As Memory Serves—An Informal History of the National Cancer Institute, 1937–57

Michael B. Shimkin, *M.D.* [1, 2]

I. FOREWORD AND EXPLANATIONS

Before you is one man's recalls and aftertastes of a lifelong involvement in cancer research with the National Cancer Institute (NCI). This report strives to recapture impressions of long ago and to orient them retrospectively to the views of a working participant. It is certainly not an official or an approved history. It also makes no pretensions to being exhaustive, thus excluding the historiographic appurtenances of lengthy footnotes and numerous references. Indeed, the references have been reduced, if not to the minimum, to a modest number short of the demands of formal scholarship. Each of the references cited contains further references. The obituaries of individuals who played major roles include the traditional memorial tombstones of complete lists of their writings.

Research is a human activity, carried out by a peculiar species of mammals that calls itself *Homo sapiens.* Although the eventual end product of research may seem independent of the sources, the process itself cannot be divorced from the research workers, fallible and faulted human beings. Thus the study of men and women in research is relevant and may be instructive.

A wide variety of people go into biomedical research. Common denominators are hard to find, as they are for other human groups identified by some one characteristic. Research workers, of course, must have a modicum of intelligence and must comply with the rules of conduct considered necessary to call an activity research. The rest is hard work and dedication, for whatever idealistic or crass motivation that might be involved. The mix of 90% perspiration and 10% inspiration, as the formula for invention given by Thomas Edison, applies to most fields of human endeavor if such endeavor is to be crowned by success, either popularly recognized or individually satisfying.

Research has its problems, but it is doubtful whether these problems are any more compelling than those in other competitive fields of creative endeavor. There always are tensions between competing scientists, competing institutions, and competing fields of interest. There also are tensions between scientists and administrators, the latter being an elusive designation of anyone who can interfere with one's decisions and between both and their financial sponsors. There are frustrations, of course, and failures. All are unavoidable and probably desirable, as long as their interrelationships are in dynamic equilibrium. In fact, the greatest danger to research is monopoly, with its entropy of orthodoxy. Several scientists of divergent views are more promising to advancement than unanimity, and several sources of funding are safer than too much coordination and cross-information to yield tidy ledger books that avoid duplication.

An important area for tensions between scientists and their sponsors is represented by the metaphysical delineations of the boundaries of the activities that are to be designated as research and the finer divisions of research into basic and applied varieties. These acquire all sorts of real or imagined attributes that fan the heat of the discussions, particularly when division of money or designation of status is involved. For example, few scientists laboring in laboratories will admit statistical and other observational investigations as legitimate members in the field of research. The study of occupational groups for cancer risks may be equated with a species of sewage inspection. Laboratory workers using mice as their material may consider clinical work as essentially not worthy of being called science. And, within the laboratory, cancer may be labeled as an applied

[1] Professor of Community Medicine and Oncology, Department of Community Medicine, School of Medicine, University of California at San Diego, La Jolla, Calif. 92093.

[2] Supported by Public Health Service contract NIH 263-76-C-0419 from the National Cancer Institute.

field, pejoratively compared with fundamental pursuits on microorganisms.

There should be no need to compare good work on cancer with good work on leprosy. Real distinctions lie in the quality, not in the material or the locus of the work. Pasteur said it all when he rejected the idea that there be such an entity as applied science—there is only one science, he said, the tree that bears fruit, and the products of science are indivisible from it. Yet, despite these admonitions, disagreements regarding basic and applied research exist and may set the tone and nature of an institution.

It is, of course, possible to identify bad research and research that is trivial, correcting or extending what is already known by another biologic decimal point. Retrospectively, also, it is possible to identify the key steps preceding a culminating discovery. Such back-tracings, however, have a high degree of tautology and are more useful for testimony before funding committees than before scientific peers.

Personal recollections do require identification of the source. I was born, of all places, in Tomsk, Siberia; the fact that I am no longer there is a matter of my prayerful gratitude. During the holocaust of the Russian revolution, my engineer father and physician mother brought me and my brother through Japan, Java, and Australia to San Francisco, California. My education was obtained from the University of California in Berkeley and in San Francisco. With an M.D. degree in hand but with little desire to practice the arts of medicine, one of the original NCI research fellowships became available to me. This was in 1938, while I was resident in internal medicine at the University of Texas in Galveston. In those days one did not apply for positions; that was considered bad form. Instead, my professor of medicine knew the Assistant Director of the National Institute of Health, an old Texas boy, and an interview was arranged. After a long train trip I stood before Dr. Carl Voegtlin at his roller-top desk in his office at 25th and E Streets, Washington, D.C. After a few sentences I was a Research Fellow; no reviews by study sections had yet been invented. In August of that year, after acquiring my wife a month previously in California, I reported to the Office of Cancer Investigations in Cambridge, Massachusetts, to begin my first self-supporting job at a salary of $3,200 per year—quite adequate for that time.

Some 40 years later, I retain my wife and my abiding interest in that impudent caricature of normal differentiation and growth called cancer. It is a deadly and implacable foe, against which science is advancing slowly—but advancing. In this advance, the National Cancer Acts of 1937 and 1971, the dedications of the United States to the solution of the problem, will be writ large on the page of history that records the eventual triumph.

The NCI has been my professional and spiritual home during the whole period, including the years following my official retirement in 1963 and academic assignments at the University of California in San Francisco, at Temple University in Philadelphia, and now in La Jolla, the land of lotus eaters. Even here, these recollections are being underwritten by public funds of the NCI. For this, and for four decades of support for endeavors which I can only hope represent contributions toward the eventual solution of the cancer problem, I am both proud and grateful.

This pride and gratitude would not be well served by too laundered an account. The world is full of manure, and manure makes the posies grow, but it is not mandatory to call it chocolate. Nevertheless, whether because age leads to greater tolerance or because there is reticence to speak too badly of the departed or those-soon-to-be-departed . . . but, really, looking back, there were so few, so occasional, so small-sized villains and villainies, and so many warm, faulted human beings. I hope we were and remain friends, for our only real foe is cancer.

II. A BEGINNING, OF SORTS

Friday, August 6, 1937, was an average, rather dull day for news. The headlines of *The New York Times* included international threats of a wider conflict by Japan, national urging of an extra session of Congress by a farm group, and local political feuding; for the sports fan, an American yacht won a racing cup. On page 19 was a 13-line dispatch from Washington, D.C., announcing that the day before President Roosevelt had signed a cancer study bill setting up a National Institute. No one seems to have bothered photographing the event.

A fuller account of the NCI bill appeared as an editorial in the August 7, 1937, issue of the weekly *Journal of the American Medical Association*, obviously written in an anonymous information office in Washington, D.C. *Science*, the publication of the American Association for the Advancement of Science, noted the event on September 3, 1937, as part of a news item about the proposed new buildings for the National Institute of Health "beyond Bethesda, Maryland," then a far spell from the District of Columbia.

Thus the creation of the NCI by the passage of a law was hardly considered an exciting happening. Yet it did mark the official recognition of cancer as a national problem and dedicated national resources toward the solution of the problem. Such dedication was not unknown in diseases that threaten livestock but was an unusual step for diseases of man, especially diseases that were neither contagious nor posed an economic threat.

