managers concerned).

14. Lung cancer: interrelationships between epidemiological observations and animal experimentation.

Gastric cancer: ditto.

Colon cancer: ditto.

15. Seroepidemiology: What plans should be made for storing sera in advance of knowing to what use they might be put?

16. Cancer and congenital defects: clues from epidemiology for laboratory research.

17. Electron-microscopic scanning of chromosomes in leukemia-prone subjects.

18. Standardization of histological classifications throughout

Etiology

We might make an effort to touch on this rather controversial subject in the near future.

19. Program Emphasis and Priorities in Etiology

In view of Chemotherapy's recent and projected "successes" in the chemotherapy of tumors of the fast-growing type, we might

discuss the pros and cons of readjusting some of our own priorities, either in the direction of trying to capitalize on these chemotherapeutic advances or, conversely, in the opposite direction to place more emphasis on the study of the more intractable slow-growing tumors.

20. Relation of infectious mononucleosis to subsequent development of leukemia or lymphoma. As soon as Dr. Miller's study has progressed far enough, this should be discussed if there is suggestive evidence of a correlation (EPMG only).

21. Human adenoviruses and cancer: We should have a review of all of the studies that have been made, and a discussion of the future course of Solid Tumor-Virus Segment activities with regard to this problem (EPMG, plus Drs. Huebner and Duff).

The Scientific Director for Etiology added five additional items:

22. The Chemistry Branch Program.

23. The Biology Branch Program.

24. Hypotheses of cancer etiology - How to rule in or out?

25. Identification of carcinogenic agents, viral or chemical, for man.

26. Developmental biology and carcinogenesis.

The First Meeting of the Etiology Program Advisory Committee

The first meeting of the Etiology Program Advisory Committee was held December 16-17, 1968. All members were in attendance. At the initial meeting, the main purpose was a broad over-all orientation of the total program in the Etiology area. Special emphasis, however, was given to carcinogenesis (further discussion of chemical carcinogenesis would be continued at the next meeting). The activities of the Third National Cancer Survey were also presented, and one member of the Committee expressed concern as to whether the value to be derived was worth the cost. It was pointed out that the Survey, which must be done in conjunction with the decennial census, would have a gap of 30 years if the Survey were delayed until the next census after the 1970 one. The staff thought that the data obtained in the few, well-functioning state registries were not accurate enough to permit extrapolation to a national basis when the updated local information was combined with the badly outdated national data derived from the previous Survey of 20 years before. The other aspects of the Program were well received by the Committee. These meetings were to be held twice a year ("The Regional Cancer Survey," from the Scientific Director for Etiology to Director, NCI, October 22, 1968).

1969

A Series of White Papers on Carcinogenesis

On April 14, 1969, the NCI Director sent the following memorandum to the Scientific Director for Etiology:

SUBJECT: Plans for evaluating carcinogenesis

As you know, I have for many years given a very high priority to the investigation of cancer etiology and the development of effective methods of prevention. Several recent incidents have intensified my already deep concern over the inadequacy of our efforts in this general area and more specifically in the following:

(1) Live vaccines, especially those given parenterally to young children. How adequate are existing methods for testing potential carcinogenicity of such vaccines, and what efforts are being made to follow vaccinated populations in order to detect increased incidence of malignant disease? What should the Cancer Institute be doing about this?

(2) Drugs that are administered to individuals over long periods of time. The same questions apply here as in number one, and I know you have a small program with Dr. Shubik in this area. There is one special area that I think should receive increasing attention, especially in view of the planned rapid expansion of research and development of better methods of contraception. In view of the fact that we have access to large numbers of monkeys and other subhuman primates, shouldn't we consider testing all contraceptive devices and medications for potential carcinogenesis, or is this already being done adequately as part of the laboratory workup to determine whether the devices or medications are effective and safe in the menstruating primates?

(3) Chemicals in wide use but not subject to adequate Federal control. The recent experience with the Bionetics's study in mice has caused me to conclude (a) that there are serious legal loopholes in the Federal legislation (b) that the standards for carcinogenicity testing are inadequate and are not even making use of the methods now available (c) that the scale of testing is grossly inadequate (d) that better methods are urgently needed.

(4) Epidemiologic methodology. In the case of more or less ubiquitous environmental carcinogenic agents, including viruses (which at least in experimental animals appear to be very widespread in nature), how does one tackle the problem from an epidemiologic standpoint in man? In the absence of unexposed populations that could serve as controls, what approach from an experimental design standpoint can the biometricians suggest? I have in mind here particularly problems such as those posed by the worldwide contamination of the environment with DDT. Of what use would studies comparing effects of the intensity and duration of the exposure? Could significant information be obtained by estimating body burden, i.e., DDT in fatty tissue?

As a result of my concern, I have discussed these problems with Dr. Berliner and find that he agrees with me that the Cancer Institute will be increasingly called upon to render judgments and provide scientific data, and he also agrees that we have a serious duty to take the initiative in these areas as rapidly and as fully as our resources will permit. I realize this is a large order but would very much appreciate it if you would ask appropriate members of your staff, with whatever outside consultation they may require, to prepare a series of white papers on the major problems above and such others as you feel I have overlooked. I think these white papers may be of great value to me in presenting the problem not only to the Government but also to the people so that adequate action can ultimately be taken.

Kenneth M. Endicott, M.D.

(“Plans for Evaluating Carcinogenesis,” Director, NCI, to the Scientific Director for Etiology, NCI, April 14, 1969.)

Following discussion at an EPMG meeting the Scientific Director for Etiology sent on May 20, 1969 the following memorandum:

TO: See below.

FROM: Scientific Director for Etiology, NCI

SUBJECT: Preparation of White Papers on Topics Included in Dr. Endicott's Memorandum Entitled "Plans for Evaluating Carcinogenesis" (Attached)

As evident from Dr. Endicott's memorandum, we are to prepare a series of papers reviewing for broad subject areas as to the current state of knowledge, and what additional efforts are needed to deal with major problems of these areas are also to be spelled out. I would interpret this request for recommendations to include some indication of the magnitude of resources required to successfully deal with the problems in the respective areas.

I am assigning each topic to a staff member of the Etiology Area and will expect him to call upon others within the Etiology Area and, if necessary, outside the Area to assist him; and I am sure when they know of Dr. Endicott's request, they will provide the necessary assistance. The deadline for these reports will be Friday, June 20. Their length should probably not exceed six double spaced pages; however, if additional information should be transmitted, these may be added in the form of attachments. In addition to answering the questions posed by Dr. Endicott, the report should include succinct statements on the present state of knowledge, the key problems remaining to be solved, the proposed course of action that should be taken both scientifically and managerially, and the magnitude of resources required.

(1) Live vaccines, especially those given parenterally to young children. -- Dr. Rauscher (It may be appropriate to ask Dr. Fraumeni, Dr. Bryan, Dr. Huebner, Dr. Eddy, and others to assist in the preparation of this report).

(2) Drugs that are administered to individuals over long periods of time. -- Dr. Gori (In the preparation of this report, which ought to also touch upon immunotherapy with antilymphocyte serum and immunosuppressive drugs, Drs. J. Weisburger, Volmer, Fink and others might provide assistance).

(3) Chemicals in wide use but not subject to adequate Federal control. -- Dr. Saffiotti (Drs. Peters and Bates may assist in the preparation of this report and much of the planning already laid out for the Carcinogenesis Area will be germane here so that labor involved for preparation of this report should not be greatly beyond what has already been done. I assume we will want to include natural product carcinogenesis in the report).

(4) Epidemiologic methodology. -- Dr. Miller (I am also asking Dr. Schneiderman to serve on this group and other suggested participants include Drs. Berg, Cantarow, and/or Klein. Should consideration also be given to studies on psychological factors in relation to carcinogenesis?).

Dr. Endicott has formulated these questions to be prepared for future developments when NCI is queried about meeting its responsibilities and perhaps may be very useful along the way in obtaining additional support for work concerned with the Etiology Area and cancer causation and prevention more broadly. I know you will devote serious efforts to providing Dr. Endicott with the kind of helpful, penetrating, definitive information he needs.

Carl G. Baker, M.D.

Distribution: Dr. Gori

Dr. Miller

Dr. Rauscher

Dr. Saffiotti

Dr. Schneiderman

Attachment (“Preparation of White Papers on Topics Included in Dr. Endicott’s Memorandum Entitled ‘Plans for Evaluating Carcinogenesis,’” Scientific Director for Etiology, NCI, to Drs. Gori, Miller, Rauscher, Saffiotti, and Schneiderman, May 20, 1969).

The White Papers prepared by the Etiology staff dealt in depth with the issues raised in Dr. Endicott’s memorandum and the guidelines in the transmittal memorandum of Dr. Baker. The Papers demonstrated again the value of having inputs from a few knowledgeable experts (without the *compromised* output required of larger committees).

In Dr. Miller’s paper he pointed out [something seemingly forgotten by many epidemiologists] the important concept that *in the establishment of a causal relationship, statistics alone are usually not enough*; implications of causality are greatly aided by demonstrating one or more of the following:

- a. a dose-response effect,
- b. a specificity of effect; that is, for certain rather than for all causes of morbidity,
- c. absence of an influence of concomitant variables,
- d. results that are consistent with other available information from laboratory, clinical and epidemiologic studies, and,
- e. *reduction in disease frequency as the environmental agent is withdrawn.*

Dr. Miller considered that the two greatest needs in cancer epidemiology were an increase in the resources for record-linkage and a new approach for increasing the competence and interest of physicians and statisticians in epidemiology. Of special importance would be establishment of the National Death Index. The White Paper also indicated the need to expand

further the recent NCI movement to relate epidemiologic information with laboratory and clinical data. Steps to implement actions needed were outlined, though political factors would make their realization very difficult.

Dr. Schneiderman's July 23 Paper discussed in depth how the scientific investigation of DDT exposure in man should be conducted. This approach would hold for other studies in man with similar exposures to other materials. Needless to say, such studies would be elaborate and costly, but sound data could be obtained. If, on the other hand, separate small grant-supported projects investigated the problem, the costs would be small, but the data would be useless for solving the problem in epidemiology. With respect to the problem of exposure to drugs of individuals over long periods of time, two population groups were identified that could be investigated. The Paper pointed out that carcinogenesis screening is a different problem from chemotherapy screening. The chemotherapy problem attempted to find (any) useful materials. False negatives could be tolerated in a situation in which it was possible that the material (or one closely related to it) would be tested again. The carcinogenesis problem was one that conceptually permits no false negatives. Failure to find a chemotherapeutic material meant that the current situation would be unchanged, and certainly not worsened. Failure to find a carcinogenic material could be followed by the introduction of the carcinogen into use--and thus a worsening of the current situation. For materials currently in use there are at least two additional things to be considered:

- a) What is the relative carcinogenicity of the material (relative to possible substitutes)?
- b) What are the economic or social costs of substitution?

[the extent of total human population exposure should also be considered in determining priorities of screening]. Genetic disposition and personality characteristics were also mentioned as two areas that should be investigated.

Dr. Saffiotti's July 1969 White Paper dealt with the five questions posed by Dr. Endicott. Of all the problems in the cancer field, those in carcinogenesis were the most difficult to solve for a variety of reasons: the number of chemical compounds and their variety of structures and reactivities were very high; the methodology for determining carcinogenicity was inadequate; the pharmacological understanding of the many different compounds was minimal; the epidemiologic data were deficient; and the complex political and economic factors made it difficult to take corrective actions. The number of known chemical compounds in 1969 was about 3 million [in 2001 over 23 million known compounds existed]. Only a small portion of these compounds had been tested for carcinogenicity. The hope was that an understanding of the mechanisms of action in cancer causation would allow preventative actions that could avoid the need for massive screening [indeed molecular biology results currently underway may lead to such results]. A plan for an expanded program in chemical carcinogenesis had been developed, but the overwhelming inadequacy of resources available compared with the magnitude of the task, necessitated that only a few small steps of the plan could then be implemented. Legal loopholes, such as those allowing tobacco to escape regulation similar to that for foods and drugs, were discussed. New legislation needed was outlined.

Dr. Rauscher's May 1969 White Paper was very extensive and included supplementary reports by Drs. Bernice Eddy, Robert Miller, and Robert Huebner. The paper made a number of points. The problem of safety testing of live virus vaccines for potential cancer producing activity had two equally important components: 1) The possibility that the substrate cells (animal

or human) which were to be used for growing the attenuated virus (live virus vaccine) might contain an indigenous oncogenic virus that could contaminate the vaccine and make it hazardous for human use; and 2) There was also the possibility that the live virus vaccine itself might possess the potentiality of acting as a carcinogen, or of participating as a co-carcinogen, to cause cancer in vaccinated subjects. It is clear that there is no such thing as a test for safety that guarantees absolute accuracy. Nevertheless, testing should make use of the most recent, up-to-date methodology applied to both the material being tested and the test system employed. For example, to the extent possible, the test system (e.g., animals or tissue culture cell lines) should be free of extraneous viruses, and as full a knowledge as possible of viruses present in the test material should be in hand. These and other reagents should be high quality and monitored for quality as well. Indiscriminate blind testing of vaccines, *in vivo* or *in vitro*, without knowledge of the sensitivity of the test systems for detecting oncogenic activity is therefore courting undetermined risks. Dr. Rauscher gave the background experience with viral vaccines and outlined the problem of possible use of live virus vaccine (especially in young children), covering laboratory and epidemiologic aspects. Examples of newer *in vitro* methods included: 1) use of highly susceptible tissue culture transformation systems (cells from Fanconi's anemia, Bloom's and Down's syndromes, and leukemia twin subjects); and 2) tissue culture cell systems that are not transformed by viruses alone or chemicals alone but will be transformed when both are added together. H. Igel, R. Huebner and H. Turner submitted a paper in May 1969 that showed that with C57BL mice, cancer induction with chemical carcinogens, as was shown earlier by M. Lieberman and H. Kaplan with irradiation, led to induction of lymphomas and the development of murine leukemia viral antigen in the lymphoid tumors. The cell-free transmission of methylcholanthrene-induced lymphomas and development of murine leukemia

viral antibody suggested that unmasking of latent leukemia virus might represent an indigenous actuating cause of the leukemia. Dr. Miller, based on experience gained from study of mass-immunization with polio-vaccine containing SV-40, suggested four steps that would greatly simplify follow-up studies:

1. to maintain samples of vaccine lots frozen in storage;
2. for manufacturers to keep records identifying persons experimentally immunized, with notation of the vaccine lot used;
3. for physicians to note on their records the lot numbers of (at least) newly approved vaccines for general use; and
4. for similar permanent immunization records to be kept by the mother for each of her children.

Dr. Rauscher outlined proposed future activities, listed the required resources, and set forth new revolutionary concepts:

“Newer techniques comparable to those developed earlier for the avian tumor viruses recently have been developed by Dr. Huebner and associates for the mouse C-type oncogenic RNA viruses. Extensive studies by Dr. Huebner and associates on the natural history and biological properties of these agents had resulted in a new working concept; namely, that most if not all strains of mice (and possibly also of other mammalian species) carry latent intracellular infections of oncogenic RNA viruses (“oncogenes”) which are transmitted vertically (i.e., from parent to offspring) along with normal genetic material. As in the case of normal genes, most of which may be repressed (“switched-off”) while others are derepressed (“switched-on”) in cells at any given

time, the parasitic oncogenes may be similarly switched-off or switched-on. Thus, many inbred strains of mice are naturally switched-on not only for virus expression but for early tumor induction, whereas other genetically closely related colonies derived often from the same inbred lines may be completely switched-off for virus and tumor expression” (see “Progress Report #6, Special Virus Cancer Program, July 1969).

This theme, quoted from Dr. Rauscher’s White Paper based on Dr. Huebner’s supplemental report, was first set forth in a May 7, 1969, memorandum from Dr. Huebner to Dr. Endicott. It led to the ground-breaking publication with George Todaro: *Oncogenes of RNA Tumor Viruses as Determinants of Cancer*, Proc. Natl. Acad. of Sci. U.S., Vol. 64, No. 3, pp. 1087-1094, Nov. (1969) (see below).

Provirus Model and Reverse Transcriptase

Howard Temin had studied Rous Sarcoma Virus (RSV) for several years and worked out many events in the viral infection process in chicken fibroblasts (or, with Mouse Sarcoma Virus (MSV) in mouse fibroblasts). The RSV (a retrovirus) is an RNA virus that in the cell converts the RNA information into complementary DNA. This DNA, called by Temin a *provirus*, is incorporated into the fibroblast cell genome. He and David Baltimore independently discovered in 1969 the enzyme that catalyzes the transfer of information from RNA to DNA. The enzyme is called *reverse transcriptase* because the direction of information flow in a dividing cell is the reverse from the usual flow (DNA to RNA). A large amount of virus was provided by the SVCP to Dr. Baltimore. A provirus model was set forth which postulated that latent endogenous provirus could become established in the germ line. Exogenous cancer-causing chemicals could activate a latent endogenous provirus and cause its expression; retrovirus particles would be

produced; and transformation in tissue culture cell lines or tumor formation in animals could be initiated. Examples of this activation are known. This endogenous provirus model might also explain heritable human cancers. The Provirus Model became popular, but lost its popularity when it became clear that, although endogenous provirus could be present in human germ lines, they do not produce infectious virus particles (unlike chicken or mouse proviruses); none of the common cancers (in the West) showed clear retrovirus involvement; and retrovirus particles in human tumors (without exception) had not been found.

The Oncogene Hypothesis

Based on the evidence at the time, Bob Huebner set forth the oncogene hypothesis, first in the May 7, 1969, memorandum to Dr. Endicott and later in the publication with George Todaro in the Proceedings of the National Academy of Sciences, U.S. entitled “*Oncogenes of RNA Tumor Viruses as Determinants of Cancer*” (see above). The evidence, derived from investigations with tumor retroviruses, consisted of extensive sero-epidemiologic data as well as animal and tissue culture results. As stated in the paper “ - *the viral information can be transmitted from animal to progeny animal and from cell to progeny cell as a repressed viral genome. In this sense these agents behave more like cellular genes than like infectious virus; consequently, horizontal transmission (from animal to neighboring animal and from cell to neighboring cell) as a natural mode of spread is infrequent and a relatively unimportant factor in the natural occurrence of cancer.*” Further, “*The new hypothesis predicts that both spontaneous cancers and cancers induced by chemical and physical agents will be the result of expression of the oncogene(s) of covert C-type RNA virus. Numerous studies, some of them only recently completed, have established these viruses as significant causes of cancer in mice,*

chickens, cats, and probably also in hamsters. The C-type RNA-virus particles have also been observed by electron microscopy in tumors of guinea pigs, rats, swine, snakes, and humans; thus, three classes of vertebrates are now known to have at least some natural expression of viruses of this class. The central hypothesis implies, therefore, that the cells of many if not all vertebrates carry vertically transmitted (inherited) RNA tumor virus information (virogenes) which serves as an indigenous source of oncogenic information (oncogenes) which transforms normal cells into tumor cells; additional phenotypic expression of viral information may or may not also occur.” And further, genetic and antigenic data “ - are most consistent with the hypothesis of endogenous viral information present in apparently virus-free cells of the chick, the rat, and the hamster. Like many cellular genes, the genes coding for the unique C-type viral functions may not be expressed under normal conditions because of potent repressors for expression. Viewed in this light, the application of radiation, chemical carcinogens, and the natural aging process are believed to ‘switch on’ the viral genome, perhaps by decreasing the level of repressor activity. And further still, “Lifetime studies of C-type viral expression in most established colonies of mice, including wild mice, have revealed no murine colonies that are wholly free of C-type RNA virus involvement. This implies that the arrangement between this virus and its natural host is a long-standing one. Its demonstration in nine different species and in three classes of vertebrates, together with the evidence of vertical rather than horizontal transmission as the chief mode of spread, suggests that this virus genome is an essential part of the natural evolutionary inheritance of vertebrate cells.”

This paper stimulated considerable interest. The hypothesis was built on extensive sero-epidemiologic evidence in humans and animals based on work conducted by Dr. Huebner and his associates. The paper led to greater attention to the genetic *information* of viral genes and

cellular genes and their possible relationships. The proposal of vertical transmission of genetic information in latent (*repression*) form gave credence to the activation (*derepression*) of genetic information that led to tumor development following aging or application of chemical carcinogens or irradiation. The implication that the arrangement between the C-type RNA virus and its natural host is a long-standing one and the vertical transmission as the chief mode of spread suggested that the virus genome is an essential part of the natural evolutionary inheritance of vertebrate cells. This research set the stage for greater understanding. Later availability of various reverse transcriptase (tumor) virus *mutants* and of *restriction endonucleases* allowed dissection of genomes so that mapping of genes in the virion and identification of particular genes could be related to transformation (as well as other activities such as viral reproduction). Later work showed that sequences in normal cell genes were similar to those in tumor viruses. However, these normal cell genes could be derepressed to lead to tumor formation without activity of viral genes.

Tumor Virus Mutants

Identification and production of mutants of DNA and RNA tumor viruses were underway in 1968-1969 by Leo Sachs, Renato Dulbecco, Howard Temin, Peter Vogt, David Baltimore, and G.S. Martin. A SVCP contract with Dulbecco was active to produce such mutants of polyoma and SV-40; they would be made available to investigators. These research activities led to very important tools: temperature-sensitive mutants. Some of these Rous sarcoma virus mutants would induce oncogenic transformation of tissue culture cells grown at 34 degrees C., but would lose that ability if growth was at 41 degrees C. These changes were reversible. The viruses would continue to multiply at either temperature. Further studies indicated that a single gene -

called *src* - was involved in transformation. Thus, the stage was set for mapping the region (about 2000 nucleotides) of the *src* gene.

Safety Precautions for Viral Oncology Research

The Chairman of the Genetics Study Section, Dr. James Crow, expressed concern in a June 13, 1969, letter to Dr. Endicott about the possible health hazard of handling large quantities of tumor viruses (though it was noted that no evidence of human hazard was in hand). He asked that some appropriate group consider the appropriate protective procedures and assume responsibility for monitoring and enforcing the necessary safety practices in relation to research grants. Dr. Crow suggested that a helpful step might be for a safety specialist to be included in the review or on site visits when large-scale production programs are considered. He also expressed appreciation of the expertise of Dr. Al Hellman, Head, Biohazards Control and Containment Section, Viral Oncology Area, Etiology, when Dr. Hellman met with the Study Section.

Dr. Endicott's sent his July 22, 1969, reply to Dr. Carew as follows;

"Your letter of June 13 on possible health hazards that might be related to large-scale virus studies has been discussed with members of the National Cancer Institute staff. As you indicated, there is no evidence that there is danger to man with the handling of virus preparations that can produce tumors in other species when low level operations are involved. It is also true that we have no evidence that the danger exists at high level operations. Because hazard might exist, however, the NCI took several steps in the initial planning and subsequent conduct of the Special Virus Cancer Program activities to deal with this possibility. This included short- and long-term research projects on transmission and infectivity of viral

preparations; ability to inactivate oncogenic viruses (e.g., by pasteurization); design and fabrication of special equipment and facilities, including a new special structure; and the preparation of a manual designed to aid investigators who might be handling potential and actual hazardous biological preparations.”

“In the conduct of the Special Virus Cancer Program, which includes joint efforts with many grantees, we have made repeated efforts to disseminate information on the program, including extensive information on possible biohazards and their handling. We have followed the general course of affairs of long standing among those working with microbiological materials; namely, that those expert enough in the field to receive funding also are knowledgeable enough and should carry the responsibility to see that appropriate safety measures are employed in the handling of dangerous materials. Most virologists I have discussed these matters with still continue to believe that this approach is the appropriate one. In general I am in agreement with this, but I think we need to make the information about handling of hazardous biological materials more broadly known, particularly to those investigators who are not virologists but who may be working with sizable quantities of oncogenic viruses. However, I do not believe it appropriate for the Federal Government staff in Washington to monitor the practices of every institution receiving research grants and to enforce the necessary safety practices. Rather, I believe it important to insist that this responsibility be maintained locally by the respective grantee institutions.”

“Your suggestion that a safety specialist be included in the review or on site visits when large-scale virus production programs are considered is a good one, and I will recommend to the Division of Research Grants that they add such specialists, most probably on an ad hoc basis, in appropriate cases. Also, in such cases we would be prepared in the Cancer Institute to

make available upon the investigator's request a copy of the manual prepared on the handling of hazardous viruses (this manual is due from the printer at the end of the this month). I will also explore with the appropriate staff in the Cancer Institute the preparation of an article on the potentiality of hazard in the field of viral oncology which might be suitable for publication in Science."

"I would be interested in your reaction to these proposals. I think we have had for some years similar problems in other aspects of microbiological research which, of course, continue. Most of the accidents in these other areas have not been due to lack of knowledge of hazard nor of the latest information on needs for handling such hazardous materials, but usually really were 'accidents'. I certainly hope we do not have any major problem of this type in the viral oncology field, and the Cancer Institute has moved ahead with several precautionary steps, even though a number of highly knowledgeable scientists in the field feel that this has not been necessary in the face of lack of evidence of hazard. I am glad to learn that Dr. Hellman was helpful to the Study Section. I look forward to hearing from you" ("Biohazard Control and Containment in Oncogenic Virus Research," edited by Alfred Hellman, NIH, NCI, US Public Health Service, DHEW, August 1969). Dr. Crow sent a thank you letter on September 4, 1969.

The September 29-October 1, 1969 NACC Meeting

The Annual Program Review Document of the Etiology Area was distributed to the NACC prior to the meeting. The Scientific Director for Etiology discussed the further enlarged plans for a carcinogenesis research program and the shortages in dollars and manpower in the area. The total investment in Carcinogenesis (contracts and intramural efforts) rose from

\$7,238,000 to \$8,466,600 over the previous year. The Viral Oncology Area stayed about at the same level, and Demography rose slightly, mostly because of the Third National Cancer Survey.

Dr. Rauscher presented the review for the Viral Oncology Area. The Viral Oncology Area, including the summary reports on each contract, covered 233 pages of the 429 pages for the Etiology Program Review Document. Dr. Rauscher discussed the Background, Scientific Activities, Management Activities, Problems and Projections, and Major Program Modifications. The four Branch Reports were part of the material. The epidemiologic and animal and tissue culture findings and the oncogene hypothesis of Dr. Huebner (see above) were presented to the Council. Also emphasized was: the switching on of the viral genome by chemical carcinogens and radiation; the finding of evidence of the C-type viruses in nine species of animals, in four of which the virus was transmitted; the sero-epidemiologic evidence in humans and animals; the finding of widespread involvement of C-type RNA viruses in most established colonies of mice; and the vertical transmission as the chief means of spread, suggesting that the virus genome is an essential part of the natural evolutionary inheritance of vertebrate cells. Results from NCI field epidemiologic studies in Africa and from collaboration between NCI and Chinese investigators had reached the stage where it was reasonable to conclude that Burkitt Lymphoma and the nasopharyngeal cancers in China are caused by the Epstein-Barr virus (EBV). Epidemiologic evidence on the association of infection by Herpes simplex Type 2 and cervical cancer made it likely that causation of this cancer was by that Herpes virus. Thus, these two findings mean that the basic assumption of the SVLP and the SVCP that at least one human cancer is virus-induced has been validated.

Dr. Rauscher presented other examples of highlights resulting from the SVCP. Of special interest was the isolation of a cat sarcoma virus that induced sarcomas in cats, dogs, hamsters,

rats, and rabbits, and is recoverable in an intact infectious form from tumors induced in these foreign species. Evidence exists which suggested that host cell genes exercise control of both experimentally induced and naturally occurring C-type RNA virus leukemia and sarcoma. The nature and degree of this control varies with mouse strain genotype and the natural sources of virus. Thus as a result of serial passage in a variety of individuals, the established standard avian and murine leukemia and sarcoma viruses exhibit well defined but broad host ranges and considerable antigenic variation in makeup and potency of oncogenic expression. New techniques are available for virus demonstration to study wild isolates of C-type RNA viruses. Several hundred isolates fall into a single antigenic group and generally have limited and sometimes highly specific host ranges. As compared to established virus strains, wild isolates have relatively low but definite oncogenic potential. Inbreeding practices, both planned and unplanned, apparently account for the differing degrees of virus (V), antigen (A), and tumor (T) expressions found in different strains of laboratory animals.

Dr. Dulbecco on contract continued to make available to investigators temperature-sensitive mutants; these mutants were important for research on the mechanisms of carcinogenesis at the sub-viral level. Dr. Maurice Green on contract continued development with radioactive isotope techniques his search for virus-specific genetic materials in human tumors. It had been shown that replication of MSV, MLV, and RLV is dependent on DNA synthesis. With collaboration of the intramural staff of the Chemistry and Biology Branches, it was shown that viral RNA from RSV and MSV is incorporated into virions about two hours after its synthesis; Actinomycin D and Cyclohexamide do not prevent assembly of virus, but inhibit the synthesis of virus components.

Dr. Rauscher discussed other examples of progress highlights. It is remarkable that the Viral Oncology NCI staff had in press 90 scientific papers in 1969 when over 80 percent of the time of many staff members went for management duties (reviewing and monitoring contracts as project officers; sitting on various committees concerned with planning new studies and evaluating new proposals; providing training to, not only NCI staff, but outside investigators as well; receiving 75 visitors, 13 of which were from foreign countries; giving over 100 lectures; and, as the Chief of the Viral Biology Branch put it, looking for a place to park). SVCP publications up to September 1969 totaled 261. The Program Review Document contained an extensive bibliography.

Critics of the use of contracts often claim that once a contract is awarded it goes on and on with little modification. The NCI staff analyzed the experience of monitoring Virology Oncology contracts, 1965-1969, with particular attention given to the reasons for modifications (terminations, changes in workscope, increases or decreases in funding, and establishment of new contracts). As reported in the 1969 Etiology Annual Report, the analysis of 180 contracts showed the following data: terminated, 61 contracts; workscope changes-deletion, 23 contracts; workscope changes-addition, 16 contracts; increased funding and activities, 13 contracts; decreased funding, 44 contracts; and establishment of new contracts, 36 contracts. The principal reasons for these actions were based on (a) changing program priorities; (b) successful project completion; and (c) availability of funds. The success of developmental contracts in providing resources and the enlarging of oncologic research effort had seen the beginning of commercialization of resource production and kits for techniques growing out of the SVCP activities. Because no additional appropriated funds were expected in Fiscal Year 1970, about

\$1.5 million had to be gleaned from existing contracts to cover the implementation of other highly important contract research, as well as other costs.

The NCI staff gave considerable attention to making sure that minutes of the Contract Review Committee meetings accurately reflected the basis for the recommendations made at the meetings (“Preparation of Minutes of Contract Review Committee Meetings,” from Gerald Myers, Administrative Officer, Etiology, NCI to Chairman and Executive Secretaries of Etiology Contract Reviews Committees, July 24, 1969).

The new biohazards building was nearing completion. The Biohazards Control & Containment Section continued to monitor potential health hazard situations and provide advice on practices, instrumentation, and facilities in the biohazard area. Of the \$26,103,000 for total Etiology contracts, \$20,619,800 was for Viral Oncology. The distribution of the total Etiology Area funds of \$33,456,000 was: Carcinogenesis; 25%; Demography: 11%; Viral Oncology: 62%; and Office of the Associate Director: 2%.

The non-governmental members of the NACC consisted of:

Dr. Hugh Butt	Mr. John Mack Carter
Mayo Clinic	Ladies Home Journal
Dr. Murray Copeland	Dr. Juan del Regato
M.D. Anderson Hospital	Penrose Cancer Hospital
Dr. Emmanuel Farber	Dr. Sidney Farber
U. of Pittsburgh School of Medicine	Children’s Cancer Research Foundation
Dr. Rubin Flocks	Dr. John Hartmann
Univ. of Iowa	The Children’s Orthopedic

Univ. Hospitals	Hospital, Seattle
Dr. Leon Jacobson	Dr. Joseph Melnick
Univ. of Chicago	Baylor Univ.
Dr. Howard Skipper	Dr. Paul Talalay
Southern Research	Johns Hopkins
Institute	University
Mr. Danny Thomas	Dr. Jane Wright
Danny Thomas Productions	New York Medical College

(“National Institutes of Health, National Cancer Institute, Etiology, Annual Program Review Document,” September 29 – October 1, 1969).

A New NCI Director

Dr. Robert Marston succeeded Dr. James Shannon as Director, NIH, on August 29, 1968. On November 10, 1969, Dr. Marston appointed Dr. Endicott Director of the Bureau of Health Manpower, a newly formed NIH entity created by the Congress to meet the personnel shortages in the health field. Dr. Carl Baker was appointed Acting Director, NCI, November 10, 1969, and Director, NCI on July 13, 1970. Bob Learmouth, Executive Officer, moved with Dr. Endicott over to the new Bureau. Mr. Calvin Baldwin was appointed Executive Officer. Dr. Jesse Steinfield, who had been Associate Director for Program, had left NCI to become Surgeon General, U.S.P.H.S.; Lou Carrese was appointed to fill this vacancy. Dr. Rauscher moved to Associate Scientific Director for Etiology, and Dr. John Moloney was appointed to head the Viral Oncology activities.

NCI Budget

On December 9, 1969, Dr. Robert Huebner took the unusual step of writing a memorandum directly to DHEW Secretary, Robert Finch. The subject was "Budget Cuts." Enclosed were two short versions of the "*new unitary theory of cancer*" that "*provide documentary evidence of its heuristic value and validity in helping to explain both natural and induced cancers.*" He expressed the hope that the Secretary would find time to read them. The opening paragraph pointed out the great expense of extending the observations on the C-type virus genome, especially in providing newly developed reagents and test systems. Further, "*The gradual erosion of the funds earmarked for viral-cancer research which had been included in the 1971 DHEW budget is a tragic denouement to what promised to be a brilliant new opportunity to make a significant breakthrough in cancer etiology and possibly control.*" The memorandum stated that recent data indicate that "*the time is ripe for a concerted attack on the virological, molecular, genetic and immunological factors in cancer.*" And further, "*The attack we envision on basic etiology and prevention of cancer cannot be mounted unless we can think and operate along 'Big' science targeted NASA-like lines. Many of those (including myself) who have been immersed in studies of this problem for many years believe that, like the moon landings, control of cancer can be achieved. It seems equally clear to us that if this is to be accomplished, it can only be done with an effort comparable but not equal to moon shot proportions. We think the effort, viewed in any context, should be worth several hundred million dollars. The talent needed in this effort is available and eager; all that is lacking is the will and support of the Administration.*" "*But the current situation is much worse than being unable to mount such an effort. The existing new program has been cut, and the projected increase authorized is being*

whittled away - presumably by persons who have little knowledge of what such cuts are effecting.”

The NIH request to the Bureau of the Budget for NCI was \$200,074,000. The figure from the Administration to the Congress was \$187,707,000, and the House Allowance was \$182,593,000. The 1969 Appropriation for NCI was \$185,149,500, an increase of \$1,793,500. At this level several planned efforts could not be initiated, and restrictions on grants would be required.

On December 18, 1969, a requested memorandum from NCI was sent to President Nixon; it was a proposal for a \$35 million increase for NCI for Fiscal year 1971. Five days later the NCI sent to Secretary Finch a requested one-page memorandum on the current status of the viral oncology field; it was for discussion with the President the next day.

Analysis of NCI Grants

Harry Canter, Head, Program Analysis and Reporting Section, OADEA, presented at the NACC September-October meeting an analysis of the 1,796 grants funded for F.Y. 1968 in the total amount of \$94.232 million. It was estimated that 1,879 grants would be funded for F.Y. 1969 in the amount of \$96.067 million.

Research Grants

Causation 289 grants (\$13.390 million)

Morphology, Biochemistry
& Physiology 224 grants (\$14.086 million)

Host-Cancer Relations	74 grants (\$3.310 million)
Diagnosis	30 grants (\$0.954 million)
Epidemiology	11 grants (\$0.262 million)
Therapy	486 grants (\$28.707 million)
Other	175 grants (\$11.556 million)
General Research Support	(\$6.899 million)
Training & Research Cancer Program	507 grants (\$15.069 million)
Grand Total	1796 grants (\$15.069 million)

(“NCI Annual Report, July 1, 1968 – June 30, 1969, Extramural Activities, Appendix I,”
September, 1969).

1970

1970-1975 Projection for the Special Virus-Cancer Program

On January 7, 1970, NCI received a request through Financial Management channels for projection of anticipated funding 1970-1975 for the Virus-Cancer Program, the response to be at NIH at close of business January 8, 1970. The request, which originated in the Bureau of the Budget, called for, in addition to tabular material, a short narrative (*of one page or less*) explaining how the program would be developed, and the progress and accomplishments expected. This *marvelous prognostication* (of one and a half pages) reached NIH on January 9, 1970. The accompanying table showed expenditure figures (in thousands) for Collaborative Research and Development for Viral Oncology activities: 1970 - \$19,570; 1971 - \$25,099; 1972 - \$46,622; 1973 - \$50,819; 1974 - \$55,392; and 1975 - \$60,377. Program projections extended current operational and planned efforts, including special emphasis on molecular biology,

immunology, and studies on cancer causation with combinations of chemical and viral agents. The hereditary (or genetic) information of tumor viruses would need to be detailed to allow the acquisition of knowledge at the molecular level about which genes were involved in tumor induction.

NCI was asked by the DHEW Budget Division (deriving from an inquiry from Congressman Moss via the White House) the cost of leukemia research. This question was difficult to answer because of definitional problems and mixtures of research efforts. The estimate for NCI programs was in the neighborhood of \$30 million, though the 1971 President's budget figure was about \$38 million ("1970-1975 Projection for the Special Virus-Cancer Program," Earle Browning, Financial Manager, NCI to Memo for the Record, with accompanying table, January 12, 1970; "NCI Leukemia Research Support," Earle Browning, Financial Manager, NCI, For the Record, February 27, 1970).

NCI Advisory Committees

The claim was frequently made that NCI did not have sufficient advice from advisors outside the Government. In 1970 NCI had advice from 48 standing advisory committees with membership containing non-NIH/NCI staff plus 40 of the 64 NIH Study Sections. The 48 committees were constituted as follows: Chemotherapy: 10; Etiology; 19; Extramural Activities: 8; General Laboratories and Clinics: 9; and Office of the Director: 2. An additional 16 committees composed of NIH/NCI staff were in operation. Needless to say, great efforts were required to service these committees, and a large amount of paper was generated to inform the committees of the continuing activities of the respective programs. Even with this many committees, many of those used to the grants systems still objected that the contract funded

programs were -- as they saw it -- “not as good as the grants” area. The criteria for evaluating the two areas were different, and the responsibilities placed on the program leaders in the former area were heavy (see the Ruina Report above). The measure of success in the contract funded areas was whether the contracts were moving the overall program toward the defined objectives, as well as whether progress in extending basic knowledge was achieved. To manage targeted research programs effectively, it was thought that considerable authority (“power”) had to be given to those who were charged with responsibilities to execute the programs (see the Ruina Report above). Moreover, the various contract efforts must be integrated within the total program, a situation not required with the projects in the grants area. However, though the staff had their hands full in managing the large, expanding program efforts, the operations of the contract funded area probably should have been more open to permit the scientific community to see or participate in the activities. Partly for this reason, in the planning of the total cancer effort requested by Congress in 1971 and 1972, the participation of over 200 scientists in the planning effort was sought and achieved (see below).

The September 28-30, 1970 NACC Meeting

As customary, the Annual Program Review Document with Reports of NCI Program segments was sent to the Council members prior to this extra meeting for program reviews. Dr. Rauscher presented the programs of the Etiology Area, including the review of the Viral Oncology activities. Of the 460 pages for Etiology, 233 pages covered Viral Oncology activities. From contacts with the scientific community, the SVCP participants noted a change in attitude towards viral oncology research. Outstanding scientists were entering this field and many became participants in the SVCP. Outstanding investigators serving as Project Directors

on NCI Viral Oncology contracts included: F. Deinhardt; J. Grace; L. Dmochowski; J. Melnick; Y. Ito; G. Klein; D. Yohn; F. Rapp; L. Hayflick; G. Henle; A. Kniazeff; F. Bang; S. Kalter; R. Luginbuhl; R. Marshak; C. Rickard; V. Groupé; J. Warren; G. Theilen; E. Lennette; M. Hilleman; R. Dulbecco; M. Green; M. Gardner; A. Giradi; L. Sachs; N. Anderson; H. Meier; S. Madin; S. Spiegelman; D. Moore; G. de Thé; and others. Several of the Project Directors were in industrial organizations. Other investigators, many of whom were grantees of the NCI, received resources from the SVCP and exchanged information, much of it well ahead of publication, often at the annual SVCP meetings. NCI grantees included were: J. Svoboda; R. Haris; M. Epstein; D. Burkitt; P. Clifford; M. Pike; B. Henderson; M. Boiron; F. Haguenu; J. Levy; W. Schaffer; A. Graffi; H. Bendixen; W. Jarret; B. Lapin; A. Sabin; B. Roizman; L. Old; J. Trentin; J. Sinkovics; A. Nahmias; D. Baltimore; and later, L. Levintow, H. Varmus, and M. Bishop. This new emphasis on viral oncology resulted from new research leads, development of testable hypotheses, development of new techniques and test systems, and broader conceptual formulations based on recent findings. As shown by the Annual Reports from the NCI Viral Oncology areas, the activities of the SVCP were playing key roles in these developments.

In his presentation before the Council, Dr. Rauscher summed up Huebner's Report on the Viral Carcinogenesis Branch, quoting : *"The highly predictable natural incidence and behavior of most cancer in animals as well as in man plus a number of new discoveries and the resulting development of new concepts and insights led scientists within the Viral Carcinogenesis Branch in FY 1970 to concentrate on the unique C-type RNA tumor virus genome as the most likely important viral cause of the generality of cancer. The new concepts and approaches, and the results of studies carried out in FY 1970, were epochal for SVCP since they led to a testable (heuristic) new hypothesis concerning the basic inherited nature of the RNA viral genome as a*

general cause of cancer and to a unitary theory capable of explaining spontaneous cancer as well as cancer evoked by exogenous environmental pollutants, endogenous physiological aberrations, genetic defects and mutations, as well as cancer clearly induced by viruses in experimental animals.”

“In fiscal year 1970 investigators, utilizing sensitive new tests for the subinfectious gs (groups-specific) antigens of the C-type RNA tumor viruses, made a number of new discoveries, as detailed in the Summary Report of the VCB, which led in turn to the new hypothesis.”

“This hypothesis of Dr. Robert Huebner, et al. proposes that cells of probably all vertebrates have RNA tumor virus genomes of the C-type, the prototypes of which are avian sarcoma virus described by Rous and the murine leukemia virus described by Gross. These genomes we postulated must be transmitted from parent to offspring, and from cell to daughter cell, as part of normal inheritance. Host regulator genes and repressors and various environmental carcinogens were regarded as factors controlling the expressions of the oncogene(s) and virogene(s) of the generally switched off viral genome. This hypothesis therefore views cancer as a natural biological event determined by spontaneous and/or induced ‘switched on’ or derepression of universally prevalent specific viral oncogenes, thus providing a possible basis for a unifying theory of cancer which is consistent with naturally occurring cancers as well as with those induced by radiation, chemicals and viral agents. Genetic defects, mutations, inducing agents, and finally the aging process itself, all appear to act to decrease the repression of the endogenous virogene(s) and oncogene(s). Other endogenous host factors, such as the immunological and hormonal systems, are viewed as probably not involved in the oncogenic process at the cell level but they are potent additional determinants of cancer as a clinical entity in the whole animal.”

“These new observations when viewed in the light of this unitary theory and the assumption of the universality of the genetic code, inevitably may have a radical influence on our thinking and overall approaches to the prevention and treatment of cancer. Thus, the concept of built-in virogenes and oncogenes, the expressions of which are recognized by both the whole organism and the individual cells as ‘self’ very likely explain the failure of current approaches to control the majority of cancers. Contemporary therapeutic efforts based on destruction of transplanted tumors in experimental animals, surgical and radiation treatments and experimental immunological vaccines might now be viewed as largely palliative and, more frequently than not, temporary in their effects on cancer. Although these therapeutic measures represent enormous advances and are life-giving in a good many instances, the only satisfactory final solution will have to start with a recognizable handle on the basic inherited genomic cause of cancer which then leads to the development of methods (1) to repress the built-in oncogene(s) from ‘doing its thing’ in the normal cells and (2) to devise ways for fortifying and supplementing the body’s natural protective immunological mechanisms. We believe, therefore, that the eventual control of cancer will have to come about at the cellular level through ‘repressor’ control of oncogene expression, and at the organism level through maintenance and/or substitution of specific immunological ‘bullets’ aimed at specific tumor cell proteins which inevitably must be produced as the result of abnormal gene expressions which lead to the neoplastic state.”

“The significance of the direct evidence for RNA tumor virus gs antigen expression in virtually all mouse embryos and indirect evidence for similar general expression during prenatal life in cats, hamsters and chickens must still be determined. While it is impossible at this stage to rule out a ‘nonsense gene’ role for the C-type virus, its involvement in 4 species and 2 classes of

vertebrates suggests that embryonic expression of the genome is a general biological phenomenon, and because of this it is logical to suspect that it must have a functional role in embryonic development. Just what this role might be is wholly undetermined but the stimulating effects of C-type RNA virus infection on cell growth in tissue culture, the cell transforming effects of certain highly oncogenic strains and their frequent tumorigenic activities in vivo suggest many possible influences on both normal and abnormal development in the embryo.”

“Increasing knowledge of host cell gene controls of the various C-type RNA genome expressions acquired by SVCP scientists in FY 1970 promise to provide some of the keys needed to explain the role(s) of the fascinating genome found with increasing frequency in embryonic and postnatal cells and in abnormal tumor cells later in life.”

In addition, Dr. Rauscher discussed at the meetings additional highlights from the Annual Program Review Document. The research results had increased markedly over previous years. Some examples follow:

Several projects on breast cancer studies in humans, monkeys, and rats had revealed with electron microscopy C-type particles in tumors and in tissue cultures derived from these tissues.