Accounts of the administrative, fiscal, and legislative affairs of the NCI are available in several publications (*1-6*) and can be backed by archival records. For a working man's account, however, the few papers on the subject are carefully depersonalized and attempt to summarize the research findings rather than the processes of research and their participants (*7, 8*). The participants themselves are mostly silent, their contributions usually summarized in obituaries that only occasionally include anything more than carefully guarded comments. Special occasions, such as presidential addresses (*9-12*) and oral histories deposited at the National Library of Medicine, provide glimpses into personalities.

Research results, the real goal of which in cancer is to find effective methods of preventing and curing the disease, are fragile entities being constantly displaced by newer findings. When the goal is eventually reached, retrospective wisdom and the choice of historians will unravel the golden thread backwards and presumably identify key contributions and enshrine investigators to whom credit is attributed, often with several competing candidates. The process is inprofitable, if for no other reason than to make some order out of the story of a complex, disorderly activity called research.

Many questions can be asked concerning the national involvement in cancer. First of all, why was there a national involvement? Second, why was there created an active, direct program as well as one of grants to States or educational institutions? Third, why did this happen in 1937 and not earlier or later?

It would be nice to record and to be able to document that the events leading to the creation of the National Cancer Program were a logical sequence of defining the problem, considering various alternatives and approaches to it, and laying out a systematic investigational program aimed at answering the questions posed by the problem. Such orderly progression is seldom encountered in human affairs, and accounts implying such order are usually rearrangements of the past to fit a good story (*13-15*).

We do know that cancer as an inexorable affliction of man was known to the ancients and was attributed to an imbalance of the four humors with an excess of black bile. Therapeutic knowledge, leading to manipulations that would stop the progress of cancer, was limited to attempts to extirpate it surgically, by means of cautery, or by escharotic pastes. The destructive approaches had to be limited to superficial cancers, since the deeper structures of the body were inviolate until the advent of anesthesia and antisepsis. A form of thinking allied to research must have gone into the transition of the belief that cancer was a disturbance of body humors to the concept that at least some cancers had a local origin that could be interrupted by complete extirpation. Certainly all requirements for identifying an occurrence as research must be granted to Jean Astruc, who in 1750 burned a piece of breast cancer and compared its taste with that of a burned beef steak. Finding that the cancer was no more pungent than the normal control, he discarded the iatrochemical theory of cancer that had replaced the humoral one. The simple, clear description of cancer of the scrotum among chimneysweeps, recorded by Percival Pott in 1775, is impressive to the modern eye as a species of observational clinical research. Less so is the injection of juice from a human breast cancer into a dog by Bernard Peyrilhe in 1776, often selected as an opening event in cancer research.

In 1838, Johannes Müller, one of the fountainheads of the preeminence of German science during the 19th century, examined cancers through the new achromatic microscope and ushered in the histologic period of oncology. Others had looked at cancers through microscopes before Müller; Müller not only looked but also saw that cancers were composed of abnormal, disorganized cells. Müller's student, Rudolf Virchow, and many of Virchow's students and contemporaries then slowly established the criteria of diagnosis, nosology, and histogenesis of cancer. Microscopic pathologists became—and remain—the final arbiters in the diagnosis and definition of cancers and allied diseases of abnormal cellular development and growth.

The pathology phase preceded the modern surgical era, opened by Joseph Lister in 1867 by his discovery of antiseptic surgery, and was soon applied to cancer by Theodor Billroth and other great surgeons of the time. Something now could be done for at least a small proportion of patients with any but the most superficial of cancers. The results were pitifully inadequate, and an obvious reason was that patients with cancer came to treatment only when their disease was far advanced. Fear was not the only reason for such delay; the belief that cancer was a loathsome disease, to be hidden as a shame, was as inhibiting. This belief was related to the fact that among the more common of cancers that were recognized were tumors of the uterus and breast of women, generative organs considered private and secret.

Physicians recognized the tragedies of neglected cancer and hoped that the results of treatment could be improved if such treatment were initiated at earlier stages of the disease. Individual surgeons in Europe and the United States during the early part of the 20th century began to speak and write for cancer education of the public. Although cautions were expressed that medical information on cancer would lead to cancerophobia among the public, there was no alternative to public education if the goals of earlier detection and treatment were to be reached. Professional medical organizations, through their cancer committees, began to encourage the systematic development of cancer education of the public.

Wealthy, socially minded citizen-leaders were recruited to become interested and involved in the subject. At the turn of the century, these were the "Lady Bountifuls" who had the time, status, and money to express their humanistic drives with the collaboration and guidance of physicians, members of the ecclesiastic and legal professions, and even some scientists who had made their economic and societal marks. The "Good Works" such aggregates espoused became manifested by formal organizations, drives for financial assistance, and eventually by the transition from volunteerism to professionalism.

By 1904, German physicians formed cancer committees and launched a cancer journal, *Zeitschrift für Krebsforschung*. In the United States, a seminal event occurred in 1913, with the organization of the American Society for the Control of Cancer (ASCC). Some prominent surgeons of the time and a statistician of an insurance company who presented stark, chilling figures of cancer mortality and its rising toll were among the identifiable ferments (*16*).

ASCC for many years was essentially a phenomenon of the northeastern seaboard, with headquarters in New York City. Publications were issued, campaigns were launched, and greater public awareness was stimulated. Inevitably, governmental participation was sought and responded to this increasingly viable and vocal citizen lobby.

In 1926, Massachusetts passed its Cancer Act, ordering the Department of Public Health to set up a cancer hospital, purchase radium, establish cancer clinics (with or without the cooperation of the medical profession!), disseminate cancer education, and make further studies (*17*). Research, however, was limited to statistical, epidemiologic investigations.

Research toward the solution of a biomedical problem becomes possible when a minimum critical mass is reached in a triad of required elements. The first of these is the availability of a core of knowledge and materials that appear ready for further exploitation. The second is a group of interested, knowledgeable people who wish to pursue the problem or topic. The third is the financial support with resultant facilities, equipment, and personnel for the endeavors. Before the advent of research institutions, such constellations were almost exclusively limited to universities.

For experimental approaches to cancer, the first suitable material was the transplanted tumor. M. Novinsky, a veterinarian in Russia, achieved this in dogs in 1876, but his work was buried and forgotten. A Danish veterinarian, Carl Jensen, made a permanent place in cancer research for transplanted tumors in mice through his careful, systematic work that was published in 1903.

Transplanted tumors were the exclusive material for cancer research until 1915 when the patient Japanese investigators K. Yamagiwa and K. Ichikawa described the induction of cancer on rabbit ears painted repeatedly with tar. Four years before that, Peyton Rous of the Rockefeller Institute reported the virus-induced sarcomas of chickens, but his contribution was rejected for several decades because it came at the time when the infectious theories of cancer had been unsuccessfully tested in the laboratory environment of the bacteriologic era. Further attention to mice as laboratory animals also showed the usefulness of the spontaneous tumors these convenient little beasts develop, especially in the breast. The effects of heredity and internal secretions on the development of mammary tumors in mice provided further experimental areas.

The second element for programmatic research, of people interested and knowledgeable about cancer, also was to be found by the turn of the century. At that time biologic science was almost a German monopoly, and morphologic, microscopic pathology was particularly so. The German model was transplanted to the United States by William Henry Welch (*18*). Welch was the key founder of The Johns Hopkins Medical School in 1893 and the Rockefeller Institute for Medical Research in 1901. Many of the investigators of the latter were graduates of the former. These institutions were made financially possible by the endowments of a Baltimore merchant, Johns Hopkins, and an oil baron, John D. Rockefeller.

The pattern of support of biomedical research by private fortunes was predominant until the massive entry of the Federal Government following World War II. There are always exceptions and earlier examples. The Buffalo cancer laboratories were founded in 1898 by a State appropriation. Its research program floundered because it bet on the bacterial origin of cancer. The institution returned to more viable cancer research after World War II, when it was renamed the Roswell Park Memorial Institute. Federal involvement with cancer research also can be dated to before 1910. McCoy (*19*) in 1909 published a report on 99 neoplasms found among 100,000 rats examined in connection with the plague control program in California. The 1910 annual report from the U.S. Hygienic Laboratory in Washington, D.C., included a section on studies of cancer (*20*). The status of cancer research was delineated and the thinking was uncomfortably contemporary, including the conviction that ". . . the solution of the cancer problem is to be found by intensive biologic studies of cell life." The endeavors were discontinued, however, when the budget for the activities was disapproved (*6*).

By 1914, some 10 institutions in the United States were doing cancer research; the more prominent ones were Rockefeller Institute, Cornell University, and Columbia University in New York City, Harvard University in Boston, University of Pennsylvania in Philadelphia, and the Skin and Cancer Hospital in St. Louis. Among the European centers were the Imperial Cancer Research Fund in London, the Imperial Board of Health in Berlin, Ehrlich's Laboratory in Frankfort, the Pasteur Institute in Paris, and the Veterinary and Agricultural School in Copenhagen. Yamagiwa transferred German pathology to Japan and in 1907 founded the Japanese journal of cancer, *Gann*.

The ASCC increasingly turned toward research as an area from which the eventual solution of the problem could be anticipated. Dr. C. C. Little, perennial director of ASCC, established The Jackson Laboratory in Bar Harbor, Maine, which became the world leader in genetic research on cancer. Several private foundations made grants for cancer investigations. In 1936, Yale University received, through careful planning by Dr. George M. Smith, an endowment from the Childs family. The initial gift of $3.5 million was by far the largest amount donated up to then for the purpose of cancer research (*21, 22*).

It all comes out as a multifactorial, kaleidoscopic series of events that involved many professional and nonprofessional people, their voluntary organizations, and the eventual expression of their desires in governmental formalizations and financing. Thus does American democracy work—not necessarily logically, not necessarily in an orderly fashion, and not necessarily for the most important purposes. It is untidy but is yet to be challenged successfully by any better system.

The direct, continuing Federal involvement with cancer in 1937 can be traced to three conditions of the time: the changed attitude concerning the role of the Federal Government in medicine and medical research during the Franklin Roosevelt administrations, the dynamic sponsorship for such involvement by some professional and public figures who found a few responsive members of Congress, who in turn enlisted their confrères in a noncontroversial, humanistically worthy field, and, finally, the ready soil created by two activities that had existed in the U.S. Public Health Service (PHS) since 1922.

It is with the last of the above three elements that this description primarily deals. But the ecology in which the events occurred is as important as the events themselves. During the period post World War I, German preeminence in science was destroyed, but American preeminence was only a promise. The economic boom of the 1920's was followed by the disspiriting economic depression which in Europe allowed the flowering of dictatorships and in the United States left an indelible mark on the spirit and conscience of a generation. It is difficult to conjure a more demoralizing national catastrophe than unemployment in the midst of material wealth, with the government being seemingly helpless to alleviate the situation. Scientists being trained in universities had little future to look forward to unless they obtained teaching positions. Their lot was to survive by any menial jobs they could scrabble. The ennobling effect of such work during one's education or development is a myth. For science, it is a crippling disease, especially since research is so much the product of the young.

One recall of that era was the importance of a few private foundations, such as the Donner Foundation, which did make small allotments to individuals, seemingly through the good impression one made on the executive secretary, a southern lady with a honeydew accent completely surrounded by perspiring and aspiring young and not-so-young men hoping for a munificent handout or perhaps a thousand dollars. This was a feature of the good old days for which few who experienced them have any attachments and who shudder when they again threaten to recur.

Scientists employed by the government were usually considered to be of lower stature than those of academia. These were the days when a university scientist who joined a commercial pharmaceutical firm automatically lost his membership in the professional society. Such societies also had quotas for government-employed scientists, a covert understanding that still extends to our highest honorific academies. But scientists working for the government had one great advantage: Their salaries, albeit reduced, came in regularly, and supplies and equipment were usually available.

Why was cancer research placed within the PHS rather than some other governmental agency?

If primary movers and doers for the events of 1937 can be designated, one in this role must be Dr. Thomas Parran, Surgeon General of the PHS (*23*). Parran was remaking not only the Service, a small agency of the Department of the Treasury, but the Federal role in human health and medicine. He could engage in such Herculean tasks because he had direct access to Franklin Roosevelt.

Parran had to contend with formidable opposition both within his own organization and its old-line officer corps as well as from organized medicine and the conservative patriarchs of medical research. The PHS was just emerging from the days of uniforms with ceremonial swords, formal visits to one's superiors with visiting cards bent down at the proper corner, and the general rule that one did what was assigned, within the specifications of the orders, replying compliance by a formal memorandum beginning with, "I have the honor to. . . ." Going *beyond* specific assignments was considered to be pushy adventurism and probably an illegal use of appropriated funds. The research area of the PHS was the National Institute of Health, headed by Dr. George W. McCoy since 1915, when it was renamed from its preceding title of U.S. Hygienic Laboratory. McCoy was a doughty microbe hunter and not a bit intrigued with the broader vistas visualized by Parran. He was replaced, painfully, by an administrator loyal to Parran and the new vistas.

Parran treated organized medicine mostly by ignoring it and leaving the necessary minimal liaison to his deputy, a handy man in cocktail intrigue and soft soap. "Organized medicine" was not much of a threat during the economic depression days and even flirted with early versions of national health insurance and similar socialistic concepts to assure its devotion to continuing regular eating habits. The inevitable confrontation did come later, under President Truman, when Parran lost the key to the White House and soon thereafter his head as well.

Parran's approach to a broadened area of biomedical research did involve consultative groups, to which he paid selective attention. The biomedical research leaders were assembled even before the official passage of the cancer act and later became official as the National Advisory Cancer Council (photo 1). It was a prestigious group, but glaringly lacking major representation from the clinical area. Another striking hiatus was in virology; Dr. James Murphy held sway over Rous at the Rockefeller Institute, and he did not subscribe to the infectious theory of cancer.

Reservations were expressed by the advisory group and by various individuals appearing before the Congressional hearings as to having the cancer research activity placed in the PHS. Dr. James Ewing, doyen of cancer from his head position at the Memorial Hospital in New York, thought that the Veterans Administration was a more appropriate agency. He was also against the new grant-in-aid mechanism; much better, in his opinion, were larger endowments to established institutions with the Memorial Hospital as a modest example.

But Parran, ably assisted by his lieutenants and his allies of the New Deal, prevailed without too much opposition. A large reason was that the PHS already had two viable foci of cancer research that had developed during the previous 15 years and had shown obvious evidences of productivity. One was in Boston, and the other in Washington, D.C.

These two units were much of the history of the NCI during the first few years and were the bedrock of the national involvement in the problem of cancer for the subsequent several decades.

The two cancer activities of the PHS that existed between 1922 and 1937 were very much the work of two men, Drs. Joseph W. Schereschewsky and Carl Voegtlin (photo 2). Schereschewsky was older, an officer of the PHS Corps; he had a wide approach to problems as behooved a public health professional. He thus included statistics and public health control in the field as part of cancer activities. Voegtlin was a civil service scientist with a laboratory orientation to whom statistics and even clinical applications were annoying diversions rather than at the heart of the problem. There was covert competition between these two men. Voegtlin probably prevailed by the accident of being younger, thus grasping the leadership after Schereschewsky's compulsory retirement for age.