Earlier reports had suggested the possibility that bovine leukemia was a viral-induced disease and that certain groups of people who consumed “improperly” processed milk or milk products had a higher incidence of leukemia and lymphoma. Other reports had suggested that exposure to certain household pets, and bites or lacerations therefrom, could predispose individuals to a higher incidence of these cancers. The Special Animal Leukemia Ecology Studies group conducted work designed to determine which cancers in man’s close animal contacts were viral-induced, and then to determine whether these together with 60 other animal cancer viruses already isolated posed any risk to man. Long-term studies have shown no

significant increase in cancer risk for people in prolonged contact with bovine and canine species or bovine food products. Pasteurization was shown to inactivate RNA and DNA viruses when milk, to which they have been added, is processed by the two methods of pasteurization currently used in the United States. At this stage, there were over 85 viruses that were known to cause virtually all kinds of cancer in every major group of animals including subhuman primates. Other studies to determine the risk of man to animal cancer viruses continued.

Dr. Robert Miller, et al., have identified family clusters of cancer that suggested a hereditary tendency. In these families healthy persons potentially at high risk of cancer can be identified for intensive study by new laboratory procedures. These tests may detect subclinical abnormalities that account for predisposition to neoplasia. One such procedure, developed by Dr. Todaro, measures the susceptibility of skin fibroblasts to “malignant” transformation in vitro by SV-40, a virus that causes cancer in laboratory animals. From skin biopsies provided to Dr. Todaro by the SVCP from several families with multiple cases of leukemia, an increased susceptibility to transformation was found in healthy as well as in leukemic family members. Many skin biopsies were also provided to Dr. Todaro from patients with various inborn defects known or suspected to carry a high risk of cancer. Analysis of the results should show whether increased transformability is related to a particular kind of chromosomal abnormality (fragility or autosomal trisomy rather than deletions or sex-chromosome aberrations), whether variants in Fanconi’s anemia show the same marked increase in transformation as does the full-fledged syndrome, and whether the response of fibroblasts varies in different parts of the body, with age, or chromosomally normal syndromes that carry high risk of cancer.

The Moloney strain of murine sarcoma virus modified by containment within the envelope of a cat leukemia virus (MSV [FeLV]) was shown to have a wide host range by

infection of cell cultures of various species. The modified virus readily infected and morphologically transformed cat, dog, pig, and human cell cultures. In each case the infection, transformation and production of progeny virus required co-infection with FeLV. The infection followed two-hit kinetics and could be used for the detection of exogenous FeLV. The infection of a variety of normal and abnormal human cell cultures was noteworthy in that morphological transformation occurred within a few days and the cultures shed high levels of progeny virus. These findings raised the possibility that the genomes of some human sarcomas might be rescued by infection of cell cultures of human sarcomas with cat leukemia virus. Cat cells infected with either the modified sarcoma virus and/or FeLV contain a novel viral-specific nucleic acid. This nucleic acid contains uridine, and on chromatography behaves similarly to double-stranded RNA and resists digestion at room temperature with RNAase. It is susceptible to attack by DNAase and certain proteolytic enzymes. The nature of this nucleic acid was being explored with a variety of biophysical tools. The structure of this novel nucleic acid might provide an understanding of interaction of the viral genome with host cell genome or with the genomes of other (possibly DNA containing) viruses.

Two chemically distinct compounds, Pyran copolymer and poly I_r:C_r were examined for their interferon-inducing capacities in vivo. Both compounds had shown excellent suppressive activity with two leukemia-inducing viruses. A limited study with mouse rabies virus showed that these same compounds afforded some protection against rabies infection.

Avian leuko-sarcoma virus structure was studied in conjunction with staff members of the Chemistry Branch, NCI. The removal of the outer lipoprotein coat exposed viral cores surrounded by the intermediate membrane. A flattened portion of the core of individual particles resembled a hole. The cores contained some viral group specific antigen, but most was

solubilized. The cores had a density of 1.26 gm. per cc. Enveloped particles had a density of 1.16 gm. per cc.

Researchers also studied the interactions of antibody with cell surface antigens. The association constants and the delta-F of antibody binding to HeLa cell surface antigens were determined, and the number of antigenic sites on the cell surface was measured. Experiments were done to determine whether the immunofluorescence reaction on the membrane of the EB virus infected lymphocytes was associated with neoantigen or viral antigen. All antibody was associated with virus and none with cell surface membranes.

In FY 1970 investigators in the Viral Carcinogenesis Branch, utilizing sensitive new tests for the subinfectious gs (group-specific) antigens of the C-type RNA tumor viruses, made several new discoveries which led in turn to the new oncogene hypothesis:

1) The demonstration of virtually universal prevalence of the RNA tumor virus genome in all strains of mice, and probably also in hamsters, cats and chickens.

2) The discovery of the gs antigen expression of the virus genome in embryonic tissues of all strains of mice tested, and in cat and chicken embryos as well; the gs antigens in the embryos were demonstrated by complement-fixation tests and their identity with purified viral antigens established by means of the gel diffusion test.

3) The demonstration of widespread to universal immunological tolerance to the gs antigen in mice, cats, chickens and hamsters also strongly supported prenatal expression in these animals.

4) The discovery that otherwise non-oncogenic viruses, when switched on in mouse and rat tissues *in vitro*, serve as determinants of transformation by carcinogenic chemicals such as 3-methylcholanthrene (3-MC), diethylnaphthylamine (DENA), and dimethylbenzanthracene

(DMBA), thus providing at the same time new and highly sensitive assay systems for carcinogenic activity.

5) The discovery that rat and mouse cells containing switched on C-type virus are enormously more susceptible to transformation by the DNA tumor viruses (SV40 and adenoviruses), thus suggesting that the RNA tumor virus genome may be the determinant of *in vitro* DNA viral oncogenesis.

6) The demonstration, through studies of 3-MC sarcoma induction in 10 or more strains of mice, of a correlated switch on of gs antigen in many of the tumors while adjacent normal mesenchymal tissues in the same mice were negative suggested that the action of tumor-inducing chemicals which lead to the derepression of the virogene and oncogene of the C-type RNA genome also implies a determining role for this genome in chemical carcinogenesis.

7) The demonstration that many inbred strains of mice at the Jackson Laboratory possess well identified host genes which have profound effects on the virogenic and tumorigenic expressions of the C-type RNA virus in normal tissues as well as in tumor tissues; they were shown to influence the types of cancer as well.

8) Drs. Kelloff, Gilden and Oroszlan succeeded in isolating and characterizing four strains of C-type virus from hamsters, all of which had envelope and gs antigens shared in common with each other, but not with the C-type RNA viruses of the mouse, chicken or cat. Activation of cells (MSV-RT-1) and the hamster specific viruses were induced by four different MSV's.

Feline sarcoma virus (FSV) isolated from a spontaneous fibrosarcoma (by Drs. Gardner and Arnstein) invariably induced fibrosarcomas in feline and canine fetuses and in newborn and very young animals. Intrauterine-inoculated individuals produced tumors rich in C-type virus and

viral antigens. Incubation periods were usually 2 to 3 weeks. Researchers thought that the domestic feline, which appeared to have an unusually high prevalence of C-type virus activity in nature, was a good candidate for a natural history study of this group of viruses. Since the mechanism for collection and monitoring of tumored animals was already available in Los Angeles and Alameda-Contra Costa counties, it was thought that these studies could bear fruit in a relatively short time. Provided that viral activity was detectable in tumored animals as well as a large proportion of normal adults and embryos, the vertical transmission of C-type viruses could be determined in a natural, random bred population. Since lymphoma and fibrosarcoma were already known viral diseases in the feline, the other tumors in this species might well be similarly reproducible by specifically coding viruses. Techniques for detecting these viruses in a covert or incomplete form might be applicable for the detection of C-type virus activity in less commonly “switched on” species such as human, bovine and canine.

Approximately 800 households having recent human cancer patients (including lymphoma, leukemia, sarcoma and carcinoma cases), and over 1000 matched cancer-negative control households were studied by means of a questionnaire survey which was designed to test the incidence and intensity of exposure of the cancer households and control households to cats. This survey (by Drs. Gardner, Hanes and Loosli) showed that approximately 80 percent of all categories in both cancer and control groups had no household exposure to cats in the 10 years prior to recent onset of cancer. There was no evidence that exposure to cats increased the risk of any of the types of cancer patients surveyed. This study was important because it revealed that exposure to cats is unlikely to represent an important factor in human cancers of the types that cats develop. To answer questions about the consequences of human exposure to lymphomatous

or cancerous cats, an additional field study had been set up as part of the California State Department of Health-Viral Carcinogenesis Branch program.

Wild (feral) mice trapped in Maryland and in Los Angeles were found (by Drs. Gardner and Estes) to have little or no spontaneous expression of C-type RNA virus gs antigen, and no infectious virus. However, sarcomas induced by 3-MC were found in many instances to contain gs antigen; older mice estimated to be over 20 months carrying 3-MC tumors had higher incidences and titers of gs antigen and some contained visible C-type particles. Recent studies of wild mouse embryos indicated that all of them had gs antigen expressed in one or more tissues. These observations were important because they showed that the C-type RNA tumor virus genome is present in the common house mouse (Mus musculus) in its natural state, and that such expression was not limited to laboratory colonies of mice. The wild mouse also appears to be similar to man in that the C-type RNA virus genome is seldom if ever expressed in normal circumstances or, for that matter, in many spontaneous cancers. It is also important to note that the natural history of the wild mouse genome can now be defined without having to resort to RNA tumor virus isolations, a matter of vital importance when complete virus expression cannot be detected and perhaps almost never is achieved in some species.

Dr. Maurice Green continued the search for viral-specific genetic material in human cancers utilizing a more sensitive “micro” DNA-RNA hybridization procedure.. Of 130 human cancers studied, none contained more than 100 molecules of adenovirus 2, 7, or 12 mRNA (the limit of sensitivity of the current test). Over 200 previously extracted human cancer RNA’s were repurified, 50 new human cancer RNA specimens were purified, 50 tritium-uridine labeled human cancer samples grown in tissue culture were prepared and large quantities of needed reagents, viral DNA and radioactive transformed cell RNA were prepared. Intracellular viral

RNA had not been detected in murine sarcoma infected and transformed cells. Studies on the homology of murine sarcoma virus RNA with cell DNA showed that there were 20,000 genes per cell that could anneal to viral RNA in mouse, rat, and human cells. It was determined that adenovirus DNA was present in multiple copies in adenovirus tumor and transformed cells. With the use of polyacrylamide gel electrophoresis, it was possible to identify different arrays of viral messengers under different physiological conditions, early and late after infection and in transformed cells. With adenovirus type 7, 50% of the genome is transcribed early after infection, 100% late and 20% in transformed cells.

After confirming the findings of Temin and of Baltimore of the existence of an RNA-directed DNA polymerase (reverse transcriptase) in oncogenic RNA viruses, Dr. Spiegelman and associates found a new DNA-directed DNA polymerase in six oncogenic RNA viruses (RLV; RSV-(RAV-1); AMV; MTV; MSV; and FeLV). They established other features of the reaction: 1) physical and chemical characterizations proved that the product was a DNA heteropolymer; 2) molecular hybridization showed that the DNA synthesized was complementary to the viral RNA contained in the enzyme preparation; and 3) RNA-DNA complexes were detected as early components in the polymerization. The specific complementarity of the synthetic DNA to viral RNA and the early appearance of RNA-DNA hybrids implied that the viral RNA functioned as a template in the synthesis of the DNA. RNA oncogenic viruses had been found to contain two DNA polymerase activities. The first uses single-stranded RNA as a template and in the process generates a DNA-RNA hybrid. The second accepts double-stranded DNA as a template and produces a product which appears to be principally double-stranded. The primary function of this latter activity may be to amplify the oncogenic DNA duplex once it is formed. The multiple copies thus produced could markedly increase the probability of a successful integration.

Resources, including purified oncogenic viruses, produced by the SVCP were provided to Dr. Spiegelman for this work.

Dr. Rauscher reported other highlights. The Viral Carcinogenesis Branch staff produced or participated in writing 65 papers in Fiscal Year 1970, plus an additional 40 reports by contract programs supported by VCB and closely supervised and managed by VCB and SVCP scientists. The Viral Leukemia and Lymphoma Branch published 48 papers for the year, gave 30 invited lectures to various research groups, and entertained 70 visitors for discussions, 20 of whom received training in a variety of experimental procedures. The majority of the VLLB senior investigators contributed up to 80% of their time in support of the SVCP. Some of these Branch publications were included in the list of the 102 F.Y. 1970 publications for the SVCP.

As of June 30, 1970, of the total budget for Etiology of \$34,544,000, the budget for Viral Oncology was \$20,847,000. Viral Oncology contracts amounted to \$17,247,000 (92 contracts). Viral Oncology grants totaled \$7,200,000 (115 grants). As usual, several modifications of Viral Oncology contracts were made over the previous year. Changes were made in 50 contracts: 10 were terminated; 17 were modified in workscope; 15 were modified to change the emphasis within the worksopes; 8 new projects were initiated (“Annual Program Review Document, Etiology, NCI Fiscal Year 1970,” prepared for the National Advisory Cancer Council, September 28-30, 1970 Council Meeting).

Budgetary Problems

The budgets for NIH and NCI for the Fiscal Years 1968-1970 were tight. For 1968 the NCI appropriation was \$183 million, an increase of 4% over the previous year. The NCI 1969 appropriation was \$185 million, up only 1% from 1969. The budget request for Fiscal Year 1970

submitted to the Congress by the Nixon Administration had included a request for the NCI of \$180,725,000, down 2% from the prior year appropriation of \$184,952,000. In November 1969 the Director of NCI discussed the budget prospects with the members of the Association of American Cancer Institutes. He said that there was an increased interest in the Congress in health care delivery as opposed to biomedical research. With the death of Congressman Fogarty and the retirement of Senator Hill a leadership vacuum was created. The Expenditure Control Act of 1968 led to further budget cuts; the NCI budget was expected to be about \$173 million. The appropriation bill was finally signed into law eight months into the fiscal year; \$190 million was the NCI appropriation. However, the Office of Management and Budget placed in reserve the additional \$10 million for cancer research provided by the Congress.

The prospects in fiscal year 1971 were no better than in the previous year. The formal budget request, submitted in January, 1970, had an estimated increase of \$104 million over the not-yet-passed fiscal year 1970 appropriation. There were in addition earmarkings, including \$30 million for health manpower. NCI fared better than the other Institutes. Mrs. Lasker used her influence in the appropriation process to increase the NCI budget: the House appropriation subcommittee recommended \$227 million; and the Senate recommended \$235 million. The NCI appropriation was \$230 million.

Chapter 5: Politics and Science

Relationships between science and politics are complex, and the interface between them is a fascinating arena. The total levels of appropriations funding for NIH and NCI are largely

based on political decisions. Distribution of funds within the NCI appropriation is mainly based on *scientific* decisions (or should be). The political decisions are made every year for NCI at the determination of the NCI appropriation by the interplay between the President and his Administration (including the Secretary of DHEW and the Office of Management and Budget) and the Congress. The NCI budget submission each year, though usually modified to conform to the President's Budget, is primarily based on scientific factors: 1) the state of the art; 2) estimate of the significance of research leads and probability of success of the research; 3) availability of tools to do the job; and 4) priority of need.

The National Advisory Cancer Council (NACC) influences the decisions. Up to half of the members of the Council are laymen and are largely political appointees. The other members are scientists or physicians nominated by the NCI. In general, lay members have been helpful. They bring a wider perspective, and often raise important issues or other points of view, and provide support to the NCI in the public arena. At times members of the Council introduced issues that went beyond advice on cancer research. For example, Council member Mary Lasker, a wealthy influential philanthropist, President of the Lasker Foundation, and very effective lobbyist for greater support from the Federal Government for health matters (including research), pushed for movement towards the social issue of universal health care. She wanted the NCI programs to provide health care in addition to research. She also wanted the Council to have more power and a more influential role and not be merely advisory. She attempted to install the requirement that the Council should have more control over approval of contracts similar to that for grants. Other members of the Council and the Institute staff did not agree, believing that such a change would unduly complicate the research efforts. Moreover, research monies and

programs should not be used to try to solve social problems (other parts of the Public Health Service should deal with this aspect of health matters).

As mentioned previously, Ms. Lasker, noting the criticism of the NCI Cancer Chemotherapy Program by the Wooldridge Committee in its review of NIH, told Senator Hill that NCI had given the NACC no information on the Chemotherapy Program – NCI refuted this by sending to the Senator voluminous material on the Program that had been provided over the past year (the Program was reviewed annually with the Council with discussion and opportunity to ask questions). She did, however, convince the Senator to put into the 1966 Senate Appropriation Language the requirement that contracts could be let only if recommended by the NACC. Action by the Secretary, DHEW, and the House Appropriation Committee led to the removal of the requirement from the Appropriation language. Yet another review committee was again called for – the Ruina Committee. This committee stated that the Council should not have this authority; indeed, such power would run counter to Government contracting in general.

Ms. Lasker was very upset. She convinced Senator Yarborough to introduce a Bill establishing a Panel of Consultants that would review current cancer research activities and propose what would be needed to cure the major forms of cancer by 1976. The Report of the Panel consisted of two parts: one, the statement on policy, functions, organization and location, and staffing; and two, an excellent technical supplement released much later. The technical recommendations were all continuations of on-going NCI Programs. Following release of the Panel Report, which called for removal of NCI from NIH, Senators Kennedy and Javits introduced a Bill supporting the Panel recommendations. President Nixon added \$10 million to the Administration's budget for cancer research. It appeared that the President and Senator Kennedy were competing for public approval by backing increases for cancer research, a popular

move as viewed by the public. Hearings on different Bills were held in the Senate (Kennedy) and the House (Rogers). The only support from the research community for removal of NCI from NIH came from the American Cancer Society. As clearly shown at the hearings held by Congressman Rogers, every other professional society, including the American Association for Cancer Research, opposed the removal. Differences between the Senate and House were resolved, and a compromise Bill was signed into law as “The National Cancer Act of 1971” on December 23 by President Nixon. The Act decreased the NCI operational control by: 1) converting the advisory NACC to a board of directors-type NCAB with greater authority than that of the Council with the Chairman no longer the Surgeon General (or the Director of NCI), but a Board member elected by the Board; 2) the activities would be overseen by a three-member President’s Panel; 3) the Director of NCI and the Director of NIH were to be appointed by the President (subject to consent of the Senate), thus making them for the first time political appointments; 4) the Cancer Control Program was reinstated with the NCI; 5) the Cancer Centers Program was to be greatly enlarged; and 6) the Board was to be enlarged from twelve Council members to eighteen Board members (plus five ex officio members).

As these activities occurred, other monumental developments were shaping up on the international science-politico front: in this period the new U.S.A. – U.S.S.R. Health Agreements established cooperation between the two countries in the fields of cancer, heart disease, and environmental sciences.

The Panel of Consultants on the Conquest of Cancer

Senate Resolution 376, introduced by Senator Ralph Yarborough and passed by the Senate on April 27, 1970, called for establishing a Senate panel of consultants who would be

asked to determine the adequacy and effectiveness of the present level of support for cancer research and to recommend the necessary action to achieve cures for the major forms of cancer by 1976, the bicentennial of the Republic. Mrs. Lasker used her influence not only to get Senator Yarborough to introduce the resolution, but to determine the make-up of the Panel. As she had done before, she had determined that the Panel composition be half scientific-medical members and half lay members. Scientific-medical members of the Panel were: Sidney Farber (Co-Chairman); Lee Clark (later Co-Chairman, replacing Dr. Farber who became ill with a mild coronary attack on August 24); Jonathan Rhoads; Frank Horsfall; Joe Burchenal; Jim Holland; Harold Rusch; Henry Kaplan; Joshua Lederberg; Wendell Scott; Paul Conerly; Mathilde Krim; William Hutchinson; and Solomon Garb. The lay members were: Benno Schmidt (Chairman); Laurance Rockefeller; Emil Mazey; I.W. Abel; Jubel Parten; Mary Wells Lawrence; Mike O'Neill; Emerson Foote; Lewis Wasserman; William McC. Blair; Anna Rosenberg Hoffman; Keith Funston; and Elmer Bobst.

The NCI Director, accompanied by Drs. Zubrod, Rauscher, Huebner, Schepartz, and Fahey, and Mr. Carrese, appeared before the Panel at its third meeting on August 24. About one hour was allotted for the NCI presentation. Dr. Rauscher discussed *Prevention* and Dr. Zubrod discussed *Treatment*. The Director discussed the great concern of the public about cancer as shown by numerous polls, the present situation and advances in the cancer field, the numerous opportunities for progress in cancer research, factors preventing an all-out effort in cancer research, and the likelihood that the public would support an NCI budget of \$1 billion a year. He indicated that the scientific know-how and managerial know-how were in hand to warrant the conduct of a massive attack on cancer. The need for strong commitment (public and otherwise) would be essential. Special attention was given to viral oncology, genetics aspects of cancer, and

developmental biology. The need for funding of *both* basic research with grants and directed, targeted research with contracts was stressed. The value of the NCI resources programs was mentioned. He stated that the requirements for NIH approval of NCI activities of minor significance needed changing. Only a few questions were asked of the NCI Director during the hour-long presentation, and none was addressed to the other NCI staff members present.

The story of the complicated political events from the appointment of the Panel in April 1970 to the signing by President Nixon of The National Cancer Act of 1971 in December 1971 is well told in the excellent book by Richard A. Rettig (*"Cancer Crusade. The Story of the National Cancer Act of 1971"*, Princeton University Press, Prince, New Jersey, 1977). This publication should be consulted for broad understanding and for details on this subject.

The Senate Panel presented its Report to the Committee on Labor and Public Welfare on December 4, 1970, (on April 14, 1971, two-hundred pages of excellent scientific and medical coverage resulting from subpanels activities were added to the Panel Report). The Report offered contradictory conceptions of the NCI program, praising the great advances made in the United States over the previous decades while at the same time calling for removing the NCI and the national cancer effort from the NIH because of inadequate management. Moreover, the listings in the Report of projected program activities were exactly those that the NCI had developed and were conducting and projecting for the future. The Panel thought that enlargement of the NCI Cancer Centers Program and expansion of regional coordination of cancer activities was called for. NCI pioneered the Centers concept and had funded Centers to the extent the funds allowed and had asked for additional funds from the Congress for this purpose. The Panel wanted more emphasis on Federal funding of health care for cancer patients, but only for those expenses necessitated by the investigations, largely at Cancer Centers. The Panel recommended that the

cancer program be removed from NIH. With creation of the new cancer authority outside NIH it was proposed that the head of the effort be appointed by the President and would be reporting directly to the President. The Panel recommended increases in financial resources, and projected the level of support at \$1 billion per year by 1976. The budget would be submitted directly to the President. The Panel offered other recommendations including: an overall cancer program plan; the availability of the use of prime contractors; no year money; special exceptions to regulations; broader construction and rental authorities; increased communications and a central data system; and grants and contracts should be the form of support, with increasing use of contracts. The Panel also recommended the replacement of the National Advisory Cancer Council with a National Cancer Advisory Board that would have greater authority. The Board would be enlarged from 12 members to 18 (initially, due to overlap of terms of members of the NACC, the number of members would be 26, plus 4 *ex officio* members). The Board members should elect the Chairman of the Board from the membership.