Accounts of the two cancer activities are best told through recalls of the chief members of the staffs. Schereschewsky had retired in 1937 but left an indelible mark on his Boston staff. They frequently spoke of him as if anticipating him to enter the door at that moment. That ceased when the Boston group moved to Bethesda, Maryland, when it became politic not to mention him.

III. NCI, 1937-41

A. The Boston Group

In 1939, a few months before the move to the NCI in Bethesda, Maryland, the staff of the Office of Cancer Investigations assembled for a picture (photo 3). By then it was strictly not the Boston group, but the Cambridge group, having been transferred in 1937 from the School of Medicine of Harvard University in Boston to the Gibbs Memorial Laboratory in Cambridge.

The only member of the group not present was the founder, Schereschewsky. His place was taken by Dr. Floyd

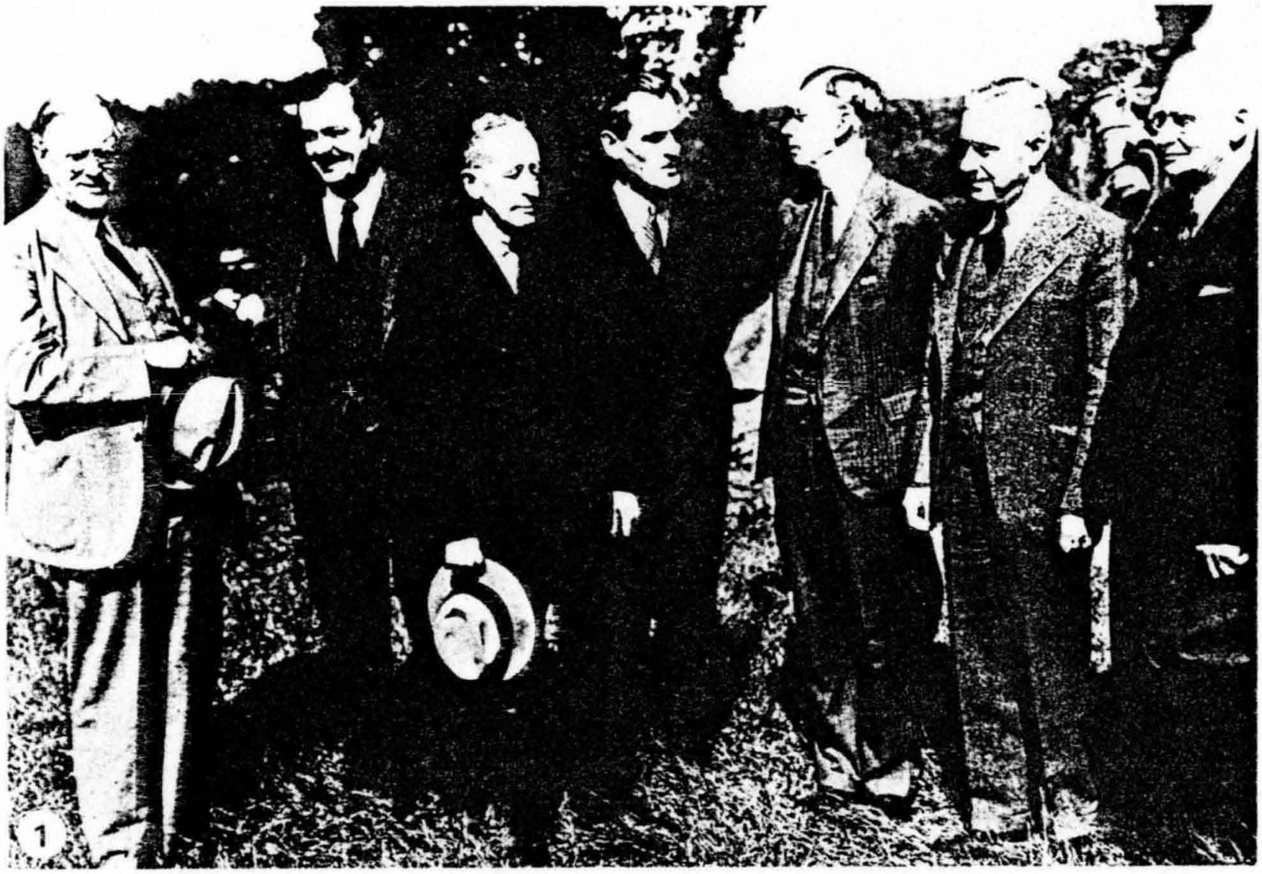


PHOTO 1.—Members of the First National Advisory Cancer Council at groundbreaking ceremonies of the NCI, 1938. *Left to right*: F. C. Wood, C. C. Little, J. Ewing, A. H. Compton, J. B. Conant, T. Parran, and L. Hektoen.

C. Turner, who snapped the photograph by means of a delayed exposure device that allowed him to get into the picture.

Dr. Joseph W. Schereschewsky (1873–1940) was an adventurous man with a restless mind and wandering feet. Son of a missionary in China, he received his medical education at Harvard and Dartmouth. His education was interrupted by some youthful escapades and enlistment in the medical corps for service in Cuba during the Spanish-American War. In 1899 he was commissioned in the PHS and served with distinction until his retirement in 1937 (*24*).

Schereschewsky's official interest in cancer was recorded in the annual report of the Surgeon General for the fiscal year 1923. He proposed investigations on cancer, starting with a statistical review of the problem as urged by the ASCC since 1913. He was given the privilege of conducting his studies at a location of his choice, which was at Harvard, with Dr. Milton J. Rosenau's Department of Preventive Medicine. It was not accidental, of course, that Rosenau was an alumnus of the PHS, nor that Schereschewsky was the medical product of New England.

Within 2 years, Schereschewsky published his findings (*25*), showing a steady increase in cancer mortality over a period of 20 years in the death-registration area of the United States. This publication was an important item that led to the increased interest and involvement of the PHS in cancer research. Cancer was obviously a national problem of health, but of a different variety than was represented by the infectious, transmissible diseases with which a sanitary corps was best equipped to deal.

The Boston operation was a one-man show, although note was made of collaboration with individuals in the area, such as the procurement of mice from Dr. Leonell Strong of the Bussey Institute in 1927. Schereschewsky became intrigued with the effects of very high frequency currents on cells and tissues, which eventually were attributed by others to the heat generated by such currents rather than to any more specific effects. Tissue culture also was started on a small scale to study the uptake and other effects of dyes on cells, but no publications resulted from these endeavors.

In 1927 a conference was organized by Schereschewsky to advise the PHS on a program of cancer research. The committee, meeting in Washington, consisted of Drs. Francis Carter Wood, W. D. Howell, Warren H. Lewis, and James B. Murphy and is a roll call of eminent men who were studying cancer at the time.

The committee of 1927 recommended, as summarized in the annual report (*26*), ". . . systematic investigations in the following fields: (1) cellular biophysics and biochemistry, (2) investigations of the effects on living cells of the spectrum of radiant energy, (3) investigations of occupational cancer, (4) cooperation in statistical research on cancer with the Bureau

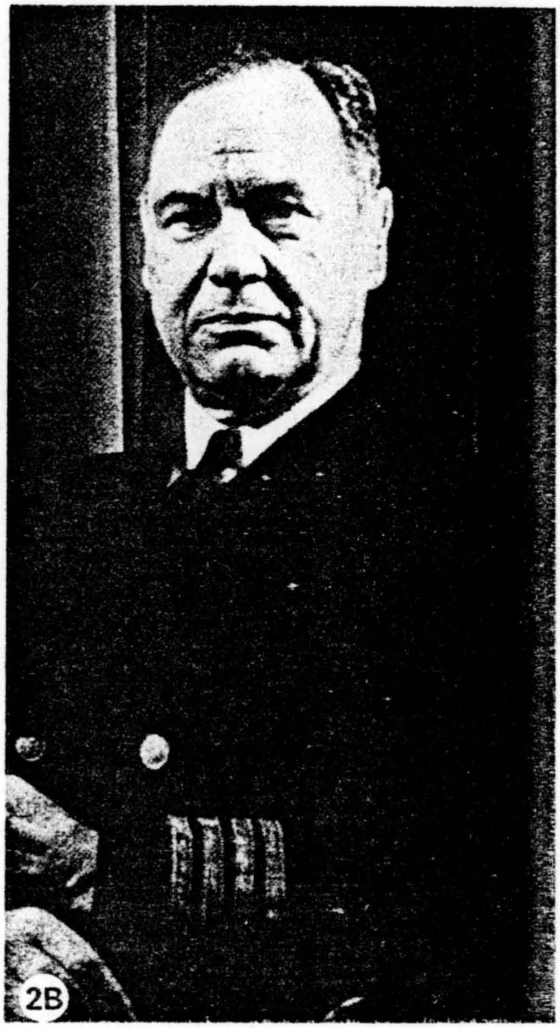



PHOTO 2.—A) J. W. Schereschewsky; B) C. Voegtlin.

of the Census." This is indeed a modest and succinct plan, at least in its statement if not in its intent, and represents one of the earlier cancer research plans that blossomed into the multivolume program plans almost 50 years later.

The stimulation by the 1927 conference led to an increase in funds for cancer to $30,000 and a promotion for Schereschewsky. He was then able to recruit several associates under the civil service, and the activity in Boston became officially the Office of Field Investigations of Cancer.

Schereschewsky's first permanent addition to his small staff was Dr. Howard B. Andervont, who already had been working with him while he was an instructor in Rosenau's department at Harvard. Dr. Murray J. Shear was employed a few years later and, soon thereafter, a cytologist and a physicist were hired. The activities of this group from 1930 to 1937 resulted in about 35 publications. As Andervont (*24*) stated, "Seldom, if ever, did Dr. Schereschewsky's name appear on any of these papers despite the fact that his advice, encouragement, and criticism played an important role in every experiment. . . . He was a firm believer in freedom of research and all who came with him were told bluntly that they were to conduct independent research. . . ." Schereschewsky's associates remember his remarkable versatility, exceptional memory, and fertile imagination. His staff uniformly called him "Sherry."

Schereschewsky's goal of a major commitment to cancer by the government was met by the passage of the National Cancer Act of 1937. But his own role ceased with his mandatory retirement at age 64. His Boston confrères would have wished that he had been selected as the first Director of the Institute for a symbolic short period, but this was not to be. Voegtlin, his competitor, was given the assignment. In the tradition of the PHS, Schereschewsky put on his hat and was never seen again at the activity he had developed. He did continue his interests in cancer by organizing a cancer control program for the State of Georgia, patterned along the lines of the 1926 cancer control act of Massachusetts, in which he also collaborated. He published a national plan of cancer control (*27*). It was characteristically modest about its predictable benefits: "A reduction of 25 to 30 percent in the cancer mortality rate. . . . This would offset the mortality due to automobile accidents." His fiscal estimate was even more modest, "in the neighborhood of $10,000,000" annually.

Schereschewsky's role in the national involvement in

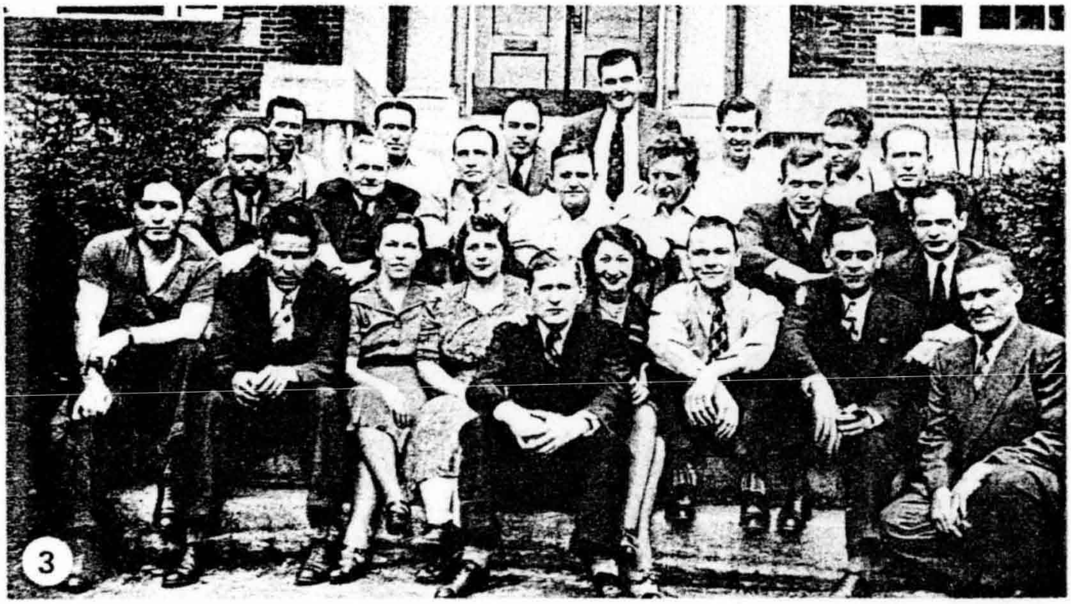


PHOTO 3.—The Office of Cancer Investigations, Cambridge, Mass., 1939. *Front row, left to right*: J. Trovato, D. Howard, R. Minor, T. Shovelton, R. W. O'Gara, D. Silverman, F. Linnell, J. Stasio, A. Perrault, and F. C. Turner. *Second row*: M. J. Shear, H. L. Stewart, H. G. Grady, H. B. Andervont, R. Lorenz, J. Leiter, and H. L. Meyer. *Third row*: F. Kennedy, W. J. McEleney, J. L. Hartwell, M. B. Shimkin, J. J. Murphy, and W. Gately.

cancer remained fairly well submerged for many years, but his memory remained bright among the staff of his Boston group. It was only in 1957, when the history of the first 20 years of the NCI was published, that an appreciation of his efforts became incorporated in the record.

Dr. Howard B. Andervont (1898-   ) continued to be the principal biologist of the NCI until he retired at the mandatory age of 70 (*28*).

Andy, as he was universally known, was a man of precise research and other habits. He was a master of the economical experiment to answer specific questions, and his publications were exact and to the point, with summary tables that could be easily interpreted. Every experiment was done personally by him, with the assistance of a faithful diener but without delegation of true supervision over any mouse, and was individually recorded in student examination bluebooks. His publications between 1924 and 1965 are a collection of small research gems. He contributed much to the study of mammary, pulmonary (*29*), testicular, and hepatic tumors, induced and spontaneous, in mice. He pioneered the use of inbred animals for such studies. Major discoveries, however, eluded him as they did all of this group of workers.