Prior to finalization of the wording in the Report, Mrs. Lasker sent word that she wanted the Report to include the recommendation that the Board would have final approval for all contracts, a position she had taken earlier when she was on the National Advisory Cancer Council. The Ruina Report had stated that the Council should not have this authority. A compromise on the issue was negotiated by Benno Schmidt: it was agreed that the Board would have prior approval for the coming year's program plan and budget, but that the head of the program would have full authority for administering the program, including contract approval.

It was about this time that Mrs. Lasker's relationships with the NCI Director cooled when he told her he was opposed to the removal of NCI from NIH.

Chapter 6: Completion of Systems Planning for Implementation of the New Cancer Act

The need for a National Cancer Institute overall plan was evident for some time, and indeed the Institute worked toward that end before 1964 (see Chapter 2). It was needed for program operations and, by 1970 it was evident well before The Cancer Act of 1971 was passed that it would be needed for implementing the new Act. Initial attempts to formulate an overall plan were made in 1963. This planning effort was too general. Better planning techniques were called for, and this led to the development of systems planning for biomedical research (the “Convergence Technique”), first applied to major NCI Program segments (the Special Virus Leukemia Program and the Cancer Chemotherapy Program).

Among the recommendations in the Report of the Senate Panel of Consultants was a call for an overall NCI plan. The NCI had in draft at that time an overall plan. This development was enlarged to include a planning effort that called for involving the active participation of the science community. The NCI wanted this participation so that the science community would feel a part of the effort of making future projections of cancer research (and funding) as well as bringing knowledge and expertise into the process.

Hopefully, an esprit de corps would be developed. Over 200 investigators accepted invitations to take part in the planning of the total cancer research programs. To obtain the inputs in an orderly manner from these outstanding investigators, the NCI Director set forth the total field of cancer research as a hierarchy of components and suggested directions and lines of research efforts directed toward a Goal and Objectives. The hierarchy, arranged in a triangular configuration, consisted of five levels with the overall program Goal at the apex. The overall

Goal was “To reduce the incidence, morbidity, and mortality of cancers in humans.” The second level consisted of seven program Objectives grouped under 1) Cause and Prevention; 2) Diagnosis and Prevention; 3) Therapy; and 4) Rehabilitation. The third level consisted of 36 Approaches, each of which delineated a broad scientific research program aimed at reaching an Objective. The fourth level consisted of 162 Approach Elements, each of which suggested research program efforts directed toward the conduct of research at the fourth level. The fifth, or lowest, level was made up of 668 individual research Project Areas (corresponding approximately to individual research grants or smaller contracts). The triangular arrangement was folded around so that the triangle was transformed into a circle, and the Goal at the apex of the triangle became the center of the circle. This center became the bull’s eye of a target for the Program effort to be aimed for (see Figure 3). The circular chart, in addition to suggesting future lines of research for the total field of cancer research, served as a basis for assignments of parts of the total for the development of plans by the respective discussion groups at the planning conference. Careful study of the Figure 3 circular chart is warranted.

A series of meetings of experts was held whereby these specialists were organized into groups (Panels), and the groups were assigned a particular segment represented on the circular chart. Reviews, discussion, and formulation of plans for the assigned segments were conducted. The first groups (Panels) that met considered the 39 Approaches organized around the seven Objectives. The seven Chairmen of these Panels plus the 32 members served as the senior advisory group for the planning exercise. The Panels reduced some segments of the circular chart. The results of the efforts of the Panels and staff led to a Report for the National Cancer Plan (NCP) in two parts: 1) a Strategic Plan; and 2) an Operational Plan. The Strategic Plan was the circular chart. The Operational Plan was the managerial aspects of the National Cancer Plan.

Later, priorities and cost estimates were determined. The NCP materials were printed and made available to the public by the U.S. Government Printing Office.

Interest of NCI in systems planning diminished after 1973.

An Overall NCI Program Plan

In late 1970, the NCI Director, for some time seeing the need for an overall plan for the NCI programs, began to draft such a plan. This plan maintained the philosophy that a cancer research effort should have two parts: 1) a program of exploratory research supporting individual scientists with grants (with no centralized control) and 2) centrally managed programs of multidiscipline, integrated goal-oriented programs aimed at solving major problems of cancer. The magnitude of the problem and the current status of cancer research were discussed, and goals and objectives were defined.

Two accompanying charts were of special significance: A. Based on the broad science stages of cancer (Pre-conception factors - Normal and identifiable pre-cancerous states - Cell transformation - Pre-diagnosable cancer - Early cancer - Advanced cancer) or based on program components (Etiology - Detection - Prevention - Diagnosis - Treatment - Rehabilitation), seven Objectives were set forth, one for loosely coordinated fundamental and applied research, four for collaborative research programs (Chemical Carcinogenesis; Cancer Detection and Diagnosis; Special Virus Cancer; and Cancer Chemotherapy), one for planned and highly coordinated research programs on prevention and treatment of specific types of cancers (Organ Site Programs), and one for Cancer Centers; and B. A science-management information system for the total program that would serve as a coordinating “nervous system”, primarily for monitoring the progress (or identifying problems) for the total program. The plan projected: research areas of opportunities for advances; manpower, training and space requirements; organizational and

managerial needs; and funding requirements. This 75 page (plus attachments and charts) draft plan for a total program on cancer research, entitled “*An Expanded Research and Development Program on Cancer*,” was sent to the NIH Director on February 2, 1971. A supplemental paper outlined (drafted by Cal Baldwin, the NCI Executive Officer).

management and administrative issues that would need attention if the cancer research effort should be greatly expanded (“An Expanded Research and Development Program on Cancer,” a draft NCI document from the Director, NCI, to the Director, NIH, February 2, 1971; “Administrative Changes Required for an Expanded National Cancer Research Program,” from Executive Officer, NCI, February 9, 1971).

1971

President Nixon’s State of the Union Address

In his January 22, 1971, State of the Union Address, President Nixon proposed additional attention to health matters and stated that he would ask for an extra appropriation of a \$100 million to launch an intensive campaign to find a cure for cancer. He compared the effort to the “moon shot” in the Space Program. Clarifying details were gradually made by the President’s Science Advisor, Dr. Edward David, and the President himself, partly in his February 18 “National Health Strategy” message, where he said he was directing the Secretary, DHEW, to establish a new Cancer Conquest Program in the Office of the NIH Director; the Director of the Program, appointed by the Secretary, would also be supported by a new management group (“Planning for a Major Research and Development Program on Cancer,” by the Director, NCI, March 1, 1971).

On March 5 and 6 Dr. Marston held a retreat with the NIH Institute Directors and senior members of his staff to discuss problems associated with the President's proposed course of action. Several documents were made available to the attendees. The February 2, 1970, document "*An Expanded Research and Development Program on Cancer*" was the basis for the presentation by the Director, NCI, focusing on the use of systems planning in NCI and research opportunities for new cancer research. This presentation by the NCI Director was repeated on March 17, 1971, before the newly appointed Advisory Committee to the Director, NIH. Members of this advisory committee were: Adelbert Ames, III, Massachusetts General Hospital; William R. Barkley, American Medical Association; Robert H. Ebert, Harvard Medical School; Carl Erbe, University of Iowa; John R. Hogness, University of Washington; Rufus Miles, Population Reference Bureau; Walter Rosenblith, Massachusetts Institute of Technology; James McN. Hester, New York University; Richard Sellars, Johnson and Johnson Worldwide; George Miller, The Rockefeller University; Deil Wright, University of North Carolina; and W. Barry wood, Jr., Johns Hopkins University. The question of whether biomedical research was ready for targeted, planned programming was debated with no clear conclusions ("Special Meeting of the Advisory Committee to the Director, NIH," NCI discussion document with attachments, March 17, 1971).

S.34, the Cancer Conquest Act, 1971

On January 25, 1971, S.34, a Bill "*To establish a National Cancer Authority in order to conquer cancer at the earliest possible date,*" was introduced by Senators Kennedy and Javits. S.34 followed the recommendations of the Senate Panel of Consultants. The most controversial issue was the Panel proposal to create a National Cancer Authority outside the NIH that would

also remove the NCI activities from NIH. Senator Kennedy scheduled hearings on S.34 for March 9 and 10. On the first day, Drs. Egeberg, Steinfeld, Marston, and Baker presented the Administration's position, which was opposition to the removal of the National Cancer Institute from the National Institutes of Health. It was strongly supported by the scientific community and scientific and medical societies and associations (with the sole exception of the American Cancer Society). The notion of separating NCI from the NIH was vigorously opposed in testimony by these groups. Although other items in the Panel Report were in favor with the Administration and the scientific community, such as more emphasis on cancer research and additional funds for research, the comparison by the President to a "moon shot" type of program was considered unrealistic. Dr. Steinfeld also cautioned against over-expectation of quick results. Senator Kennedy made an issue of whether NCI had an overall plan for the total effort of cancer activities, and he directed his insistent questions at the NCI Director. Dr. Baker pointed out that the NCI had more planned programs, especially in Chemotherapy, Viral Oncology, Chemical Carcinogenesis, and Breast Cancer Programs, that utilized systems planning more than the other NIH Institutes. However, many areas of basic research were exploratory and did not lend themselves to this type of planning. NCI purposely did not plan such areas in detail since, in exploratory research, central control is undesirable. Senator Kennedy said, "But NCI does not have an *overall* plan, does it?" The NCI Director said, "No." [Although an overall plan in draft had been sent to NIH from NCI on February 2, the NCI Director did not claim that NCI had an overall plan because the plan had not yet been approved at higher levels. This was a mistake. The answer should have been yes, referring to the February 2 document.]

Senator Kennedy asked Dr. Egeberg to provide specific details as to how HEW would formulate the kind of priorities in the NIH that were discussed at the March 9 morning session.

This question was followed up in a March 17 letter from Senator Kennedy to Secretary Richardson. A strategy session was held in the Secretary's office on March 19. Present were the Secretary; the President's Science Advisor, Dr. Edward David; his aide, Dr. Leonard Laster; Dr. Marston; Dr. Baker; and others. Dr. Steinfeld had prepared a discussion document for the meeting. After this meeting, a letter dated April 2, 1971, was sent to Senator Kennedy in response to his request of March 17. The Secretary Richardson's letter proposed three objectives: 1) to provide a context for mobilizing scientific and managerial resources for an attack on cancer; 2) to assure increased, continuing priority would be given to progress in cancer by DHEW and NIH officials; and 3) to build upon the existing strengths of NCI and other Institutes in cancer research, and on the *"significant experience of the NCI in the adaptation of new management techniques to biomedical research planning, and avoid wasting or encumbering important capacity and momentum on cancer already established within NIH."* The plan to attain these objectives would have the following significant characteristics: a) Elevation of the Cancer Research program to Bureau status within NIH and the assignment of the Cancer Conquest program to the Bureau; b) Designation of the Bureau Director as a Deputy Director of NIH; c) Placement of all cancer research appropriations within NIH under the Bureau Director and the assignment to him of authority to allocate those funds within and without NIH in accordance with program priorities; additional authorities would be sought if needed; d) Establishment of a Cancer Conquest Advisory Council containing scientists and management experts to provide guidance in policy and program formulation, management overview of the program and review of grants; and e) Creation of an Executive Task Force on the Conquest of Cancer to assure that HEW and other Federal top management officials give increased time and attention to the program and to guarantee frequent access of the Director of the Bureau of Cancer Research to

the Secretary; membership would include: the Secretary, DHEW; the Assistant Secretary for Health and Scientific Affairs; the Director, NIH; the Director, Bureau of Cancer Research; and the President's Science Advisor or his delegate. The Cancer Conquest Advisory Council would provide guidance in policy and program; management overview of the program; and specific review of grants (but not contracts).

Following testimony by the Administration witnesses, representatives of the scientific community and scientific societies were heard. They were opposed to removing NCI from the NIH, believing that such a move would be destructive to the very productive system developed by NIH. The former NIH Director, Dr. James Shannon, in a letter entered into the record, stated *“The creation of an independent Cancer Authority, removing the NCI from the ambit of the NIH, would, in my opinion, not accomplish anything that could not be done within present NIH processes, or trivial and easily realized modifications thereof. On the other hand, it would unleash forces of a divisive character which would quickly destroy the integrity of the NIH.”*

On March 10, prior to testimony by members of the Panel on S.34, Senator Charles Mathias (R.,Md.) proposed that Fort Detrick, previously a U.S. Army biological warfare research center, be converted to use for cancer research. Since February the NCI had been formulating plans for utilization of Fort Detrick as a cancer research facility; should the facility become available, NCI preference was for the operation of the facility to be managed by a major contractor.

The remainder of the day was devoted to testimony favorable to S.34 by Panel members and representatives of the American Cancer Society.

NCI Conference on Plans for a Major Expansion of Cancer Research

On March 11, 1971, the NCI Director called together a small group of advisors and senior staff to discuss the NCI plans for a greatly expanded program of cancer research. The non-NIH members were Ivan Bennett, R. Lee Clark, Sidney Farber, Gerald Murphy, David Nathan, Harold Rusch, Albert Sabin, and Wendell Stanley. The staff included Robert Marston, John Sherman, Carl Baker, Gordon Zubrod, Frank Rauscher, Palmer Saunders, and Nathaniel Berlin. Dr. Baker presented the current plans and planning activities of NCI and outlined his concepts to bring more investigators into the planning process. He was considering bringing together a large number of investigators expert in various areas of cancer and basic research who would be organized for discussion purposes so that they would be able to make recommendations in their respective areas of expertise. There seemed to be cautious support of the actions outlined, although there was awareness of the resistance to planning by many investigators.

Dr. Sabin, shortly after the meeting, sent to the participants copies of his paper entitled "*Collaboration for Accelerating Progress in Medical Research*" published in *Science*, June 23, 1967 when he was a member of the Advisory Council of the National Institute of Allergy and Infectious Diseases; it was quite germane to the discussions at the meeting. He stated in his paper that federal agencies, especially NIH, have "*special opportunities and special responsibilities for assuming leadership for planning and implementing research on the complex problems that are not now receiving sufficient or adequate attention through the efforts of individual scientists.*" He did not think that that existing procedures for the establishment of long-range plans and priorities and for their implementation were commensurate with the needs. Those active in the respective fields should participate in the planning. And "*there must be some system for establishing priorities not only in each Institute but also for all the Institutes, so that the people of this country and their representatives in Congress can be apprised of specific health research needs,*

their relative importance, their cost, and what might be appropriated in the light of all sorts of other needs.” “The success or failure of collaborative, coordinated research programs ultimately will depend on the willingness of scientists to participate in such programs, and this in turn will depend on the extent to which they can participate in the original planning and critique of the total research plan and on the extent to which opportunities for individual initiative and ingenuity remain in the cooperative enterprise.”

Dr. Sabin proposed that after selection of high priority areas, the leading investigators in the respective areas should lay out plans as to how to proceed, and conduct the research under their leadership, and be supported with funds and administrative support by an Institute staff member. [This way of operating was used under the urgency of World War II by the Armed Forces Epidemiological Board. The NCI Director tried to institute this approach with some of the areas of cancer research, but on informal inquiry with members of the National Advisory Cancer Council, he was told that he could try proposing it, but that he did not have the votes on the Council to have it accepted.] (Albert Sabin, “Collaboration for Accelerating Progress in Medical Research,” *Science* 158, pp. 1568-1571 (1967)).

The 1971 Annual Seminar for Science Writers

The 13th Annual Seminar for Science Writers, sponsored by the American Cancer Society, was held April 2 and 3 in Phoenix. The Director of the National Cancer Institute reported to the science writers that childhood leukemia probably could be listed among the relatively few cancers that are curable. In special centers 95 percent of leukemic children could be made free of symptoms and signs of the disease and 75 percent of these were alive two years after diagnosis. Prior to the advent of the new multidrug therapy, 70 percent of the children were

dead two months after diagnosis and nearly all at 3 to 4 months. The current status of viral oncology was a major topic at the meeting. The NCI Director stated his preference for the NCI to be the main thrust of *cancer research* and for *cancer control* responsibilities to be in another part of the Public Health Service. Not only were the problems to be solved in cancer research extremely complex and difficult, but if cancer control functions were added to the research activities, very different functions would drain off operational capabilities in research. A totally different clientele, including political forces and various pressure groups, would result. Such a change would also open up the Cancer Institute to the difficult political issues related to the mechanism to be employed to deal with health care.

Additional NCI Planning for an Enlarged Cancer Research Program

Intensive planning efforts (based in part on the February 2, 1971 document) were made by NCI from March 1971 through mid-1973 to develop an overall plan for an enlarged cancer research program and to engage a sizable segment of the scientific community in the planning and carrying out of the enlarged program. To ensure participation and an appreciation of engagement in the process, about 250 expert investigators were invited to attend planning sessions to help develop overall plans. Between March 1971 and August 1971 the NCI Director Carl Baker developed a science-based *strategic plan*, based on current scientific information, with an overall Goal and seven Objectives. The Goal was “To reduce the incidence, morbidity and mortality of cancers in humans”.

The research Objectives were grouped under Cause and Prevention (Objectives 1 through 4); Diagnosis and Prognosis (Objective 5); Therapy (Objective 6); and Rehabilitation (Objective 7). A five-level *hierarchical* triangular arrangement was developed with the Goal at the top and

the Objectives at the second level. At the third level in this initial version were 36 Approaches, consisting of broad scientific research program efforts, each of which was aimed at reaching an Objective. Lower in the hierarchy for each of the Approaches were a total of 162 Approach Elements, and at the lowest level in the hierarchy were 668 Projects (at this lowest level would be the projects more or less corresponding to grants or contracts).

The seven Objectives were:

1) To reduce the effectiveness of external agents in increasing the probabilities of development of cancers in existing individuals or in subsequent generations (five Approaches).

2) To modify individuals (e.g., by vaccination) to decrease the likelihood of cancer development, both in the current generation and in subsequent offspring (six Approaches).

3) To prevent conversions of cells to those capable of forming cancers (i.e., block, or interfere with the proximate step, or steps, involved in conversion to cells capable of forming cancers) (five Approaches).

4) To prevent tumor establishment from cells already capable of forming cancers (e.g., transformed cells, cells constituting precancerous tissues, etc.) (five Approaches).

5) To achieve an accurate assessment of the presence, extent and probable course of cancer risks in population groups (including attention to precancerous lesions) and of cancers in individuals alone (diagnosis) and in groups (detection) as an aid to prevention, cure, or prognosis (seven Approaches).

6) To cure as many patients as possible, and to maintain maximum control of the cancerous process in patients not cured (six Approaches).

7) To restore patients with residual deficits as a consequence of their disease or treatment to as nearly a normal functioning state as possible (two Approaches).

The Director drafted the 36 Approaches statements which were suggested for further discussion. A few changes were made in the Approaches statements, Approach Elements, and Project Areas after this initial chart was constructed. The NCI staff was concerned that the original wording of the Objectives might imply that the NCI would be responsible for providing total health care for cancer subjects. The wording was changed to “develop the means to -- ” to reflect that the program would be directed toward research (and development).

Lou Carrese made the interesting suggestion that if the triangular charted hierarchy of efforts directed toward the Goal and Objectives were folded around, the triangle would be converted into a circle. The Goal at the apex of the triangle would thus be transformed into the center of a circle, thus graphically illustrating the targeted or goal-oriented program. The circular chart of the NCI National Plan is shown in Figure 3 (dated August 1971). Careful study of the figure will clarify the nature of the components and their relationships. This program plan would become the guideline for discussions with a large group of investigators and the basis for organizing them into discussion groups later in 1971 and early 1972. The number of Approach Elements and Projects was tentative, but could serve to stimulate discussion.

Modifications were made later [Later there were 35 Approaches, 146 Approach Elements, and 621 Project Areas]. As the planning progressed, intensive efforts, especially on the logistics, administrative matters and development of the Operational Plan, were made by Lou Carrese and members of his staff (Jack McShulskis, Leon Elwein, Michael Brown, and Richard Terselic) and by Cal Baldwin, NCI Executive Officer and Bayard Morrison, NCI Assistant Director. Charles Fricker, JRB Associates, Inc. and Auerbach Associates, Inc. contributed very

valuable contract managerial and logistical services. By June a Gantt chart projected a 55-week schedule of steps to be taken to complete the full plan.

S.1828, a Bill to Amend the Public Health Service Act so as to Promote the Public Health by Strengthening the National Effort to Conquer Cancer

S.1828, introduced by Senators Dominick (on behalf of the Administration) and Griffin on May 11, 1971, was the subject of hearings called by Senator Kennedy on June 10, 1971. Much had happened between May 11 and June 10; behind the scenes compromise had been reached between the Administration, the Subcommittee, and the Chairman of the Panel of Consultants. Testifying for the Administration was HEW Secretary Richardson, NIH Director Marston, and HEW Under Secretary Kurzman. The Secretary's testimony differed from the contents of his letter of May 11. The Secretary said that the program would have full support of the President's power, prestige, and personal interest. The Director of the program, appointed by the President with the advice and consent of the Senate, would report directly to the President. The program would have independent budgetary status. The OMB would give budget guidelines to the program, not through HEW and NIH. The program in turn would submit the budget request each year directly to OMB for the President's approval. A Cancer-Cure Advisory Committee would be established, and the President would appoint the members and chairman. Secretary Richardson continued: "*The Committee shall advise the President, the Secretary, and the Director of the cancer-cure program on ways and means of conquering cancer and on matters of policy, organization, and management arising in the administration of this Act and relating to the conquest of cancer, including the development of general criteria for approval of*

applications under the Act for the award of grants, contracts, and other assistance.” Certain limitations on the use of appropriations for construction were removed in the Bill.

On July 7, 1971, the Senate voted on S. 1828. Eighty Senators were present, and the vote was: the Yeas-79; and the Nays-1. Senator Gaylord Nelson of Wisconsin had cast the single vote against S. 1828 (Rettig, *Cancer Crusade*, pp. 194-196).

Budget Projections for Further NCI Program Planning

On June 10, 1971, the NCI sent to NIH its Preliminary Fiscal Year 1973 Estimates for the Budget (with projections through 1977). The 1973 and subsequent year estimates were in line with the ones made by the NCI Director in the February 2, 1971, document entitled “*An Expanded Research and Development Program on Cancer*”:

	(Millions of Dollars)	
	<u>1973</u>	<u>1976</u>
February 2nd Plan	\$508	\$1,000
Current Preliminary Budget	\$550	\$1,066

This budget included a requested increase of 265 positions for 1973 and an overall increase of 1,031 through 1977 over the 1972 level. This would require about 190,000 square feet of additional space.

Construction of a new building on the Bethesda campus, estimated to cost \$22 million, was proposed.

Another area that NCI administrators thought needed further consideration was the desirability or feasibility of adding selected aspects of the Cancer Control Program to NCI. If this should be done, emphasis should not be on health care but on *research* dealing with problems of cancer control, e.g., research on rehabilitation needs or research on quality of life issues. NCI had initiated a program called “Diagnostic Research and Prevention Program”; at this stage it was grant related. If such a new program should be initiated, NCI would propose budgeting for it of \$4.5 million in 1973 and \$14.4 million by 1977. These estimates were not included in this preliminary budget.