Perhaps his high points were demonstrations of the protection of mice against the "milk factor" by passive immunity through serum of rabbits immunized against tissues containing the factor (*30*) and the role of the environment in the occurrence of breast cancer in mice (*31*). The latter study, showing that female mice raised in isolation develop mammary tumors earlier than mice housed communally, was suggested by Strong. Andervont, however, showed it precisely and convincingly, with the usual minimum number of animals.

Andervont's publications are notable for the absence of statistical treatment and of lengthy, theoretical discussions. His great contributions to cancer research, made over four decades, were modestly designed, modestly but thoroughly performed, and modestly published in obscure outlets such as the *Public Health Reports*. It is too bad that they were too soon forgotten, for many were rediscovered and repeated without knowledge of his prior contributions.

Andy was a modest man, fond of his family and his work. He eschewed academic and administrative battles, preferring to withdraw to his own council. Moreover, Andy thought that all administrative matters at the laboratory level could be done by one good secretary, with professional supervision one day a month. He commanded much natural loyalty, but not as a forefront fighter for the group.

Dr. Murray J. Shear (1899-   ) was a biochemist, a small, bright native of Brooklyn. He was among the pioneers in chemical carcinogenesis and experimental cancer chemotherapy. Shear stimulated an association with Professor Louis F. Fieser of Harvard. Fieser synthesized many analogs of the carcinogenic polycyclic hydrocarbons that had been isolated from tar by the group at the Royal Cancer Hospital in London, under the direction of Dr. Ernest Kennaway. A formal agreement was reached by an exchange of letters in 1934 between Schereschewsky and Fieser, although Fieser never did fully accept inbred mice for the work because he considered them abnormal.

An important series of papers (*32-36*) emanated from these endeavors between 1936 and 1942, paralleling similar studies being carried out in London by Dr. James Cook and his associates. The implied hypothesis of both groups was that cancer might be an inborn error of metabolism in which cholesterol gave rise to endogenous carcinogenic compounds. This possibility became particularly attractive when Fieser and Cook independently synthesized 3-methylcholanthrene from bile acids and when the sex hormones were shown to be structurally related to the carcinogenic hydrocarbons and, in turn, to cholesterol.

PHOTO 4.—H. B. Andervont, about 1965.

Shear introduced the term and the concept of "cocarcinogenesis" from observations that crude tars contained too low a concentration of benzpyrene to account for the carcinogenic potency. Thus tar had to contain other materials that enhanced the carcinogenic process, which were dubbed "cocarcinogens." This turned out to be a fertile field of investigation, with later modifications and permutations of the concept by Drs. Isaac Berenblum and E. Hecker.

After reading a paper that reported hemorrhage in transplanted tumors in guinea pigs inoculated with bacterial toxins, Shear became interested in cancer chemotherapy and suggested that the phenomenon resembled the Schwartzman reaction. Bacterial mixed toxins were, of course, the material reported by Dr. Bradley Coley at the turn of the century as being of clinical use in sarcomas. Shear initiated a systematic program aimed at isolating the active principle from *Serratia marcescens* (*Bacillus prodigiosus*) (*37-40*). A bacterial polysaccharide was eventually isolated, but its clinical use was not exploited because of its severe and unpredictable reactions. It was also inconvenient to mention that the effects of this endothelial toxin could be reproduced in transplantable mouse tumors by anaphylaxis (*41*) and antiplatelet serum (*42*).

Late in his career, Shear persuaded that a special laboratory be created for him, which he entitled Chemical Pharmacology and for which he recorded his rationalizations (*43*). Shear was a good speaker, persuasive on the podium and in smaller groups, who dilated his attractive brown eyes to indicate his interest and sincerity. But in the clutch his help was seldom available, since, to his great regrets, he was already overburdened with other responsibilities. Thus he included himself out and was not pursued when the national cancer chemotherapy program was organized. To him, a role less than one at the top was unthinkable.

Dr. Egon Lorenz (1892-1954) was a slender, blond German physicist who joined the Boston group when Schereschewsky was interested in high frequency currents and mitogenetic radiation, a dubious discovery from the Soviet Union. He was a graduate of German universities, with Breslau as the last stop in the student wanderings after service in the German army. He came to the United States on a Rockefeller fellowship and stayed, having had enough of war and all that it meant (*44*).

Egon, as he was known to his associates young and old, swung slowly into the biophysical applications to cancer. He quickly disproved the existence of mitogenetic radiation and became involved in the role of physical properties of polycyclic hydrocarbons in the carcinogenic reactions. He worked out techniques for spectral analysis of the compounds and for preparation of colloidal dispersions, emulsions, and monomolecular layers of the chemicals. The biologic work was done with Andervont and other biologists, but eventually Egon took over the animal end of the experiments as well.

The needs of biologists for hydrocarbons that could be injected iv and into tissue were extensive, and the preparation of a 3-methylcholanthrene dispersion in horse serum, in liter volumes, was a recurrent event. During hot weather, since this was long before air conditioning, the ether solution would occasionally explode, spattering the carcinogen over Lorenz and his long-suffering assistant, Henry Meyer. No cancers are known to have resulted from the exposure, but some apparel was badly damaged.

Interest in environmental factors in the production of pulmonary cancer stimulated Lorenz to design a complicated multi-jar contrivance housing mice under dustfree conditions (*45*). The amount of dust was carefully monitored, and the mice were oiled to reduce hair and skin debris sources. During the New England hurricane of 1938, Lorenz drove through its apogee to sustain the animals by manual pumping of the air until the electrical power source was restored.

Lorenz got into his real element during World War II, when he became involved in radiobiology via participation in the Manhattan Project (*46*). His programmatic, expensive, and extensive study of several species exposed to various levels of daily radiation led to the lowering of the accepted tolerance levels for man. He participated in studies showing that partial body shielding protected animals against otherwise lethal doses of radiation and discovered that bone marrow injections had a similar protective effect. He also discovered that total-body irradiation in small doses had a synergistic effect in the radiation treatment of experimental lymphosarcoma in mice (*47*).

Lorenz lived a full life, enjoying the good things of life: music, winter sports, wine, and women. He was a hard worker when he was interested, but he suffered fools badly, whether they wore scientific or administrative vestments. He was a hard man not to like, except by hostesses whose invitations he neglected.

Dr. Harold L. Stewart (1899-), a bonafide pathologist from the faculty of Jefferson Medical College in Philadelphia, joined the Boston group in 1937. A small, redheaded man of definite opinions and unquestioned competence in his field, he immediately laid claim over all pathology in the laboratory and later at the NCI.

Stewart was and remained a classic morphologic pathologist (*48*), to whom the clarification of the histogenesis of the neoplasm was the main purpose and end of research. He and his associates, especially Dr. Thelma B. Dunn (1900-), became international authorities on the histology of mouse neoplasia. His criteria for the diagnosis of experimental gastric cancer and Dunn's classification of mouse lymphomas (*49*) remain unchallenged. Dunn became the first woman to be elected president of the American Association for Cancer Research (AACR) and has published her reminiscences (*50*).

Stewart's primary interest for several years was to induce adenocarcinoma of the stomach in mice. He finally succeeded, on a limited scale, by injecting dispersions of 3-methylcholanthrene into the glandular wall of the stomach (*51, 52*). The aim was also partially achieved by an aminofluorene analog fed to rats by Morris et al. (*53-56*), but best achieved by Sugimura and Fujimura (*57*) in Japan by means of a nitrosoguanidine compound.