May 18, 1971 Meeting of the NCI Ad Hoc Management Group

On May 10, 1971, the NCI Director asked a group knowledgeable of large-scale technological management if they would review with NCI staff the course NCI was projecting for the Cancer Conquest Program and give their reactions. In attendance were: Dr. William O. Baker (Vice-President for Research, Bell Telephone Laboratories); Dr. Rodney H. Brady (Assistant Secretary for Administration and Management, DHEW); Dr. Harry Eagle (Department of Cell Biology, Albert Einstein College of Medicine); Mr. V.G. Nielson (Vice Chairman, Aerospace Corporation); Dr. Arnold Pratt (Director, Division of Computer Research and Development, NIH); Mr. Gerald R. Riso (Deputy Assistant Secretary for Management & Agency Operations, Office of the Assistant Secretary for Health and Scientific Affairs, DHEW); General Bernard A. Schriever, USAF (Ret.) (Industrial Consultant); and Dr. Alvin M. Weinberg (Director, Oak Ridge National Laboratory). Unable to attend were: Mr. Jonathan Moore

(Counselor to the DHEW); Professor Jack P. Ruina (Professor of Electrical Engineering, MIT); and Mr. Richard L. Seggel (Staff Director, Secretary's Committee to Study the PHS Commissioned Corps, DHEW). NCI had sent several documents to the Group prior to the meeting on current and projected activities of the NCI, including NCI's use of systems planning. The question of a "moon shot" type program was raised, and discussion followed on whether a sufficient knowledge base existed to permit this type of program. Most felt that the state of knowledge at the time did not allow the type of engineering program used by NASA. However, with one exception, the Group thought that systems analysis, planning, and management along the lines used by NASA would be useful in carrying out the Cancer Conquest Program. Dr. Eagle stated his long-held objection to planned programming in biomedical research, a view representative of many in the academic world. He finally admitted that some problems in cancer required multidiscipline efforts that would need to be planned and coordinated. The Group thought that the NCI was going about the task in the right way with extension of its previous systems planning. They endorsed the projected engagement of expert investigators in further planning to provide representation of the scientific community ("NCI Management Group Meeting, May 18" with six attachments, May 10, 1971, Office of the Director, NCI, to Members of the NCI Management Group).

Planning for the Engagement of Expert Investigators in Further Planning of the Cancer Conquest Program

In June, the NCI began to compile a list of outstanding investigators who would be asked to participate in a Planning Conference on further planning of the expanded cancer research effort. The NCI solicited names of candidates from many individuals and 15 biomedical

professional and volunteer societies and associations, including the American Association for Cancer Research, the American Cancer Society, the American Association of Cancer Institute Directors, the American Association for the Advancement of Science, the National Academy of Sciences and the Institute of Medicine, the Federated Societies for Experimental Biology, the American Chemical Society, the American Medical Association, the American Surgical Association, the Society of University Surgeons, and the American Society of Therapeutic Radiologists. The extensive roster of expert consultants to the NIH was also perused. Names were sought from the NCI and NIH staffs, the NACC, and individual outstanding investigators in the cancer field. Also the NCI Director, in an article in *Science*, invited submittal to NCI of names of suitable candidates and of ideas for consideration in the national plan (over 100 responses were received and replies from NCI were sent to each).

Over 800 names constituted the list from which more than 250 individuals were selected (approved by the NCI Director) to participate in the planning sessions. Seventy-one percent of those invited accepted. As discussed above their participation would be organized around: 1) the Goal and the seven Objectives; and 2) the Approaches shown on the circular science-based strategic plan chart (Figure 3). That is, there would be 36 Panel Chairmen corresponding to the 36 Approaches on the chart (The number of Approaches and Panel Chairmen would later be changed to 39). At the first session of the Planning Conference these 36 Panel Chairmen would receive orientation from the NCI Director and other NCI staff at the Planning Conference on the projected planning efforts. Extensive written material sent to participants prior to the Conference included the circular chart, the Director's statement of the Objectives and Approaches, and other orienting information. These outstanding investigators had no difficulty understanding the overall Goal and Objectives nor the Project Areas designation (generally corresponding to

grants), but they had some difficulty understanding Approaches and Approach Elements. This difficulty appears to derive from the lack of experience in dealing with blocks of research efforts of the size larger than grant proposals. The Goal and Objectives were general enough in nature to not cause problems. Careful and in-depth study of the circular science-based chart should make clear the meanings of Approaches and Approach Elements. The concepts of Approaches and Approach Elements developed by NCI staff grew out of experience of preparing NCI budget justifications where larger blocks of cancer research efforts had to be described and justified to the Bureau of the Budget staff, the White House staff, and the Congress. The Approaches would form the basis for the broad research thrusts or major programmatic efforts aimed at achieving the Objectives. Understanding Approaches and Approach Elements was very important since each Panel under leadership of the Chairman was to discuss, and modify if required, the suggested Approaches and Approach Elements before the Project Areas under each Approach were considered. Also discussed by the NCI Director and Lou Carrese, the Associate Director for Program, and John McShulskis and others of the planning staff, would be the documentation distributed, the way the planning sessions were to be conducted, and the logistics. Lou Carrese and Jack McShulskis did an outstanding job in preparing the written material for the participants. Each Chairman of the Panels Considering the Approaches would have a Panel of about five to eight expert members selected and assigned to the Panels by NCI. The 39 senior investigators (plus 5 Rapporteurs) as a group formed the senior advisory level for the total program. These 39 Chairmen, organized by Objectives, were:

Objective 1

Harold Rusch, University of Wisconsin - *Chairman*

Paul Kotin, Temple University

Joseph Melnick, Baylor University

James Miller, University of Wisconsin

Norton Nelson, New York University

Ernst Wynder, American Health Foundation

Helen Baldwin, University of Wisconsin - Rapporteur

Objective 2

Arthur Upton, State University of New York at Stony

Brook - *Chairman*

Harris Busch, Baylor University

Maurice Hilleman, Merck Institute for Therapeutic

Research

Victor McKusick, Johns Hopkins University

Albert Sabin, The Weizmann Institute

I. Bernard Weinstein, Columbia University - Rapporteur

Objective 3

Sol Spiegelman, Columbia University - *Chairman*

D. Bernard Amos, Duke University

David Baltimore, Massachusetts Institute of Technology

Harry Eagle, Albert Einstein College of Medicine

Theodore S. Hauschka, Roswell Park Memorial Institute

Donald F. Parsons, Roswell Park Memorial Institute

Objective 4

Hilary Koprowski, The Wistar Institute - *Chairman*

Renato Baserga, Temple University

Bernard Fisher, University of Pittsburgh

William V. McDermott, Jr., Boston City Hospital

Richard T. Smith, University of Florida

Graham Campbell, The Wistar Institute – Rapporteur

Objective 5

Abraham M. Lilienfeld, Johns Hopkins University - *Chairman*

John K. Frost, Johns Hopkins University

Alexander R. Margulis, University of California

Robert S. Schwartz, New England Medical Center

Michael B. Shimkin, University of California at San Diego

Irving I Kessler, Johns Hopkins University - Rapporteur

Objective 6

James Holland, Roswell Park Memorial Institute - *Chairman*

Anthony R. Curreri, University of Wisconsin

Loren J. Humphrey, University of Kansas

Henry S. Kaplan, Stanford University

Howard E. Skipper, Southern Research Institute

Sydney Salmon, University of California at San

Francisco - Rapporteur

Objective 7

J. Herbert Dietz, Jr., Institute of Rehabilitation

Medicine, New York - *Chairman*

Kenneth L. Artiss, Wildwood Medical Center, Bethesda, MD.

John E Healey, Jr., M. D. Anderson Hospital

Arthur I. Holleb, American Cancer Society

David M Kaplan, Stanford University

Charlotte T. C. Tan, Memorial Hospital for Cancer and

Allied Diseases

Louis R. Wasserman, Mt. Sinai Hospital.

The plan would be based on two coordinated components: Research Strategy; and Operational Strategy. Research Strategy was directed toward the scientific aspects of the plan. Operational Strategy was directed toward the management aspects of the plan. To define adequately these strategy components it was necessary to establish a logical basic framework for the upper levels of the hierarchy, *i.e.*, Goal, Objectives, and Approaches. The Research Strategy was depicted in the circular chart. The Operational Strategy was related to management aspects for program implementation. The operational objectives included: balanced coverage of the total research system; new modes of operation; information systems needs; peer review procedures; research data utilization; coordinated efforts; and training goals. Estimates would be needed for: costs; manpower and training levels; supporting technology; facilities and space needs; equipment; and numbers and types of patients. The estimates of resource needs would provide important justification for requests to the Congress (and the Office of Management and Budget).

It was clear that a series of reports giving definitions and recommendations would be required as products from the various Panel deliberations. These reports would also include estimates of resource requirements and recommendations of priorities. After the reports of the Panels Considering the Approaches under the seven Objectives became available, the Panels Considering the Project Areas would conduct their reviews, make recommendations and estimate resource needs, and produce their reports. The contents of all the reports would be melded into an overall plan and, after review by the various Panel Chairmen, released to the public.

The 39 Approaches were reduced by the Panel Considering the Approaches to 28 Approaches under the seven Objectives; there were therefore 28 Panels to consider the make-up of each Approach. The resulting Approach Elements totaled 146 and the Project Areas discussed totaled 621. The NCI assigned Chairmen of the 28 Panels Considering Project Areas were:

Objective 1

Charles J. Kensler, Arthur D. Little, Inc

Marvin Zelen, SUNY at Buffalo

John H. Weisburger, National Cancer Institute

Edwin H. Lennette, California State Department of Health

Gerald N. Wogan, Massachusetts Institute of Technology

Objective 2

Maurice Green, St. Louis University

Paul C. Zamecnik, Harvard University

Salvadore E. Luria, Massachusetts Institute of Technology

Ernest Borek, University of Colorado

Sidney J. Cutler, National Cancer Institute

Helmut R. Wakeham, Phillip Morris Inc.

Objective 3

Harry Rubin, University of California at Berkeley

Charles Heidelberger, University of Wisconsin

Hewson Swift, University of Chicago

Edward A. Boyse, Sloan-Kettering Institute for Cancer
Research

Phillip Siekevitz, Rockefeller University

Objective 4

Howard A. Schneider, University of North Carolina

Arnold M. Seligman, Sinai Hospital of Baltimore

Eugene Van Scott, National Cancer Institute

H. Stanley Bennett, University of North Carolina

Richard Bellman, University of Southern California

Objective 5

Brian MacMahon, Harvard University

Erich Hirschberg, College of Medicine and Dentistry
of New Jersey

David A. Wood, University of California

William B. Wartman University of Virginia

Lauren V. Ackerman, Washington University

Gregory T. O'Connor, National Cancer Institute

George James, Mt. Sinai Medical Center, New York

Objective 6

Emil Frei, III, M. D. Hospital and Tumor Institute

Saul A. Schepartz, National Cancer Institute

Seymour S. Cohen, University of Colorado

Jonathan E. Rhoads, University of Pennsylvania

Alfred Gellhorn, University of Pennsylvania

R. Lee Clark, M.D. Anderson Hospital and Tumor Institute

Objective 7

J. Herbert Dietz, Jr., Institute of Rehabilitation

Medicine.

Hearings Before Congressman Rogers

On September 15, 1971, Congressman Paul Rogers, Chairman of the Subcommittee on Public Health and Environment of the Committee on Interstate and Foreign Commerce, began extensive hearings on S. 1828 and other Bills. On that same day Mr. Rogers introduced his Bill, H.R. 10681, "*The National Cancer Attack Amendments of 1971*," co-sponsored by five other Subcommittee members: Satterfield (D., Va.), Kyros (D., Me.), Preyer (D., N.C.), Roy (D., Kans), and Hastings (R., N.Y.). The main difference between the House and Senate Bills was that H.R. 10681 would keep the NCI in the NIH and S. 1828 would make the cancer effort "*independent but within the NIH and DHEW*". H.R. 10681 would broaden the coverage to

include heart and lung diseases and stroke. Instead of the head of the cancer effort reporting directly to the President, in the House Bill the NCI Director, along with the Directors of the National Heart and Lung Institute and the National Institute of Neurological Diseases and Blindness, would be made NIH Associate Directors. The House Bill provided that the NCI Director prepare and submit his annual budget directly to the President; the NACC, the NIH Director, and the Secretary, DHEW could comment on the request, but could not change it. Specific authorizations of \$400 million, \$500 million and \$600 million for fiscal years 1972, 1973, and 1974 were in the House Bill, while in the Senate Bill “such sums as may be necessary” were authorized. Both Bills would make the head of the cancer effort an appointment by the President with the advice and consent of the Senate, thus making it for the first time clearly a political appointment. Other differences were less significant.

Mr. Rogers, who controlled when the hearings were held and the selection and scheduling of witness, scheduled hearings on September 15, 16, 20, 21, 27, 28, 29, 30 and October 4, 7, and 11, 1971. On October 7 Representative Ancher Nelson (Minn., R), who frequently looked for compromise as a way through stalemate issues, proposed that a three person President’s Cancer Attack Panel be included in the House legislation. It would have a monitoring function of the overall effort. By this device, it would provide for direct access to the President and keep the cancer effort in the NIH. Two of the three members of the Panel would be distinguished scientists or physicians. Mr. Rogers immediately accepted the proposal. He skillfully conducted the hearings, was an excellent questioner, and was fair in hearing all sides. During the earlier hearings, he called mostly those supporting S. 1828 (mostly the Panel of Consultants and the American Cancer Society representatives), giving them their chance to state their case. Later, the witnesses opposed to S. 1828 testified (outstanding scientists and numerous

representatives of various scientific and medical organizations); most preferred the House Bill, but many offered suggestions to modify H.R. 10681. Representative Rogers decided a clean Bill was necessary to move the legislation along, and the Subcommittee reported out a clean Bill, H.R. 11302, "*The National Cancer Attack Act of 1971*", on October 15, 1971. This Bill reduced the scope to cancer only, but still elevated the Directors of the National Cancer Institute, the National Heart and Lung Institute, and the National Institute of Neurological Disease and Stroke to be Associate Directors of NIH. It stressed that cancer research would remain within NIH, and it authorized the NCI Director to use all of the biomedical resources of NIH and insure open linkages between NCI and other Institutes and other organizations. The NCI Director was to use the existing peer review system for grants to the fullest extent possible, but could, with approval of the NIH Director and the NACC, establish other peer review systems. The Director would submit his annual budget request directly to the President; the NACC, the NIH Director, and the Secretary, DHEW could comment on the budget, but could not change it. The NCI would receive all funds appropriated by Congress for obligation and expenditure and not be blocked by the Office of Management and Budget or the President. The NCI Director was directed to support manpower programs of training in basic research and clinical disciplines. He could award grants up to \$35,000 after scientific review without NACC approval. The Bill called for the strengthening of existing cancer research centers and establishment of 15 new ones. Additional construction authorities were included. Perhaps the most far-reaching change from previous NCI activities was the re-introduction of the cancer control program into NCI with authority to NCI for the prevention, control, and eradication of cancer; funds authorized for cancer control were \$20 million, \$30 million, and \$40 million for fiscal years 1972, 1973, and 1974, respectively.

The Subcommittee presented its report and H.R. 11302 to the full Committee on November 3 and 4. This Bill was adopted by the Committee by a 26-to-2 vote on November 4.

A Film on Cancer Research

At the March 10-11, 1970, NACC meeting the importance of keeping the public informed of the advances in cancer research was discussed. Danny Thomas, who was on the NACC, suggested that the NCI have a film made on current cancer research activities. The Council recommended this action (Minutes, NACC March 10-11, 1970 Meeting). Mr. Thomas said he was sure he could get some of his Hollywood friends to help make the film. Danny Thomas, his daughter Marlo, John Wayne, Gregory Peck, Dionne Warwick, and Ann Baxter all volunteered (at no pay) to be in the film. John Wayne and Gregory Peck discussed smoking and lung cancer (John Wayne was at the time a lung cancer patient). Ann Baxter emphasized the importance of the Pap smear and Dionne Warwick discussed breast cancer and mammography. Marlo Thomas discussed activities of cancer centers; she interviewed young cancer patients at St. Jude Children's Research Hospital in Memphis. In the film, about 40 outstanding cancer investigators were interviewed from cancer centers, universities, and the NCI. Mr. Thomas served as host for the film, and on September 22, 1971 concluding comments were made by the NCI Director and Danny Thomas. Originally planned to last an hour, the film was cut to a good half-hour public relations product. After some delay, the film was released. It was shown many times throughout the country.

The October 4-6, 1971 NACC Meeting

While the busy political activities were taking place, the NCI had to also carry on its usual functions, such as planning and presenting its annual reporting of on-going programs to the NACC. At the annual meeting in 1971, Dr. Rauscher discussed the Etiology Area and Dr. Moloney discussed the Viral Oncology programs. The Viral Oncology printed report occupied 457 pages of the 664 pages for the Etiology Area. This tremendous volume resulted from review groups asking for more information and from the larger program efforts. The material, which was as usual sent to the Council members before the meeting, was arranged with the general aspects up front and with the more specific aspects further back in the volume (the final section was made up of abstracts for each contract). In the Special Virus Cancer Program, because of new research leads and development of new techniques, a new segment on breast cancer (Dr. Ray Bryan, Chairman) was added and the Immunology Segment activities were enlarged.

During July and August, the SVCP Research Logic Flow Systems Chart was extensively revised and updated with additional Decision Points, more detailed Criteria required to make the decisions, and more precise spelling out of the kinds of data that should be sought in order to meet the Criteria. As noted above Monitoring Points were added to the SVCP Systems Chart. Each contract was matched to a specific part of the chart. There were 120 contracts in force; the consultants to the SVCP totaled 105.

Six new contracts focused on RNA-Dependent DNA Polymerase (Reverse Transcriptase) (Baltimore, Bishop, Green, Oak Ridge staff, Schactman, and Spiegelman). Drs. Huebner, Todaro, and Gallo were also working with reverse transcriptase. Reverse transcriptase was found in all the RNA-containing cancer viruses tested. They were derived from many different animal species: reptile, chicken, mouse, hamster, and cat. The enzyme was found in the rather similar viruses - Type C - known to induce leukemias and lymphomas and sarcomas in these species.

The SVCP utilized its ability to modify program output with contract definitions and did so to make available to investigators participating in SVCP activities large amounts of virus and high molecular weight RNA, as well as large amounts of reverse transcriptase. A contract was awarded (Drs. Joseph and Dorothy Beard, Project Directors) to produce large amounts of avian myeloblastosis virus (AMV). These large amounts allowed investigators to isolate and purify RNA and the enzyme from the virus for additional studies. The enzyme associated with other cancer viruses was also purified for other studies. The reverse transcriptase from AMV could also be used to prepare DNA complementary copies of the RNA of other cancer viruses. In Dr. Spiegelman's laboratory, DNA complementary to the RNA of mouse leukemia virus (MLV) and mouse mammary virus (MTV) had been prepared. This finding derived its importance from the availability of specific hybridization procedures. It had been established earlier that single stranded nucleic acid molecules combined to form duplex molecules only with nucleic acids bearing complementary base sequences. Such duplexes could be of the DNA/DNA or RNA/DNA types. The formation of such specific hybrids could be sensitively detected by labeling one or both of the nucleic acids employed with radioactive nucleotide and separating the resulting duplex hybrid molecule by chromatography, binding to filters, or density separation on a cesium sulfate gradient. These developments and others could not have been pursued without a greatly enlarged supply of certain resources made available from contracts of the SVCP.

Reverse transcriptase was also found in the somewhat differently structured virus - Type B, the mouse mammary tumor virus (MTV) - known to be implicated in the development of breast cancer in the mouse. Type B viruses possess certain properties in common with Type C viruses, such as having genetic material of the RNA type and being transmitted from parent to offspring along with the normal genetic inheritance. But they also differ in: 1) the manner in

which the nucleoid is formed during reproduction; 2) the fine details of their ultrastructural appearance; and 3) transmission in infectious form, under natural conditions. The potential existence in humans of an infectious breast cancer virus similar to that of mice, together with epidemiological evidence of “clustering” of breast cancer in some human families similar to that observed in the earliest studies of cancer in mice, led to systematic viral studies on this human disease. Particles resembling the Type B virus of mouse breast cancer were observed in 40% or more of milk specimens from women with breast cancer, as well as from healthy women of high-risk populations (high breast cancer families; inbred Parsi sect of Bombay, India) as compared with a frequency of only about 6% for specimens from healthy women of the general population. Similar particles were also observed in two tissue culture lines of human breast cancer that had been successfully grown in the laboratory. Moreover, Spiegelman and Moore and colleagues demonstrated the presence of appropriate RNA and reverse transcriptase in purified viral particles isolated from human milks. These studies were extended to examine human breast tumors. Nineteen of twenty-nine specimens of human breast cancers yielded microsomal fractions that hybridized with DNA complementary to mouse MTV RNA. Normal breast tissue specimens or breast tissue from various benign lesions gave microsomal RNA fractions that did not hybridize with DNA complementary to MTV. The above findings suggested that human breast tumors contain functional genes that are related to the genes contained in the virus known to induce mammary tumors in mice.

The use of mutant bacteria and mutant infecting viruses for investigations greatly advanced our knowledge of microbiology, especially in defining the genetics of the host cell and infecting virus and of some of the molecules involved. Although the knowledge of analogous systems involving mammalian cells and viruses was rudimentary, as noted above advances in

viral oncology by 1971 were beginning to provide additional important leads with the discovery and use of temperature-sensitive mutants of tumor viruses. These temperature-sensitive mutants, first isolated by Martin (Berkeley), Vogt (U.C.L.A.), and Hanafusa (City of New York Public Health Institute), were highly significant because they allowed the beginning of dissecting the tumor virus genomes to learn which part of the viral genome provided genetic information directing cell transformation into cancer, as well as which part(s) directed other activities such as the synthesis of viral structures and reproduction of complete virus. Dr. Hanafusa had isolated a temperature-sensitive mutant of a chicken sarcoma virus, the t-s mutant. This mutant, like the parent (wild-type) virus, can infect and propagate in chicken cells at either 36° or 41°. However, the t-s mutant virus transforms the cell only at 36°. Once the transformation has occurred, however, the capacity for transformation is transmitted as a genetic trait to all daughter cells. The expression of the cancer trait is dependent on temperature. Thus, if cells transformed by the t-s mutant virus are subjected to a temperature of 41° they revert to normal cellular type within 4 hours, whereas cell division at that temperature requires about 12 hours. Cells that have reverted to normal remain normal through several generations as long as the temperature is maintained at 41°. However, once the temperature is dropped to 36° they revert to cancer-type morphology within 4 hours. This system was very important for studying the biochemical lesions attending expression of cancer genes in the cell. Metabolic antagonists, which block either DNA replication or DNA transcription to RNA, were found not to inhibit the cellular alterations attendant on temperature shifts on the t-s mutant virus-transformed cells. However, the presence of antagonists such as cycloheximide (known to block protein synthesis) did prevent the cellular alterations. Other investigators on SVCP contracts studying temperature-sensitive mutant tumor viruses included Giampiaro di Mayorca, Howard Schactman, Maurice Green, and Walter

Eckhart. Dr. Eckhart (Salk Institute) was continuing studies with temperature-sensitive mutants of polyoma virus to identify the viral functions required for transformation. He identified two viral gene functions required for transformation. One is required transiently to initiate or stabilize the transformation, and the other is required continuously to maintain certain aspects of the transformed phenotype, particularly cell surface alterations that affect cell growth control. These studies were mostly concerned with the ts3 mutant, which is defective in a gene function required for induction of cellular DNA synthesis in resting Balb/3T3 cells, and for initiating and maintaining surface alterations detected by agglutination of infected or transformed cells by wheat germ agglutinin or concanavalin A. Work was continuing to clarify the genetic relation between mutants defective in the functions required for the transformation and other mutants (such as host range mutants of polyoma). Studies on genes of tumor virus mutants and of cellular genes were of top priority in the SVCP programs, and they would be enhancing understanding at the molecular level. These studies on cancer were designed to enhance the growth of molecular biology.