Stewart was a battler for his rights as he saw them and for the rights of his pathology associates. This gained him great loyalty. The price was unquestioned acceptance of his leadership, manifested by daily obeisances at his noon gatherings for lunch. Woe be it to anyone who would ask for his presence somewhere else instead of reporting at his office.

Stewart became involved in international affairs of the International Union Against Cancer and in various registries of the Armed Forces Institute of Pathology and had an increasingly important voice in such affairs, directly or through the selection of people acceptable to him. He did not consider appointments of pathologists, within or without the NCI, as nominations; rather they were his direct emissaries. On decisions involving the NCI as a whole, he could be counted on to take a position that would embarrass whomever he had tagged as an administrator.

Stewart traveled widely, chaired more meetings than anyone else in the place, and retired at 70 to begin garnering more honorary memberships and medals than any of his associates. The top positions of the NCI and of the International Union Against Cancer escaped him. His mark on the pathology of experimental cancer, however, was real and lasting.

Dr. Floyd C. Turner (1889-1960) looked like a farmer, with a weather-beaten face and rough hands. He was a commissioned officer of the PHS and was sent from Washington, D.C., to become the officer in charge of the Boston group upon Schereschewsky's retirement (*58*).

Turner's wife had died of breast cancer, which was the compelling motivation of his involvement in cancer research. His approach was direct. He was going to discover an effective therapeutic agent for breast cancer in mice, and spontaneous mammary tumors were the only acceptable test material. He used transplanted tumors grudgingly. Every source of mice with breast lumps was mobilized, and every mouse was started on one chemical or some other preparation that same day, Sundays alone excepted. Turner handled every mouse and made every injection himself, with an assistant sometimes holding the beast.

The empirical testing of chemicals was tolerantly accepted by the group as a vagary of the chief, with little chance of payoff or lasting results. Every so often, however, Turner would find a report in an exotic foreign publication, claiming wonderful effects in treating tumors with plant or animal extracts, such as autolysates of spleen or heart. The theoretical reason for selecting those particular organs was that primary and metastatic tumors were rare, and thus the tissues must have substances that were antineoplastic. Flasks would appear, in which minced meat was permitted to autolyze, to release the magic necrotoxins. In the process, the whole laboratory would become suffused with an intolerable stench—not a clean chemical stench but a complex sweet, organic stench that induced nausea. A luckless attendant was ordered off a bus for being too odoriferous after working with one of these candidate cancer cures. Eventually, a modest negative report of 132 chemicals was published (*59*) but left out literally thousands of tests with crude, unidentifiable materials that had attracted his attention.

Turner's chemotherapeutic approaches resembled those accepted for the National Cancer Chemotherapy Program almost two decades later, although the program had to depend on transplantable rather than spontaneous tumors, a much harder target. But Turner will retain a place in cancer research because he saved some rats given subcutaneous implants of Bakelite disks. These were controls for Lorenz's studies on monomolecular layers of carcinogens, and one developed a sarcoma at the site of the presumably inert, untreated disk. Turner gave implants of similar disks to 13 rats, 4 of which eventually developed sarcomas at the implant site (*60*). This is now referred to as the first report on "solid-state" carcinogenesis, which remains an enigma within the cancer mystery. However, the Bakelite disks were hardly inert; they had a characteristic odor, which indicated that something detectable by our olfactory apparatus was being given off.

Soon after the United States entered World War II, Turner was sent to man a quarantine station. This literally as well as figuratively broke his heart. He was retired and for some years continued his cancer chemotherapy in a small town in California. It is heartening to record that he was supported by a small grant from the NCI. He was an honest, dedicated man.

Four brand-new Research Fellows joined the group during 1938. Dr. Jonathan L. Hartwell, a Ph.D. in organic chemistry, was transferred from Fieser's department to that of Shear. He was assigned the job of gleaning the published

PHOTO 5.—T. B. Dunn and H. L. Stewart, about 1969.

literature for compounds that had been tested for carcinogenic activity. Joseph Leiter, who was to acquire his doctorate later in Washington, D.C., came from New York and took care of the animal work involved in the testing of compounds for carcinogenic activity. He also was responsible for the collection of atmospheric dust samples from several cities, an arrangement developed by Shear to test whether such pollutants could be related to the higher incidence of lung cancer in city populations as compared with the general population (*61*).

I was assigned to Andervont, to work on lung tumors in mice and to test the air pollutant samples (*62*). Characteristically, Andervont suggested that I browse through his collection of reprints and derive my own ideas. The heritage of Schereschewsky, "sink or swim" in research, was clearly passed on to Andervont.

Dr. Hugh Grady, a student of Harold Stewart at Jefferson Medical School in Philadelphia, was a tall, nearsighted pathologist who hummed Irish ballads; he and Stewart began to study the histogenesis of primary pulmonary adenomatous tumors in strain A mice (*63*). This involved serial sections following the inoculation of the animals with a polycyclic hydrocarbon, as described by Andervont, and remains a classic in histogenesis.

It was a young crowd. Turner was the officer in charge and the oldest of the group. Andervont was the next in chronologic seniority.

The Gibbs Memorial Laboratory, the interim home for the group until their amalgamation to Bethesda, was a red brick edifice constructed solidly for the determination of atomic weights. It was off the main Harvard campus, along the eastern Cambridge extension of Massachusetts Avenue, on the greenswald between the Peabody Museum and the Mallinckrodt Laboratory. The third floor was occupied by the biochemists, except for Grady's room. The second floor housed the administration, consisting of Turner and two secretaries, and the laboratories of biophysics and pathology. The first floor was divided between the biology section and Andervont's special strains of mice and the pathology preparation room. In the basement were the animals and their attendants.

The animals' attendants and other assistants were initially selected from the Works Program Administration (W.P.A.), which had plenty of candidates in the depression-stricken Boston area. The young men were the intellectual cream of the lot, but many bore the physical marks of long economic deprivations. Their stature was stunted, and their teeth were atrocious. Their mental spark, however, soon came to the fore. Within weeks they were thoroughly bored with changing cages, keeping water bottles filled, and performing related diener tasks. They wandered around the building to find something more interesting to do and attached themselves to the histology preparation or operative procedures of one or another investigator. In absence of such outlets, water fights would begin in the basement, or rats would be taught to perform tricks. One such trained rodent proceeded to yank out identifying cards on cages, to the consternation of members of the staff who had not learned the need for individual identification of experimental animals.

Most of the attendants were young and unmarried and moved with the group to Bethesda. During World War II, many were drafted or went into service voluntarily. Their teeth were replaced by dentures, their weight was increased by better diet, and they returned for visits to the NCI, smart and orderly in their uniforms. After the war they took advantage of the excellent investment made by the Nation in its most precious commodity, its citizens, through the G.I. Bill of Rights, with its provisions for education. Among the underprivileged men employed under W.P.A., there arose several physicians and other professionals. Dr. Roger W. O'Gara (1915-71) was one of these; he rejoined the NCI as a pathologist and contributed to its research program (*64*). Another one, Dr. Majic Potsaid, selected radiology and returned to the Boston area for his career. Such levels of achievement may have been beyond their reach without the assistance they received.

B. The Washington Group

Some time before their amalgamation with the NCI, the Division of Pharmacology of the National Institute of Health also gathered for a group portrait (photo 6).

Their story too is best told by describing some of the professional members of the staff who made their impress on cancer research.