Evidence in support of the Oncogene Theory of Huebner and Todaro continued to increase during 1971. More examples in several species were reported of the vertical transmission of the C-type virus information and the switching on of the information by chemical carcinogens, the aging process, chromosomal alterations, and genes derepressing the oncogenes. By 1971 more than 100 viruses had been shown to cause cancer in animals. For example, the C-type viral genomic information was not expressed until a chemical carcinogen was applied to mice; the C-type genomic information was expressed before the tumors appeared. Moreover, in other studies without chemical carcinogens, the C-type information was not expressed in mice until the animals were aged. The large number of different strains of inbred mice at the Jackson

Laboratories in Maine provided an important testing ground for demonstrating the different effects of host-gene control of C-type RNA tumor virus-expression and tumorigenesis (Meier and Huebner). These studies also demonstrated again that this viral genomic information was not spread horizontally. Some of the aged mice, depending on the strain of mice, showed expression of C-type RNA tumor virus information (gs antigen) before tumors were present. Sensitivity of immunological assay techniques continued to improve and were used in determining expression of viral and cellular genes.

Seroepidemiological field studies were conducted in California in 1971 (McAllister, Gardner, and Huebner). This large multifaceted, highly integrated contract effort was designed to determine the actuating and contributing roles of viruses, physical and chemical carcinogens, as well as other factors associated with cancer development to the etiology of human and animal cancer in a natural urban ecology. The contract had four parts: 1) the collection, distribution, growth and study of specified human and animal cancer and control materials as well as tissues derived from genetically defective individuals; 2) epidemiologic studies of the incidence and prevalence of contemporary cancers in relation to (a) exposure to environmental pollutants; (b) possible genetic or ethnic influences; (c) dietary and other cultural and individual patterns which are suspected to have possible cancer-inducing properties; (d) development and organization of hospital based registries; and (e) computerization of data; 3) environmental and ecological studies to measure relative exposures to environmental pollutants on a residential and occupational basis, and as determined by leads developed in areas 1) and 2); materials collected were characterized and disseminated for study in animal and tissue culture systems at the University of Southern California and other collaborating laboratories; and 4) co-carcinogenic studies to determine effects of naturally occurring environmental carcinogens in various animal

species, with particular emphasis on free-living animals (wild mice, cats, etc.), which share man's ecology. Through March 15, 1971, 228 human tumors and 68 specimens of human fetal tissues were obtained and processed. Tumors included 24 sarcomas, 5 lymphomas, 155 carcinomas, and 44 benign conditions. Five non-tumor specimens of interest (rejected transplanted kidneys) and biopsied muscle and nerve tissues were studied. Sera were obtained on 91 patients (38%) and normal tissue from 79 (33%). In other categories, 83 field cats and four dogs, carrying a variety of tumors, were referred by agreement with local veterinarians. In addition to on-site serological, immunological, biochemical, and electron microscopy studies, human and feline tissue and extracts were sent to the Viral Carcinogenesis Branch, NCI, and other contract and collaborating laboratories, as appropriate.

In the serology and immunological studies, positive complement fixation reactions in a large number of human tumor and fetal tissue extracts with several MSV rat sera pools suggested the presence in these tissues of an interspecies cross-reacting antigenic component.

Researchers had found that broadly reactive MSV rat sera pool 21 and FSV dog antisera generally react in CF with tissues from those feline conditions most commonly associated with C-type viruses, namely spontaneous lymphoma, infectious peritonitis and anemia, and experimental FSV sarcoma. No success had been achieved so far in isolating additional feline RNA tumor viruses by inoculation of cat fetuses with several naturally occurring feline sarcomas and carcinomas, some containing demonstrable C-type particles. The DNA polymerase activities of FeLV and FSV using natural and synthetic templates were studied. The DNA directed enzyme activity of FSV with a synthetic duplex required simultaneous copying of both template strands of a homopolymeric duplex. Nearest neighbor analyses of DNA products of representative feline,

avian and murine RNA tumor viruses suggested interspecies variation in the nucleotide sequence of the RNA genome copied *in vitro*.

Studies of spontaneously occurring cancer in the cat revealed an unusual predilection for oral cancer, which in view of feline grooming habits, raised the question of possible carcinogen induction (i.e., smog particulates collected on the coat and transported via licking to the mouth and tongue).

Serological tests indicated that there was good correlation between tissues containing C-type particles and positive reactions in the complement fixation test. Studies to determine possible horizontal transmission of feline cancer cells or leukemia viruses by the common cat flea were proved negative, although it was ascertained that cells could technically be transferred from one cat host to another. In addition, examination of two of the seven modified live vaccine products grown in feline embryo tissue cultures for possible contamination with the feline leukemia virus proved negative for infectious virus and in the electron microscope.

The Epidemiology and Cancer Surveillance Program of this contract was being developed to utilize a rapid reporting system from hospital pathology and hematology laboratories. Pilot efforts were underway in three large hospital centers in the Los Angeles area. Cases referred would be utilized initially to study the relationship of several factors, including a) maternal and paternal age of cancer patient; b) birth order; c) family history of cancer, allergic conditions, diabetes, and congenital abnormalities; and d) ethnic background to the risk of cancer. A questionnaire was to be tested shortly.

For the Environmental Studies, the contract established four sampling trailers at defined high and low smog areas. A comprehensive fractionation was started on an annual composite of organic extracts of airborne particulate matter. When separations are complete, fractions will be

distributed for biological testing. Crude fractions were tested *in vitro* under another contract and were found to produce cell transformations.

In vitro co-carcinogenesis studies: with the use of broadly reactive MSV rat sera pool 21, gs antigenic expression was commonly detected in different tissues from freshly trapped untreated wild house mice never housed in the laboratory. C-type and intracisternal A-type particles were also seen on occasion in many of the tissues. This indicates that the C- and A-type viral genomes must be ubiquitous in this natural feral species. Infectious C-type virus had not yet been isolated from any source despite the use of all the more recent virus isolation procedures. B-type virus particles were seen in breast tissue from two normal lactating wild mice never housed in the laboratory. A polyoma virus infected ecology of wild mice had been defined and would be studied for RNA tumor virus expression with aging in comparison with polyoma free mice. Attempts to activate infectious virus by UV irradiation from a Ki-MSV transformed non-productive rat cell line and monocellular clones and from spontaneous transformed foci of rat cells were unsuccessful.

The proposed course of work was as follows:

Part 1): two biochemical units would be added which would focus on the following problems: a) the role of the C-type RNA viral genome and RNA-dependent DNA polymerase in normal and cancer replication, as well as in normal embryonic cell growth and differentiation; b) to determine the presence or absence of double-stranded viral RNA and the RNA-dependent DNA polymerase or their products in human and animal cancer cell lines; c) attempt to isolate and characterize possible inhibitors or repressors of RNA tumor virus expressions; d) attempts to characterize virus derepressing mechanisms of chemical

carcinogens; and e) determine whether components of a human sarcoma virus genome are incorporated into human sarcoma cell lines infected with animal C-type viruses and utilize animal model system cell hybridization techniques in efforts to detect and rescue components of the human C-type RNA genome and its associated polymerase.

The serological unit would be enlarged to accommodate the increased specimen load. An immunology unit would be established; its initial focus would be directed to isolating human C-type particles or viral genomes utilizing immunological procedures which proved successful in unmasking covert animal cancer viruses. Methods to be employed would include: a) screening of a variety of genetically susceptible individuals with leukemia, stimulating the leukemic lymphocytes with phytohemagglutinin (PHA) in efforts to detect the human C-type genome; b) performing parallel studies in human and animal tissues from a variety of age groups; c) combining hydrocarbon carcinogens with PHA in efforts to “activate” viruses and transform lymphocytes; d) establishing long-term lymphocyte cultures from selected patients; and e) culturing animal tumor viruses in long-term and PHA-treated human lymphocyte cultures.

Part 2): the epidemiology program, designed to gain information on the contemporary occurrence of cancer within several defined subenvironments of Los Angeles County was being expanded to provide back-up service and training for a proposed county-wide cancer surveillance registry. When fully implemented, it was estimated that Project Directors would have access to most of the major hospitals in the Los Angeles area, covering 70-80% of all cancer patients including their physicians and families and their medical, residential, and occupational histories.

Part 3): for the environmental studies, facilities for sampling four reasonably distinct areas of Los Angeles County in terms of air pollution were in full operation. Smog specimens were collected, concentrated, and disseminated for *in vivo* and *in vitro* studies at USC and in

related and NCI laboratories. Characterization of components had been expanded from benzopyrene and various gases and to a number of additional hydrocarbon and tar constituents.

Part 4): Proposed co-carcinogenesis studies would explore the interaction of chemical carcinogens with the C-type viral genome, particularly in the cat and feral mouse. Atmospheric residues, demonstrated by Freeman, *et al.*, to be carcinogenic *in vitro* (collected and distributed by the Part 3) air sampling program) would be utilized to determine their effects in vivo and in vitro under a variety of host, host cell, and environmentally defined circumstances.

In addition to the work directed by Drs. M. Gardner and R. McAllister at USC and the Children's Hospital in Los Angeles, including the supplying of human and animal materials to SVCP participants, Dr. Huebner coordinated these efforts with other contracts, including those with Microbiological Associates, Flow Laboratories, St. Louis University, Naval Biomedical Research Laboratories, and the California State Department of Public Health, and with programs at NCI.

These program efforts were described here in considerable detail for two reasons. *First*, they illustrate the leadership capabilities of Dr. Huebner in formulating, organizing, and managing large multidisciplinary programs targeted to solving disease problems; an effort of this scope and size carried out in an integrated fashion was perhaps unique in biomedical research. Awards to Dr. Huebner included the Pasteur Medal, the Rockefeller Public Service Award early in 1971 and later the President's National Medal of Science. *Second*, they raise the question as to whether more programs of this type should be developed around other disease problems. One often hears the call for a "War on Cancer." Such a war needs generals as well as privates. Dr. Huebner illustrated the effectiveness of generalship. There are other outstanding investigators

who could lead larger multidisciplinary efforts if funds were made available in larger blocks than was customary.

Dr. Todaro and co-workers were studying eight patients with acute leukemia and their identical twins with evaluation by a variety of techniques. Lymphocyte cytotoxicity, mixed lymphocyte culture and skin testing were used to determine whether cellular immunity factors could identify a tumor specific antigen, and whether there was evidence that this antigen caused immune reactivity in family members and controls. Cells from the patient and his identical twin were used as sources of antigens directly, and materials were also placed in tissue culture. Skin fibroblasts from family members were tested to determine whether any genetic factors could be associated with acute leukemia. Electron microscopy and immunofluorescence, using antisera against Rauscher and feline leukemia viruses, would be utilized to determine whether any of the antigens detected by cellular immunity tests were related to any known animal leukemia viruses. An antigen that appeared to be a leukemia-associated antigen was detected in five of seven sets of identical twins. This study would continue in an attempt to define more carefully the specificity of the leukemia associated antigens and the immune response of humans to these antigens.

Evidence continued to increase that Epstein-Barr virus causes nasopharyngeal cancer in southern China and Burkitt lymphoma in Africa and elsewhere. Seroepidemiology studies on the relationship of Epstein-Barr virus (EBV) to nasopharyngeal cancer were being conducted through the International Agency for Research on Cancer (IARC). A study in the West Nile District of Uganda to determine the feasibility of further studies on EBV in relation to Burkitt's tumor was nearing completion. The Board of Directors of the IARC, a member of which was the NCI Director, reviewed these studies. The association between cervical cancer and Herpes Virus

Type 2 (HSV-2) continued to appear stronger. A study in Texas showed the presence of serum antibodies to this virus in about 85% of cases of invasive cervical carcinoma in comparison to 22% in controls. Findings in Colombia showed a much higher incidence of antibody in the control population selected, approximating the incidence in the tumor-bearing group. The incidence of cervical cancer is very high in Colombia. Interferon therapy was effectively applied in mice infected with the Moloney sarcoma virus plasma-variant (MSV-PV). The survival rate of virus-infected mice treated with interferon-inducing poly Ir:Cr-poly-D-lysine complex was nearly twice that achieved with poly Ir:Cr alone. Mice immunized with formalized MSV-PV were also refractory to challenge with MSV-M and Friend leukemia virus as well as with MSV-PV. When serum interferon responses were determined in different strains of mice, activity varied by a factor of about 100 from the most to the least responsive mouse strain.

Many other highlights of research progress of the SVCP were reported to the NACC. Many services and resources, some in large amounts, continued to be provided to SVCP participants and grantees. These were not yet available commercially. The amounts and types of resources developed and supplied were being continually modified to meet the changing needs.

The total number of publications emanating from the SVCP reached 604 (294 published and 310 in press). As of June 30, 1971 the funds for the Etiology Area were \$55,722,000 of which \$36,050,000 was for Viral Oncology (Viral Oncology contracts accounted for \$31,873,000). The 188 viral oncology grants in Fiscal Year 1972 totaled \$11,006,000. As usual, several modifications were made during 1971: 19 contracts were terminated and 29 were changed to modify workscopes or areas of emphasis. Forty-two new contracts were awarded. The total number of contracts in Fiscal Year 1971 was 120: Project Directors on NCI contracts included: N. Anderson, D. Baltimore, J. M. Bishop, R. Good, M. Green, H. Hanafusa, L.

Hayflick, M. Hilleman, J. Holland, G. Klein, E. Lennette, J. Melnick, H. Oettgen, F. Rapp, L. Sachs, G. Santos, H. Schachtman, S. Spiegelman, and P. Zamecnik. The SVCP had 105 consultants; included were: D. Baltimore, J. Beard, M. Green, H. Hanafusa, M. Hilleman, L. Levintow, E. Lennette, B. MacMahon, J. Melnick, L. Old, W. Rowe, A. Sabin, H. Temin, P. Vogt, and J. Watson (“National Cancer Institute Etiology Annual Program Review Document,” for the NACC October 4-5, 1971 Council Meeting”).

The SVCP Annual Joint Working Conference was held at Hershey Pennsylvania, October 24-27, 1971.

At the June NACC meeting, in anticipation of Congressional action to enlarge cancer research, the Director, NCI, appointed a Council subcommittee to prepare a report to the Council and NCI on “Key Problems in Cancer Research.” Members were: Dr. Philippe Shubik (Chairman); Dr. Arnold Brown; Dr. Leon Jacobson; Mr. James Gilmore; and Dr. Bayard Morrison, III (representing Dr. Baker). The subcommittee eight-page draft report was sent to Council members for comment. It consisted of a preamble and summary and a central section that was a modified version of Dr. Baker’s February 2, 1971 document. Fifty-five key problems were listed on five pages of the document. In June the Director, NCI asked the senior staff of the Institute to submit for their respective areas of responsibility: the OBJECTIVES; IDENTIFICATION OF ESPECIALLY PROMISING PROGRAMS; LISTING OF POTENTIAL PROBLEMS, CONSTRAINTS AND LIMITATIONS; and ASSUMPTIONS USED IN ARRIVING AT THE FUNDING LEVELS. These documents provided information as added input for planning the response to anticipated Congressional expansion of cancer research.

The Etiology Area Advisory Committee consisted of:

Dr. Richard Mason (Chairman), American Cancer Society
Dr. Charles Evans, University of Washington
Dr. Maureen Henderson, University of Maryland
Dr. Joseph Melnick, Baylor University
Dr. Guy Newell, Tulane University
Dr. Frank Putnam, Indiana University
Dr. Harold Rusch, University of Wisconsin
Dr. Michael Shimkin, University of California, San Diego
Dr. Gio Gori (Executive Secretary, NCI.

The membership of the National Advisory Cancer Council was;

Dr. Carl Baker (Chairman), Director, National Cancer Institute
Dr. Arnold Brown, Mayo Clinic
Dr. Juan del Regato, Penrose Cancer Hospital, Colorado Springs
Dr. Sydney Farber, The Children's Cancer Research Foundation
Mr. James Gilmore, Gilmore Broadcasting Corporation, Kalamazoo
Dr. Karl Habel, Scripps Clinic and Research Foundation
Dr. John Hartmann, The Children's Orthopedic Hospital and
Medical Center, Seattle
Dr. Leon Jacobson, University of Chicago
Dr. Kenneth Krabbenhoft, Wayne State University
Dr. William Shingleton, Duke University
Dr. Philippe Shubik, University of Nebraska

Dr. Paul Talalay, Johns Hopkins University

Mr. Danny Thomas, Hollywood, California

Dr. Murray Angevine (Alternate Ex Officio), Armed Forces

Institute of Pathology

Dr. Lyndon Lee (Alternate Ex Officio), Veterans Administration

Dr. J. Palmer Saunders (Executive Secretary), NCI.

Briefing of President Nixon and Conversion of Ft. Detrick to a Cancer Research Facility

President Nixon had decided to convert the U.S. Army germ warfare facilities at Frederick, Maryland to a cancer research facility. On October 18, 1971 he dedicated the modified facility, giving an address on the needs to increase cancer research and to reduce germ warfare weapons. The NCI Director was asked to brief the President immediately prior to his talk. Dr. Baker covered the general aspects of cancer and the programs of NCI. Dr. Zubrod covered Therapy; and Dr. Rauscher covered Viral Oncology.

National Cancer Plan Planning Conference, Airlie House, Virginia

On October 24, 1971, the Planning Conference for further development of the National Cancer Plan began with a series of sessions at the Airlie House Conference Center at Warrenton, Virginia. The initial sessions were held October 24-29 and November 15. The first part consisted of an orientation by the NCI Director before a plenary session of the 39 Chairmen of the Panels Considering the Approaches also known as the Approaches Panels. The orientation presented the philosophy of and need for planning for the total cancer research efforts, the establishment of the suggested Goal and (seven) Objectives, and the Approaches or courses of action considered

necessary to achieve each Objective. He gave the background of the recent activities related to cancer in the Executive and Congressional Branches, including the budgetary and other Hearings. President Nixon and Senator Kennedy both had stressed the need for planning and management to a greater extent. The presentation utilized the circular chart for showing the overall perspective and the suggestive content and organization of the components of the plan, both the Research Strategy and the Operational Strategy. The Research Strategy was given the primary importance since the Operational Strategy components are derived from the Research Strategy. Lou Carrese and Jack McShulskis had prepared an excellent briefing document (123 pages) that was sent to the participants prior to the Conference. Carrese and McShulskis spent the rest of the first day orienting the group to the briefing document.

The remainder of the five days (and additional time spent in writing and revision of Panel reports) was spent by the Approaches Panels to develop their revisions and to make their recommendations. They generally accepted the formulation of the Goal and the Objectives as developed and proposed by NCI staff. Some minor changes were made in the Approaches, and the number of them was reduced to 35 Approaches (Approaches 1 and 2 under Objective 4 were compressed into one Approach). Viral Oncology efforts were in 5 of the 7 Objectives. Recommendations included suggestions for implementation strategy. After the initial briefing by the NCI senior staff, they did not participate in the activities of the Approaches Panels because the NCI wanted to ensure that the deliberations and conclusions would be those of the scientific community and not be overly influenced by the NCI staff.

After development of the initial Approaches, multidisciplinary Panels were established to describe the scientific efforts necessary to implement the Approaches. These Panels were known as Project Areas Panels. NCI staff members were permitted to serve in limited numbers

on these Panels when they possessed special expertise in the area being considered by the planning Panels. One Project Area Panel was established for each Approach. The Panel members received ahead of time the briefing document and were briefed by Carrese and McShulskis before meeting as individual Panels. [Finally, there were 34 reports, 762 Project Areas, and 211 investigators participating in the Project Areas report formulation.] The reports produced by the Panels also included estimates of resources judged to be needed to accomplish the research. The schedule of the Project Areas Panel meetings, under each Objective, was:

- Objective 1 November 29-December 2, 1971
- Objective 2 December 5-8, 1971
- Objective 3 December 5-8, 1971
- Objective 4 December 14-17, 1971
- Objective 5 December 14-17, 1971
- Objective 6 January 3-6, 1972
- Objective 7 Completed in the week of October 24, 1971.

In contrast to the reports from the Approaches Panels, the reports from the Project Areas Panels showed several modifications and detailed changes from the suggestions included in the NCI briefing document. The outlook for research developments over the following five years was included in the reports. These changes were considered by NCI as signs of good participation by the scientific community. After these sessions, the 39 panel chairmen were called together (March 13-15, 1972) in a plenary session to review the reports and resolve any differences or discrepancies that might have arisen.

The priority judgments and the estimates of resources required for the recommended research were difficult to make. These judgments included estimates of the time frame needed

for accomplishment of the projected research, the impact of successful research, and the probability of success, in addition to the priority indications. Some of the participants thought it not possible to make such judgements. However, these estimates were useful in the subsequent analysis phase of the planning and in putting together the complete plan. Such projections would also be useful in justifying funds sought from the Congress. As noted above the resource parameters included manpower, facilities, equipment, supplies and materials, numbers and types of patients, and others. For each category, dollar amounts (based on an annual budget figure of \$1 billion) and projected quantities of resources were included. In addition, priorities were assigned to the 7 Objectives and the 35 Approaches by all the participants. By June 1972 the reports from the Approaches Panels were ready for distribution. As Richard Rettig stated in his book *Cancer Crusade* (pg.299 “*Carl Baker initiated an NCI-directed effort that must rank as the largest, most extensive planning effort ever undertaken within biomedical research.*” It was expected that the scientific community would continue to be called upon to update periodically the plan and participate in the Program. It was to be hoped (and perhaps expected) that an *esprit de corps* would be developed that would enhance the total research effort.

Much more work would be required for developing the Project Areas reports and still more for developing the Operational Plan and its implementation. The analysis of the responses of the 250 scientists at the Airlie House Planning Conference carried the effort into 1974, though the first draft of the Strategic Plan was available by January 1973. The Operational Plan took much longer to develop; in some ways it became over-elaborate, making it difficult to implement.

Dr. Seymour Cohen of the Department of Microbiology, University of Colorado Medical Center at Denver, presented a paper on October 26, 1971 at a National Academy of Sciences

Symposium in which he stated that “ . . .existing institutions, universities, institutes, pharmaceutical companies, etc. in this country had not developed comprehensive integrated programs in cancer research”. He pointed out that any such program, should it be developed, would require for its success, participation of the scientific community. He felt that the Cancer Centers program of the NCI Extramural Programs was an important step in the right direction. In view of the extensive planning efforts of the NCI and the on-going Airlie House Planning Conference at the same time as the NAS Symposium, it is of interest to see Dr. Cohen’s footnote to the printed version of his talk: “*It has been brought to my attention that even as this paper is being given (October 26, 1971) meetings are being held under the auspices of the NIH and NCI to begin an extensive effort intended to involve hundreds of working scientists in the planning of a Cancer Research Program. It goes without saying that the author is pleased that this initiative has been taken.*” (Seymour Cohen, “On the Development of Programs in Cancer Research,” Proceedings of the National Academies of Science, U.S.A., vol. 69, no. 4, pp. 1048-1051, (April 1972).

Joint House-Senate Conference Committee

On December 1, 1971, the joint House-Senate Conference Committee met to resolve differences between H.R. 11302 and S. 1828. The leading players were Senator Edward Kennedy and Congressman Paul Rogers. The administration took a hands-off position toward the activities of the Conference. Although the White House was still formally committed to S. 1828, it had let it be known that H.R. 11302 was acceptable. The main aspect of the controversy between the two Bodies was the organization of the cancer efforts and their location in the governmental structure. The Senate Bill would create a new cancer agency as an independent

agency within the NIH; the House Bill provided that the NCI Director report to the NIH Director except on the matter of budget submissions. Unexpectedly, the Senate accepted the House version on this issue. The next two days of the Committee deliberations were spent on the composition of the President's Cancer Attack Panel. The Senate Conferees wanted to add the NCI Director to the Panel. The House was adamant in opposing any arrangement that included the NCI Director. Congressmen Paul Rogers and Ancher Nelson saw the Panel as an oversight body. The Panel was responsible for bringing problems to the attention of the President for his resolution, but its role was not that of direct program management. Thus, at the end of December 2, it appeared that a stalemate existed. The Conference adjourned on December 2 and reconvened on December 7. On December 6, in response to a letter from Senator Kennedy and eight other Senators, the President indicated that he would accept either the Senate version or the House version. On reconvening the Senate representatives accepted the House version.

The House Bill would have kept the NACC as established in the 1937 legislation. The Senate Bill would establish a National Cancer Advisory Board with 18 members, no more than 12 of whom would be scientists and physicians and no more than 8 would be laymen. The Board would have greater authority than the Council. The President would appoint the members and the Chairman. The House accepted the Senate proposal with the addition of 5 *ex officio* members. The final version of the Bill authorized the NCI Director to provide for establishment of 15 new comprehensive cancer centers in addition to existing centers (Sloan-Kettering Institute; M.D. Anderson Hospital and Tumor Institute; Roswell Park Memorial Institute; and NCI Intramural Programs; plus 10 smaller institutes including Dr. Farber's Children's Cancer Research Foundation). The greatest change was the re-establishment of the Cancer Control Program within the NCI (with authorization of appropriations of \$20 million for fiscal year ending June 30,

1972, \$30 million for fiscal year ending June 30, 1973, and \$40 million for fiscal year ending June 30, 1974). All references to diseases other than cancer were eliminated. The House Bill would make the Directors of the NCI and of the NIH Presidential appointments; the Senate side accepted this proposal. Thus, for the first time these appointments became political appointments. The House received the Conference Report on December 9, and Congressmen Harley Staggers and Paul Rogers spoke in favor of the Report. Mr. Rogers concluded with: “*I can think of no better Christmas present for the American people than to have this Bill passed by this body and signed by the President without delay.*” The House of Representatives agreed to the Conference Report on December 9. The Senate accepted the Conference Report on December 10. The vote in the Senate was 85 in favor and none opposed. The measure was sent to the President for signature.

On December 23 the President signed the Bill into law as The National Cancer Act of 1971. The happy occasion of the signing took place at the White House, beautifully decorated for Christmas. The President announced that he was appointing Benno Schmidt Chairman of the President’s Panel, and he gave Mr. Schmidt the pen that Mr. Nixon used in signing his first name. He gave the pen he used in signing his last name to Dr. A. Hamlin Letton, President of the American Cancer Society. In addition to several members of Congress, 137 invited guests were at the signing, including members of the Panel of Consultants: William McC. Blair, Joe Burchenal, Lee Clark, Emerson Foote, Anna Rosenberg Hoffman, Mathilde Krim, Mary Lasker, and Jonathan Rhoads. NIH was represented by Bob Marston, John Sherman, and Ken Endicott. NCI was represented by Carl Baker and senior NCI staff: Gordon Zubrod, Palmer Saunders, Dick Rauscher, Nat Berlin, Cal Baldwin, Lou Carrese, Jim Kieley, Bud Morrison, and Tony Bruno.

Many outstanding investigators were among the guests. Included was Dr. Ernest Borek, Professor of Microbiology, University of Colorado School of Medicine in Denver. He described the White House event in the Preface of his *The Sculpture of Life* (Columbia University Press, New York, 1973, pp.viii-ix):

“ . . . The Congressmen and Senators who had guided the law into being smiled broadly as the cameras focused on them. Most of the scientists in the audience did not smile; they were worried. The hoopla surrounding the Cancer Act implied the conquest of cancer in the near future because a couple of hundred million dollars a year more were to be channeled into cancer research.”

“Those of us there who knew the ‘state of the Art’ had cause to worry”.

“Some of us had just returned from a series of conferences on what is not known about cancer, and what is yet to be done”.

“The Director of the National Cancer Institute, Dr. Carl Baker, had launched a unique program. He assembled some 250 of the leading biological scientists and cancer specialists, divided them into groups of 8 to 10, assigned each group to a well-defined area of the problem, and locked them up for three days in a resort outside Washington”.

“Since this was probably the first time that working scientists were called in to assess current knowledge and to plan for the future, they responded and worked with a sustained intensity equaled only by the days before examinations for their Ph.D. ’s or National Boards. The result is the National Cancer Plan, which is an inventory of research yet to be performed to understand and to control cancer. The list in fine print on both sides of 8 X 10 sheets is over a foot high.”

“That is why some of us there did not smile.” - - -

“Our disquiet stemmed from two sources. Promise of a cure within a defined time of any disease, especially something as complex as cancer, should never be made. There is no more cruel disappointment than promise of health not fulfilled. Moreover, what will be the effect on the attitude toward science and scientists of a public, already disenchanted with us, if we are copartners in making what amounts to a fraudulent promise.” Dr. Carl Baker as Director of NCI and in various other roles at NCI over a 23 year career at NIH, in testifying before Congress and other bodies, in writing many, many Institute documents, in giving many talks, and in meeting with the press, never slipped and made a prediction of when cures or preventions would be reached.

Cancer Research Activities at the Time of Signing of the National Cancer Act of 1971

After signing of the Act the enlarging budgets for the NCI and the National Cancer Program allowed an increased size and rate of expansion of many activities already in existence:

a) Various mechanisms had been developed for reviewing, funding and implementing a variety of projects and programs that utilized grants and contracts; a large-scale contractor-operated program (at Fort Detrick) was initiated.

b) The concept of cancer centers was well developed, and the first centers had been funded with centers grants.

c) Classification schemes for diseases and associated factors, analysis of research results, and data generated from such activities laid foundations that later permitted widening of information distribution to laymen and professionals.

d) Cancer statistics and epidemiology and their methodologies were maturing (biochemical epidemiology, now molecular biologic epidemiology, had been initiated).

e) As early as 1968, the NCI was testifying before Congressional committees about what could be done with an annual NCI budget of \$1 billion.

f) The NCI continually sought additional funds for research on carcinogenesis (hundreds of chemical compounds were known to be carcinogens, including about 25 known to be carcinogenic in humans; cocarcinogens were known; and relevant metabolic pathways had been discovered). The Ames Test was in use. Although studies on cancer prevention had been initiated, the state of knowledge at the time was insufficient to allow development of a major effort.

g) It was well established that tobacco accounted for carcinomas of the lung and other sites.

h) Although radiography, mammography, and the Pap smear were successful tools for diagnosis, other techniques for diagnosis and screening were awaiting further development.

i) Cancer chemotherapy, task forces, and clinical trials were well developed; leukemias, childhood cancers, lymphomas, and testicular carcinomas had been cured with chemotherapy.

j) The Organ Site Program had been initiated in 1969 for an intensified research effort on carcinomas of the large bowel, prostate, urinary bladder, breast, and pancreas.

k) Systems planning of biomedical research programs had been pioneered, a plan for a national cancer research program had been initiated, and the plan was further developed when 250 cancer investigators and other scientists met at Airlie House, a conference center in Warrenton, Virginia.

l) Growth and differentiation factors, signal compounds and communicating metabolic pathways, and cell receptors and metabolically active compounds on the cell surface had been discovered.

m) Studies in developmental biology were revealing related genes in various species that provided new insight to the role of gene expression, including in humans. Scientists in the fields of genetics, developmental biology, and evolution were beginning to work together thus increasing understanding at a fundamental molecular biology level.

n) The NCI Viruses and Cancer Programs, with their developments of resources, research results, collaborations, and communications through annual meetings, provided much greater understanding of cancer and its causes, and laid foundations for the new era of understanding at the molecular level and the growth of biotechnology and molecular biology.

o) Reverse transcriptase had been reported in 1970, and its role in cancer virology was studied with intense excitement. Hybridization techniques for DNA and RNA moved ahead the field of hereditary structure understanding.

p) Restriction endonucleases (excision enzymes), which, along with cloning, allowed the development of gene identification and the mapping of genes in chromosomes.

q) Evidence for oncogenes had been recognized in 1969, setting the stage for the cloning of oncogenes and repressor genes and for deeper understanding of cancers including hereditary ones.

The enlarged budgets following the signing of the Act allowed program developments that were not possible before. A good example was in the further development of information activities including availability and distribution of information to professionals and laymen. The

reintroduction of Cancer Control Program into NCI was the most far-reaching change in the cancer research picture.

1972

Continuing NCP Planning – Results from the Planning Conference

Planning for the National Cancer Plan continued intensively into 1972 and beyond. The Associate Director for Program and his staff spent much time and effort on this activity. By February 1972 the first draft of the Strategic Plan was available; this version would be revised later to accommodate the results of the analyses of the recommendations for priorities and resource estimations resulting from the Planning Conference. Also by mid-1972 a digest of the scientific recommendations from the Airlie House meetings were available. Although work on the Operational Plan was begun in 1971, a definitive Plan could not be written until these analyses of the recommendations were available. As indicated above the Conference participants who were considering the Project Areas were asked to fill out two forms, one for priorities and one for resource estimates. The *priorities form* had eleven segments: Project Area objective; Project Area description; key research events; present research status; research inputs required; form of results; research time frame; progress criteria; impact on Approach Element of successful achievement of objective; and relative priority of Project Area. The *resources form* had seven categories: manpower; facilities; equipment; materials & supplies; other, including types of patients; and total costs.

During 1972 a very detailed analysis was made of the data obtained from the Planning Conference and other information by the NCI Planning and Analysis staff and JRB Associates, Inc. staff. The methodologies used and the results were made available in documents published

as Government documents (U.S. Government Printing Office). The results were used to make the projections which included in addition to dollar amounts, projections of manpower needs, space and construction requirements, cancer center additions, information increases, development of the Fredrick Cancer Research Center, and the International Activities. Cancer Control developments were set forth later.

Eighty-seven participants at the Airlie House Conference filled out the *priorities form* and the *resources form*. The Objectives and the Approaches were ranked in orders of priority, and dollar amounts were allocated on the assumption that the program total budget would be about \$1 billion. These projections by the 87 participants were compiled by NCI staff. The rankings for the seven Objectives, with the exception of Objective 7, were very nearly the same (about 3.3 on a scale of 1 to 7). The rankings for the Approaches, on the other hand, varied considerably, ranging from 1.5 (highest) for Approach 7.1 to 4.7 (lowest) for Approach 2.3. Approach 7.1 was to increase the National capacity to provide cancer patient rehabilitation services. Approach 2.3 was to alter genetic makeup or gene expression to reduce the rate of cancer development [a very high priority of the NCI Director]. *Priorities* for the Objectives and the *dollar projections from the participants* are as follows:

<u>Objectives</u>	<u>Rank</u>	<u>Dollars</u> (millions)
Objective 1	3.2	\$160.3
Objective 2	3.5	\$141.3
Objective 3	3.1	\$162.7
Objective 4	3.4	\$134.6
Objective 5	3.4	\$143.7
Objective 6	3.3	\$231.0

Objective 7	5.7	<u>\$38.5</u>
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Total: \$1012.1

Approaches

7.1	Highest (best)	1.5	
6.1	“	“	\$86.5
2.3	Lowest	4.7	
4.5	“		\$10.2

Approach 6.1 dealt with combined modalities of treatment, and Approach 4.5 dealt with mathematical models for carcinogenesis.

The NCI staff, using sophisticated planning techniques, and taking into account resources data and inter-relationships in addition to the data from the Planning Conference, made funds projections for the *NCI research programs*. These projected funds were distributed among the seven Objectives for 1974 and 1980 as follows (millions of dollars):

<u>Objectives</u>	<u>1974</u>	<u>1980</u>
1	\$61.4	\$118.5
2	\$51.0	\$79.8
3	\$53.2	\$84.5
4	\$24.2	\$41.2
5	\$24.7	\$51.2
6	\$203.7	\$353.1
7	\$1.1	\$1.7
<u>Totals:</u>	\$419.3	\$1083.1

The 1974 allocation to Treatment (Objective 6) was 49%; the 1980 figure was 48%. Cause and Prevention Activities (Objectives 1-4) for 1974 were 45% (\$189.8 million); for 1980 the figure was 44% (\$324.0 million). Detection and Diagnosis efforts (Objective 5) were, for 1974, 6% (\$24.7 million) and, for 1980, 7% (\$51.2 million). Rehabilitation (Objective 7) totaled less than 1%.

The projected growth for the NCI and non-NCI *cancer activities* was made for 1973 through 1989. A variety of resource data was consulted to estimate cancer research efforts outside NCI programs. Low estimates and high estimates (millions of dollars) were made:

	<u>1974</u>	<u>1980</u>
NCI		
Low	505	981
High	588	1309
Non-NCI		
Low	302	406
High	302	406
Totals		
Low	807	1387
High	890	1715

NCI projected budget dollars (millions) for *direct research* and *cancer control activities* for 1974 and 1979 were:

	<u>1974</u>	<u>1979</u>
Direct Research		
Low	388	685
		357

High	431	923
Cancer Control		
Low	34	125
High	34	172

The Projected dollars (millions) for the *Viral Oncology Activities* were:

	<u>1974</u>	<u>1979</u>
Viral Oncology (Grants)	13.620	18.740
Viruses Cancer Program		
(including Contracts)	54.422	76.863

The implementation strategy consisted of major program policies and resource projections and allocations. To formulate the major program policies, the legislation was first analyzed to identify and interpret the responsibilities defined by the Act. Current policies were then analyzed in the light of new and/or modified responsibilities, the recommendations of the planning session participants, and the program strategy. Based on this analysis, major policies were formulated and included in the Strategic Plan.

Major policy areas included in the Strategic Plan cover the range of management/administration activities necessary to implement the Program:

- Program management
- Planning and budgeting
- Program content development
- Organizational patterns

Program priorities
Contract and grant review
National program coordination
Information systems
International activities
Manpower resources
Cancer control program
Cancer centers.

The planning session recommendations were reviewed to remove unwanted duplication or overlap, to review the validity of resource estimates, and to evaluate interrelationships, and then, based on these results, a Program target operating level was established. This level was assumed to represent the most effective exploitation of the available cancer science knowledge base and was used as the end point to determine the projected growth rate of the Program. Alternate growth rates were examined, and a “best-fit” rate was established based on the interactions of manpower, facilities, and supporting resource availability and needs. Five-year resource projections were developed (at three different levels); they were strategic projections in the sense that they dealt with overall program projections rather than individual action program projections.

The Operational Plan was the means for continuing translation of the Goal, Objectives, and policies of the Strategic Plan into the specific operational procedures and action programs necessary to maintain and sustain the National Program. The Operational Plan was to encompass the following areas:

1) Program operating procedures would define inter- and intra-organizational functions, responsibilities, interfaces, and information flows for the administrative and management processes necessary to implement the policies presented in the Strategic Plan.

2) Action programs would encompass both scientific and managerial/administrative efforts necessary to achieve specific well-defined objectives that would, in turn, contribute to the achievement of overall NCP objectives.

3) Program resource allocations would be defined in terms of the individual action programs, and alternative levels and projections of the resources would be presented to provide options for decision-making.

Very active planning extended into 1974. The Associate Director for Planning and Analysis (Lou Carrese) added to his Office a Systems & Operations Planning Branch (Jack McShulskis) and a Program Analysis & Formulation Branch. Systems planning expertise was increased. More sophisticated systems planning techniques were to be brought to bear on the cancer programs. Special attention to information activities and to cancer control efforts was needed. However, by the end of 1974, the planning activities were much diminished. The Plan was never directly used as a management tool - one of the main reasons for developing it.

The First Meeting of the National Cancer Advisory Board

In preparation for the first meeting of the NCAB to be held March 20-22, 1972, the NCI Director and the senior NCI program leaders met with the Chairman of the President's Panel, Benno Schmidt, for the afternoon of January 25 to brief him on the activities of the NCI, the projected program activities, and the status of the National Cancer Plan. Earlier in the day Mr. Schmidt met with the Director, NIH and the Director, NCI. As usual, documentation related to the NCAB agenda was sent to members of the Board prior to the meeting.

The first NCAB meeting was hectic. About 200 people were in the room. The Chairman of the Board, Dr. Jonathan Rhoads of the University of Pennsylvania, did not know he was to be Chairman until the night before the Board meeting; hence, he had not been briefed nor had he been apprised of areas needing special attention. The NCI staff did not know who the Chairman was until just before the meeting started. The *National Cancer Advisory Board* consisted of seven members carried over from the *National Advisory Cancer Council* (including the NCI Director) and eighteen newly appointed members to the Board. The three members of the President's Cancer Panel (Benno Schmidt, Chairman; Dr. R. Lee Clark; and Dr. Robert Good) were present. There were four *Ex Officio* members, and the NCI Director, making a total of thirty-three at the table. Dr. Leonard Laster represented Dr. Edward David, Director, Office of Science and Technology and President Nixon's Science Advisor. Also in the room were representatives of several organizations (the National Cancer Institute of Canada; the American Association for Cancer Research; the American Cancer Society; the National Science Foundation; and the Atomic Energy Commission). By the time the 38 introductions were made, it was 10:30 a.m. and time to break for coffee.

The chairmanship functions for the meeting were not clear. At the head table were the Chairman of the Board, Dr. Rhoads, the Director of the NCI, Dr. Baker, (previously functioning as Chairman of the Council), and the Chairman of the President's Cancer Panel, Mr. Schmidt. Although the legislative mandate indicated that the President's Panel was to be a monitoring Panel and not a managerial body, the President's Panel Chairman frequently contributed to the NCI management issue discussion of the Board. With Mr. Schmidt's commanding presence, it would have been almost impossible for him not to have taken part in and influenced the Board's

deliberations on management issues. Thus, it was somewhat unclear at times which of the three at the head of the table was functioning as Chairman of the Board.

Mr. Schmidt gave a brief report on the President's Cancer Panel. The NCI staff spent the remainder of the morning orienting new members to the NCI activities: a) general aspects of NCI activities and responsibilities under the National Cancer Act (Dr. Baker); b) the Chemotherapy Program (Dr. Zubrod); c) the Etiology Program (Dr. Raucher); d) the General Laboratories and Clinics Area (Dr. Berlin); e) the Extramural Program (Dr. Saunders); f) administrative aspects (Mr. Baldwin); and g) the National Cancer Plan (Dr. Baker and Mr. Carrese). The regular report to the Council (now Board) by the NCI Director included the following items: 1) action on implementation of the National Cancer Act; 2) legislative developments; 3) budget information; 4) NCI contract-supported activities; and 5) preliminary report on the *End Results in Cancer, Report No. 4, January, 1972*.

During presentation of the contract-supported activities, some new members raised questions about the use of contracts and wondered if the money going for funding of contracts might not be better spent on grants. These comments were not unusual from those without experience with contracts. Dr. Baker again pointed out the need for funding *both* basic exploratory research (grants) and multidisciplinary targeted research and developmental efforts, as well as development and distribution of defined resources (contracts). When a particular contract proposal was being discussed, Mary Lasker made a motion to approve the individual contract proposal, thus again attempting to establish that approval of *individual* contracts would require Board approval. Attempting to avoid the setting of precedent, Dr. Baker stated that he did not need this recommendation from the Board to fund the specific contract. Mr. Schmidt tactfully reminded the group that the new Act did not allow this action to be one the Board could take,

though the Board could act on *program plans* for programs employing the contract mechanism of funding.

Several NCI Extramural Activities were next discussed:

A) NACC (now NCAB) reports on the Subcommittee on Diagnosis and Treatment (Dr. Shingleton), on the Subcommittee on Carcinogenesis and Prevention (Dr. Jacobson), and on the Board Editorial Committee (Dr. Hartmann);

B) the National Organ Site Programs: 1. the Bladder Working Cadre (Dr. Gil Friedell); 2. the Bladder-Prostate Cancer Advisory Committee (Dr. Ruben Flocks); 3. the Large Bowel Cancer Program (Dr. Murray Copeland); and 4. the Colon-Rectum Cancer Advisory Committee (Dr. J. Ross);

C) the NCI staff reviewed and reported on several Extramural Program activities: 1. identification of new program areas (Grants under \$35,000 and National Cancer Research and Demonstration Centers) (Dr. Saunders); 2. review of Highlights in Selected Areas - carcinogenesis (Dr. Domanski), pharmacology (Dr. Nadkarni), and epidemiology (Dr. Gordon); and 3. Regional Medical Programs Service Activities (Dr. Edwards); and

D) review of Research and Training Facilities applications (Dr. Jay); and

E) consideration of pending applications.

Jane Collins (Acting Head, Research Information Branch) gave a report on the NCI public information activities. The film for the lay public, "Progress Against Cancer" was shown to the Board.

The meeting was difficult with so much to cover and with so many that were new to the NCI activities. Some of the new members were surprised at the wide scope of coverage and the

large amount of work expected from the Board members (and the staff). There were at the time nine types of applications for funds from NIH: 1) New; 2) Competing Renewal; 3) Supplemental; 5) Non-competing Continuation; 6) Change of Institute or Division (New; Training Programs); 7) Change of Grantee/Training Institution; 8) Change of Institute or Division (Non-competing Continuation); and 9) Change of Institute or Division (Competing Renewal). There were nine Programs: RO1, Research Projects (Traditional); R10, Cooperative Clinical Research, Chemotherapy & Psychopharmacology; R13, Conferences; PO1, Research Program Projects; PO2, Categorical Research Centers; TO1, Graduate Training; T12 Clinical Training; KO3, Research Career Development Awards; and KO4, Modified Research Career Development Awards.

Only 10 members of the Board were present for the full three days of the meeting, and most of these were members of the National Advisory Cancer Council. Fifteen members left before noon on the third day, and three more left by the middle of the third day. Three did not participate in the meeting.

The staff and Board spent much time drafting definitions, policies, guidelines, rules and regulations for training programs, grant applications under \$35,000, cancer centers, construction of cancer facilities, and the cancer control program. These required much time on the agenda of subsequent Board meetings. The value of NCI efforts to move the Council and Board away *from* so much time spent on smaller *individual grant* applications *to* time spent on broad *program* plans and reviews was beginning to be more fully realized with this March, 1972 meeting.

Presentations of the Programs of the Chemotherapy, Etiology, and General Laboratories and Clinics areas over the past decade, however, did bring to the Council and Board full information on the status and planned future courses of direction for these research Programs.

The up-dating of the Viral Oncology efforts would be presented at the fall meeting of the Board; these efforts would be extensions of the earlier efforts. The molecular biology developments were moving closer to identifying genetic information crucial for cancer causation, both as to understanding and to availability of techniques and special resources.

The seven members carried over from the *National Advisory Cancer Council* were: Dr. Arnold Brown, Mayo Clinic; Dr. Sidney Farber, The Children's Cancer Research Foundation; Dr. John Hartmann, The Children's Orthopedic Hospital and Cancer Center, Seattle; Dr. Leon Jacobson, University of Chicago; Dr. Kenneth Krabbenhoft, Wayne State University; Dr. William Shingleton, Duke University; and Mr. Danny Thomas, Danny Thomas Productions, Hollywood, California plus the regular *Ex Officio Council* members, Dr. Lyndon Lee, Veterans Administration and Dr. Murray Angevine, Armed Forces Institute of Pathology, Department of Defense.

The new *Board* members were: Dr. Jonathan Rhoads, University of Pennsylvania (Chairman of the *Board*); Dr. Harold Amos, Harvard University; Mr. Elmer Bobst, Warner-Lambert Company; Dr. Frank Dixon, Scripps Clinic and Research Foundation; Mr. James Gilmore, Gilmore Broadcasting Corporation, Kalamazoo; Dr. John Hogness, Institute of Medicine, National Academy of Sciences; Mr. Donald Johnson, Advertisers Press, Inc., Flint, Michigan; Mrs. Mary Lasker, Albert and Mary Lasker Foundation; Dr. Irving London, Harvard-MIT Program in Health Sciences; Dr. Gerald Murphy, Roswell Park Memorial Institute; Mr. Laurance Rockefeller, Rockefeller Brothers, Inc.; Dr. Harold Rusch, University of Wisconsin; Dr. Wendell Scott, Washington University School of Medicine; Dr. Frederick Seitz, Rockefeller University; Dr. Howard Skipper, Southern Research Institute; Dr. Philippe Shubik, Eppley Institute for Research in Cancer; Dr. Sol Spiegelman, Columbia University; Dr. James Watson,

Cold Spring Harbor, New York; and Dr. Clarke Wescoe, Sterling Drugs. *Ex Officio* members, in addition to Dr. Lee and Dr. Angevine, were: Secretary Elliot Richardson, DHEW; Dr. Edward David, Director, Office of Science and Technology; and Dr. Robert Marston, Director, NIH.

The U.S. - U.S.S.R Health Agreements

President Nixon wished to explore the possibility of reaching an agreement in the health field with the Soviet Union. A preliminary agreement to explore this possibility in cancer, heart disease and environmental sciences was signed by DHEW Secretary Richardson and U.S.S.R. Ambassador Dobrynin during ceremonies held at the NIH in February 1972. A U.S. Delegation was sent to Moscow March 25-31, 1972, to see if specific agreements could be reached. Roger Egeberg, Assistant Secretary for Health and Scientific Affairs, DHEW, was Chairman of the Delegation, and the other members were: Ted Cooper, Director of the National Heart and Lung Institute; Dave Rall, Director of the National Institute of Environmental Health Sciences; Carl Baker, Director of the National Cancer Institute; and Paul Ehrlich, P.H.S. Acting Surgeon General. After meeting with counterparts of the P.H.S. members at the U.S.S.R. Ministry of Health and with the Head of the Academy of Sciences and the Deputy Minister of Health, Delegation members split up. Ted Cooper went to the main heart research center, Dave Rall to the environmental research institute, and Carl Baker to the main cancer hospital and the Institute of Experimental and Clinical Oncology, headed by Professor Nickolai Blokhin. After a tour of the facilities, discussions were held as to possible areas of cooperation. At the discussions were the heads of four other cancer institutes and other staff members. Agreements were easily reached in the fields of treatment, diagnosis, and cancer causation. An agreement was made to exchange drugs and other materials (including viral oncology resources), information, and

personnel. Dr. Baker proposed that exchange agreements be set up in biometry and epidemiology, but this was not accepted. It seemed to the NCI Director that with the large diverse population groups of the U.S.S.R. significant epidemiology investigations would be possible. Perhaps in much of the Soviet Union the data and the apparatus for collecting demographic information were inadequate. Next a meeting was held to draft formal statements of agreement. Officials of the U.S. Department of State who were at the meeting could hardly believe that agreements had been reached so easily; they had not experienced such a thing before. The final meeting was for formal signing by representatives of the two Governments with Dr. Egeberg signing for the U.S. The Delegation members were treated very well during their stay with tours of the Kremlin and the Kremlin Museum, the Parliament buildings, the Dormition and Upensky Cathedrals, and attendance at the ballet "Giselle" at the Bolshoi Theater and the famous Russian circus. Excellent food and wines were enjoyed by the Delegation members.

A New NCI Director

On May 4, 1972 Benno Schmidt told Dr. Baker that he was being replaced by Dr. Frank J. Rauscher, Jr.

Epilogue

The progress made in understanding cancer causation, especially with regard to the role of genetics, was outstanding between 1953 and 1972. Even more impressive has been the progress made after that period. Viral oncology efforts contributed greatly to this progress. The scientific aspects of these advances have been well documented. The science-administrative

aspects and the managerial decisions behind these program developments, however, have not been well set forth. This manuscript attempts to correct this deficiency. Many people, especially the staff of the NCI, who played important roles in these developments, are identified. These developments made possible the decisions that gave stronger administrative support to viral oncology and the successful justifications for the requests for additional funding. The viral oncology Program and indeed the whole field of virology, benefited.

The NCI funding of the SVCP resources programs with contracts not only made possible more rapid scientific advances, but also led to the creation, as needs arose, of new commercial developments and even a whole new industry.

The 1969 discovery of oncogenes, viral and cellular, was an exceptionally important advance in cancer research because it demonstrated more concretely the role of genetics in cancer development at the molecular level. This finding, along with the discoveries of excision enzymes (allowing selective chemical dissection of DNA), and, later, cloning and oncogenes present in “normal” chromosomes, have led to explosive advances in cancer causation, genetics and developmental biology. Chemistry developments continue to yield new analytic procedures and syntheses (in the past 30 years the number of known chemical compounds has increased from 3 million to 23 million). Many signal chemical compounds that switch on or off reactions in the body’s metabolic pathways are being discovered. Other signal compounds switch *off* gene actions (repressor compounds) or switch *on* gene actions (derepressor compounds). Relationships between DNA coding and the protein structures are being worked out, and the way the proteins assume different configurations under different conditions and how the shapes affect the reactions are being discovered. Three dimensional computer imaging of these proteins is aiding drug discovery and development. Administrative decisions to put more funds into

developing various resources needed for viral oncology research were also of great importance. These viral oncology program components made additional contributions to the laying of groundwork for further development of molecular biology and biotechnology. The current increased rapid rate of reporting of new findings is leading to greater understanding of cancer, one of mankind's most feared enemies. NCI viral oncology activities in the years between 1953 and 1972 deserve to be recognized as a strong foundation for subsequent investigations in the virology area of research.

Reading List

1. Ackoff, R.L., Gupta, S.K. and Minas, J.S., *Scientific Method: Optimizing Applied Research Decisions*, John Wiley & Sons, New York (1962).
2. Albritton, Jr., C.C., *The Abyss of Time*, Jeremy P. Tarcher, Inc., Los Angeles (1986).
3. Bernard, C., *An Introduction to the Study of Experimental Medicine* (first published in 1865), Henry Schuman, Inc., New York (1949).
4. Barrett, P., Editor, *The Collected Papers of Charles Darwin*, The University of Chicago Press, Chicago (1977).
5. Bernstein, L., *The Joy of Music*, Simon and Schuster, New York (1959).
6. Blum, H.F., *Time's Arrow and Evolution*, 2nd Edition, Princeton University Press, Princeton (1955).
7. Bonner, J.T., *Morphogenesis, an Essay on Development*, Princeton University Press, Princeton (1952); Reprinted by Atheneum, New York (1963).
8. - *On Development: The Biology of Form*, Harvard University Press, Cambridge, MA (1974).

9. - *The Evolution of Complexity by Means of Natural Selection*, Princeton University Press, Princeton (1988).
10. Briggs, J., *Fractals. The Patterns of Chaos*, Simon and Schuster, New York (1992).
11. Broda, E., *Ludwig Boltzmann. Man – Physicist – Philosopher*, Ox Bow Press, Woodbridge, CT (1983).
12. Bronowski, J., *The Ascent of Man*, Little, Brown and Company, Boston (1953).
13. - *The Common Sense of Science*, Vantage Books, New York.
14. - *A Sense of the Future*, the MIT Press, Cambridge, MA (1977).
15. - *The Visionary Eye: Essays in the Arts, Literature, and Science*, The MIT Press, Cambridge, MA (1978).
16. - *The Origins of Knowledge and Imagination*, Yale University Press, New Haven (1978).
17. Bronowski, J. and Mazlish, B., *The Western Intellectual Tradition*, Dorset Press (1986); first published by Harper & Brothers (1960).
18. Brooks, D.R. and Wiley, E.O., *Evolution as Entropy: Toward a Unified Theory of Biology*, (Second Edition), The University of Chicago Press, Chicago, (1988).
19. Burk, J.N., *The Life and Works of Beethoven*, Random House, New York (1943).
20. Burkhardt, F., Editor, *Charles Darwin's Letters. A Selection*, Cambridge University Press, Cambridge (1996).
21. Clark, K., *Civilisation*, Harper & Row, Publishers, New York (1969).
22. Churchman, C.W., *The Systems Approach*, Dell Publishing Co., Inc., New York (1968).

23. Cleland, D.I. and King, W.R., *Systems Analysis and Project Management*, McGraw-Hill Book Company, New York (1968).
24. Cooper, G.M., *Oncogenes*, Jones and Bartlett Publishers, Inc., Boston (1990).
25. Darnell, J., Lodish, H. and Baltimore, D., *Molecular Cell Biology*, Scientific American Books, Inc., New York, (1986).
26. Darwin, Charles, *The Voyage of the Beagle*, Bantam books, New York (1958) [The voyage lasted from 1831 to 1836].
27. - *Journal of Researches*, P.F. Collier and Son, New York (1900 [Originally published in 1845]).
28. - *The Origin of Species by Natural Selection or, The Preservation of Favored Races in the Struggle for Life*, A.L. Burt Company, Publishers, New York (6th Edition) [The First Edition was published in 1859].
29. - *The Descent of Man and Selections in Relation to Sex*, P.F. Collier and Son, New York (1900) [Originally published in 1871].
30. - *The Different Forms of Flowers on Plants of the Same Species*, The University of Chicago Press, Chicago (1986) [Based on the 1888 Edition; the First Edition was published in 1877].
31. - *The Autobiography of Charles Darwin and Selected Letters*, Dover Publications, Inc., New York (1958) [Edited by Francis Darwin; first published in 1892].
32. Davidson, M., *Uncommon Sense. The Life and Thought of Ludwig von Bertalanffy (1901-1972), Father of General Systems Theory*, J.P. Tarcher, Inc., Los Angeles (1983).
33. Dawkins, R., *The Selfish Gene*, Oxford University Press, New York (1976).
34. - *The Blind Watchmaker*, W. W. Norton & Company, New York (1987).

35. - *Unweaving the Rainbow*, Houghton Mifflin Company, Boston (1998).
36. Dubos, R. J., *The Professor, the Institute, and DNA*, The Rockefeller University Press, New York, (1976).
37. Einstein, A. and Infeld, L., *The Evolution of Physics. The Growth of Ideas from Early Concepts to Relativity and Quanta*, Simon and Schuster, New York (1938).
38. Elsasser, W.M., *Reflections on a Theory of Organisms; Holism in Biology*, The Johns Hopkins University press, Baltimore (1987).
39. Farrant, P.A., *Color in Nature*, Cassel & Co., London (1999).
40. Gallo, R., *Virus Hunting: AIDS, Cancer, and the Human Retrovirus: A Story of Scientific Discovery*, Basic Books, New York, (1991).
41. Gardner, M., *Fractal Music, Hypercards and More . . .*, W.H. Freeman and Company, New York (1991).
42. Gleick, J., *Chaos*, Penguin Books, New York (1987).
43. Goodwin, B.C., *Temporal Organization in Cells*, Academic Press, New York (1963).
44. - *Analytical Physiology of Cells and Developing Organisms*, Academic Press, New York (1976).
45. Gould, S.J., *Wonderful Life: The Burgess Shale and The Nature of History*, W.W. Norton & Company, Inc., New York (1989).
46. Gross, L., *Oncogenic Viruses*, (Third Edition), Two Volumes, Pergamon Press, New York (1983).
47. Groves, L., *Now It Can Be Told: The Story of the Manhattan Project*, Harper, New York (1962) [Unabridged paperback edition with a new Introduction by Edward Teller, published by Da Capo Press, Inc. (1983)].

48. Hanson, J.K. and Morrison, D., *Of Kinkajous, Capybaras, Horned Beetles, Seladangs, and the Oddest and Most Wonderful Mammals, Insects, Birds, and Plants of Our World*, HarperCollins Publishers, New York (1991).
49. Helmholtz, H., *On the Sensations of Tone as a Physiological Basis for the Theory of Music*, Dover Publications, New York (1954) [Second English Edition, based on the last German Edition of 1877].
50. Hiscocks, E.S., *Laboratory Administration*, Macmillan & Co, Ltd., London, England (1956).
51. Hoerber, R., *Physical Chemistry of Cells and Tissues* (with the collaboration of Hitchcock, D., Bateman, J., Goddard, D., and Fenn, W.), The Blakiston Company, Philadelphia (1945).
52. Hogben, L., *Mathematics for the Million*, W.W. Norton & Company, Inc., New York (1940).
53. - *Mathematics in the Making*, Crescent Books, Inc., London (1960).
54. Kaandorp, J.A., *Fractal Modelling. Growth and Form in Biology*, Springer-Verlag, Berlin (1994).
55. Kauffman, S.A., *The Origins of Order*, Oxford University Press, New York (1993).
56. - *At Home in the Universe: The Search for Laws of Self-Organization and Complexity*, Oxford University Press, New York (1995).
57. Kuhn, T.S., *The Structure of Scientific Revolutions*, 2nd Edition, University of Chicago Press, Chicago (1970).
58. Laplace, P.S., *A Philosophical Essay on Probabilities* (translated from the Sixth French Edition; the Third Edition dates from 1820), Dover Publications, Inc., New York (1951).

59. Lavoisier, A., *Elements of Chemistry* (1789), Dover Publications, Inc., New York (1965).
60. Lewis, G.N. and Randall, M. (revised by Pitzer, K.S. and Brewer, L.), *Thermodynamics*, 2nd Edition, McGraw-Hill Book Company, Inc., New York (1961).
61. Lindley, D., *Boltzmann's Atom*, Simon & Schuster, Inc., New York (2001).
62. Lotka, A.J., *Elements of Mathematical Biology*, Dover Publications, Inc., New York (1956) [Published in 1924 as *Elements of Physical Biology*].
63. Luria, S.E., *Life, The Unfinished Experiment*, Charles Scribner's Sons, New York (1973).
64. Lwoff, A., *Biological Order*, The MIT Press, Cambridge, MA (1962).
65. Mach, E., *The Science of Mechanics. A Critical and Historical Account of its Development*, 4th English Edition, The Open Court Publishing Co., Chicago (1919) [First Edition published in 1883].
66. - *The Analysis of Sensations*, from the 5th German Edition of 1906, Dover Publications, Inc., New York (1959) [First Edition published in 1885].
67. - *Space and Geometry in the Light of Physiological, Psychological, and Physical Inquiry*, The Open Court Publishing Company, LaSalle, Illinois (1906).
68. Malthus, T., *A Summary View of the Principle of Population*, published in 1830, reprinted in *Three Essays on Population by Thomas Malthus, Julian Huxley and Frederick Osborn*, The New American Library of World Literature, Inc. (1960).
69. Mandelbrot, B.B., *The Fractal Geometry of Nature*, W.H. Freeman and Company, New York (1997).
70. Minsky, M., *The Society of the Mind*, Simon and Schuster, New York (1986).

71. Monod, J., *Chance and Necessity*, Alfred A. Knopf, New York (1971).
72. Needham, J., *Order and Life*, The MIT Press, Cambridge, MA (1936).
73. Newman, J.R., *The World of Mathematics*, Four Volumes, Simon and Schuster, New York (1956).
74. Nicolis, G. and Prigogine, I., *Self-Organization in Nonequilibrium Systems. From Dissipative Structures to Order through Fluctuations*, John Wiley & Sons, New York (1977).
75. Nossal, G.J.V. and Coppel, R.L., *Reshaping Life*, 2nd Edition, Cambridge University Press, Cambridge (1989).
76. Pearson, K., *The Grammar of Science*, J.M. Dent & Sons Ltd., London (1937) [First published 1892].
77. Peitgen, H.-O. and Richter, P.H., *The Beauty of Fractals*, Springer-Verlag, Berlin (1986).
78. Peitgen, H.-O. and Saupe, D., Editors, *The Science of Fractal Images*, Springer-Verlag, Berlin (1988).
79. Pledge, H.T., *Science Since 1500*, Peter Smith, Gloucester, MA (1969).
80. Posin, D.Q., *Mendeleev. The Story of a Great Scientist*, McGraw-Hill book Company, Inc., New York (1948).
81. Poston, T. and Stewart, I., *Catastrophe Theory and Its Applications*, Pitman Publishing Limited, London (1978).
82. Prigogine, I., *The End of Certainty*, The Free Press, New York (1996).
83. Prigogine, I. and Stengers, I., *Order Out of Chaos*, Bantam Books, Inc., New York, (1984).

84. Prusinkiewicz, P. and Lindenmayer, A., *The Algorithmic Beauty of Plants*, Springer-Verlag, Berlin (1990).
85. Quastler, H., Editor, *Information Theory in Biology*, University of Illinois Press, Urbana (1953).
86. Raff, R. A. and Kaufman, T. C., *Embryos, Genes, and Evolution*, Indiana University Press, Bloomington, IN (1991)
87. Raff, R. A., *The Shape of Life: Genes, Development, and the Evolution of Animal Form*, The University of Chicago Press, Chicago (1996).
88. Rettig, R. A., *Cancer Crusade: The Story of the National Cancer Act of 1971*, Princeton University Press, Princeton (1977).
89. Rosen, R., *Dynamical System Theory in Biology. Stability Theory and Its Applications*, Wiley-Interscience, New York (1970).
90. Russell, B., *A History of Western Philosophy*, Simon and Schuster, New York (1945).
91. Schoenheimer, R., *The Dynamic State of Body Constituents*, Harvard University Press, Cambridge (1946).
92. Schottenfeld, D. and Fraumeni, Jr., J., Editors, *Cancer Epidemiology and Prevention*, Oxford University Press, New York (1996).
93. Schrodinger, E., *What is Life? The Physical Aspect of the Living Cell*, The Macmillan Company, New York (1945).
94. Shimkin, M.B., *Science and Cancer*, U. S. Government Printing Office, Washington, D.C., (1964).

95. Smith, H.W., *From Fish to Philosopher*, The Natural History Library, Doubleday & Company, Inc., Garden City, New York (1961).
96. Smith, J. Maynard, *The Problems of Biology*, Oxford University Press, Oxford, England (1986).
97. Strickland, S.P., *Politics, Science, and Dread Disease*, Harvard University Press, Cambridge, MA (1972).
98. Suner, A.P., *Classics of Biology*, Philosophical Library, New York (1955).
99. Thom, R., *Structural Stability and Morphogenesis*, W.A. Benjamin, Inc., Reading, MA (1975).
100. Thompson, D'Arcy W., *On Growth and Form* (Second Edition), Cambridge University Press, Cambridge, England (1942).
101. Tufte, E.R., *The Visual Display of Quantitative Information*, Graphics Press, Cheshire, Connecticut (1983).
102. - *Envisioning Information*, Graphics Press, Cheshire, Connecticut (1990).
103. Varmus, H. and Weinberg, R.A., *Genes and the Biology of Cancer*, Scientific American Library, New York (1993).
104. Vogel, S., *Life's Devices: The Physical World of Animals and Plants*, Princeton University Press, Princeton (1988).
105. Von Bertalanffy, L., *Problems of Life. An Evaluation of Modern Biological Thought*, John Wiley & Sons, Inc., New York (1949).
106. - *Theoretische Biologie. Band II, Stoffwechsel, Wachstum*, A. Franke, Bern (1951).

107. - *Modern Theories of Development. An Introduction to Theoretical Biology*, Harper & Brothers, New York (1962). [Originally published in 1933].
108. Waddington, C.H., *The Nature of Life*, George Allen & Unwin, Ltd., London, England (1961).
109. Waldrop, M.M., *Complexity: The Emerging Science at the Edge of Order and Chaos*, Simon & Schuster, New York (1992).
110. Wallace, A.R., *The Malay Archipelago. The Land of the Orang-Utan and the Bird of Paradise. A Narrative of Travel with Studies of Man and Nature*, Dover Publications, Inc., New York (1962) [The Tenth Edition was published in 1890. Wallace dedicated the book to Charles Darwin. The First Edition was dated 1868].
111. Watson, J.D., *The Double Helix*, The New American Library, New York (1968).
112. Webb, J.E., *Space Age Management: The Large Scale Approach*, McGraw-Hill Book Company, New York (1969).
113. Wheeler, L.P., *Josiah Willard Gibbs. The History of a Great Mind*, Yale University Press, New Haven (1952).
114. Whewell, W., *Theory of Scientific Method*, Edited by R.E. Butts, Hackett publishing Company, Indianapolis, Indiana (1989) [Largely based on Whewell's *History of the Inductive Sciences* (1837), *The Philosophy of the Inductive Sciences* (1840), and other writings].
115. Whitehead, A.N., *Science and the Modern World*, The Macmillan Company, New York (1925).
116. - *The Aims of Education*, The Macmillan Company, New York (1929).
117. Wilson, E. O., *The Diversity of Life*, W.W. Norton & Company, New York (1992).

118. Woodgate, H.S., *Planning By Network*, Business Publications Limited, London, England (1964).