Dr. Carl Voegtlin (1879-1960), a large, taciturn Swiss-born biochemist-pharmacologist, headed this second focus of cancer research in the PHS and became the first chief (or Director, a later official designation of the office) of the NCI (*65*).

Voegtlin was educated in several Swiss and German universities. He came to the United States in 1904, where a year's fellowship stretched to a lifetime. His pivotal position was on the faculty at Johns Hopkins, where he participated in the identification of the role of the parathyroid in calcium metabolism. In 1913, he was selected to head the Division of Pharmacology at the U.S. Hygienic Laboratory in Washington, D.C., the predecessor of the National Institute of Health as the research arm of the PHS. He remained with the PHS until his retirement in 1943, shifting from civil service to the commissioned corps upon his designation as chief of the NCI. At that time it was traditional that such posts were occupied by commissioned officers. Voegtlin retained close relationships with Johns Hopkins. Four of his staff of eight who were engaged in cancer research by 1936 were graduates of Johns Hopkins.

Voegtlin was a well-trained investigator in the German tradition. The research program of the Division of Pharmacology included many obviously self-generated problems that can be termed basic, yet related to such practical problems as the mechanism of action of chemotherapeutic agents, particularly arsphenamine for syphilis. These studies led to investigations of the role of sulfhydryl enzymes in tissues.

Voegtlin's interest in cancer dated to 1922, although the actual reasons are not clear. Dr. Helen M. Dyer recalls that rats with transplantable tumors were imported from the Crocker Institute and the Buffalo Institute and used for studying the effect of salts of gold, lead, and copper, as well as arsenic on tumor growth for possible chemotherapeutic effects. At that time, Dr. Blair Bell in Liverpool was claiming clinical responses in cancer patients treated with lead, which is recorded in the progress reports as one of the rationales for the work. The results in rats were negative and remained unpublished. Interest shifted toward identifying differences between normal and tumor tissue and to factors involved in cell proliferation.

The investigations led to a number of solid contributions (*66, 67*) on the reducing power of normal and malignant tissue, content of glutathione and ascorbic acid in normal and tumor tissues, and effects of amino acid deficiencies on tumor growth. By 1935, some two dozen publications had appeared, with Voegtlin as the senior author on half and another seven as junior authors (*68*). Drs. James M. Johnson, Herbert Kahler, and Mary E. Maver were the senior associates during the earlier period. By 1938, Drs. Harold W. Chalkley and Wilton R. Earle added their studies on cell proliferation and tissue culture to the program.

Voegtlin made a transition from a research director exercising tight control over the program in his pharmacology

PHOTO 6.—The Division of Pharmacology, National Institute of Health, Washington, D.C., about 1938. *Front row, left to right*: H. Kahler, J. M. Johnson, M. I. Smith, C. Voegtlin, W. R. Earle, M. E. Maver, and H. Bauer. *Second row*: W. Lindner, T. H. Stark, J. W. Thompson, E. W. Emmart, M. Farrell, K. Harlow, O. Marshino, Rosen, and C. I. Wright. *Third row*: C. A. Doane, R. H. Boltz, Springstern, M. Feeser, W. Pitkerton, E. L. Schilling, R. V. Bishop, M. Goldberg, G. O. Jarrels, and Collison. *Fourth row:* T. Hawley, S. M. Rosenthal, R. Holbrook, R. R. Spencer, E. Davis, B. B. Westfall, and F. De Eds.

division to a more liberal director of cancer research. At the NCI, he allowed—within their disciplines—considerable freedom of choice to his senior workers. However, he maintained direct interest in all phases of the program and steadfastly refused to allow set subdivisions in his organization. With the exception of pathology, he visualized the senior people as temporary chairmen of the activity, a plan that obviously gave him more direct control but in the long run was not compatible with bureaucratic personnel practices. His exemption of pathology from this pattern was probably influenced by pressures from higher levels to have pathology centralized for the whole of the National Institute of Health.

It was not wise to undertake large new departures in research without his knowledge and consent, and he was well known for his recurrent question: "What does that have to do with cancer?"

Voegtlin was respected but aloof. He was certainly the logical choice for the first Director, if such direction had to come from within the PHS. He recognized roles for cancer control activities, including statistics, and for clinical resources, which were developed at the Marine Hospital in Baltimore. However, he firmly believed that the laboratory had to provide the leadership in cancer research, and this pattern was laid for the NCI for over a decade.

Dr. James M. Johnson (1883–1953), a chemist born in South Carolina and educated at Johns Hopkins, was the senior member—by age and years of service—of Voegtlin's staff. He transferred from the Division of Pharmacology to the NCI. Johnson carried out Voegtlin's leads and orders. Earlier in his career he was involved in the synthesis of arsphenamine, the flow of which from Germany was interrupted by World War I, and in research on the role of glutathione. He characterized various chemical constituents in normal and tumor tissues. One of his last contributions was to show that the reports of higher dextro-glutamic acid content in tumors than in normal tissues were the results of a laboratory artifact (*69*).

Johnson was unswervingly loyal, and it would have been unthinkable for him to question his chief, whom he called Professor Voegtlin.

During a period of expansion of cancer research at the Division of Pharmacology, 1928–30, the core of the staff that was eventually transferred to the NCI was added.

Dr. Harold W. Chalkley (1887–1976) was an English-born graduate of Johns Hopkins in physiology. He was interested in cell division and regeneration and used free-living animals such as the amoeba and hydra for his subjects. Chalkley had a fine feel for quantitative biologic measurements and is best known for a method of quantitative morphologic analysis of tissues that became known as the Chalkley technique (*70*), which he devised during his collaborative studies with Dr. Glenn H. Algire (1907–58) on the development of blood vessels around tumors (*71, 72*).

Chalkley was an ardent discussor of any topic, scientific, cultural, or political, an able artist, and a charming companion. He labored not mightily at the laboratory bench but spread his ideas and his enthusiasm to others. For years after Voegtlin's retirement, it was Chalkley's self-imposed duty and pleasure to keep the chief's portrait in good repair by regular applications of oil.

Dr. Herbert Kahler (1896–1962), born in Oregon and educated in biophysics at Cornell University, was one of those convenient gadgeteers who could invent, devise, or repair anything mechanical (*73*). He made electrodes for measuring electrical resistance in tissues and an apparatus for milking mice (*74*). He was a pioneer in the use of ultracentrifuges and electron microscopes because he knew how they worked, and dysfunction on their part was a challenge to be resolved (*75*). A thin, dark man with a slight moustache, he kept to his last and took no part in the little conspiracies and undercuttings that are inevitable in human groupings. He was always pleasant, approachable, and helpful, but ruthless when he was holding a good poker hand. Herb died of leukemia and refused to associate this with his exposures to ionizing radiation.

Dr. Wilton R. Earle (1902–64), born in South Carolina and educated at Vanderbilt University, was the tissue culture expert (*76*). For many years only Dr. George Gey of Johns Hopkins was his competitor in devising increasingly more complicated methodology for their work. Both made practically impossible demands of their art, and their instrumentation placed tissue culture beyond the reach of any other investigators to whom equal facilities were not available.

Earle demanded that everything had to be at least in duplicate, whether this be a gross of pencils or a set of sterile transfer rooms.

Earle and Gey both sought to convert normal cells into neoplastic cells in vitro by exposure to carcinogenic hydrocarbons or radiation. Both observed such changes, which could not be related to the carcinogenic exposure and were probably spontaneous in origin (*77–82*).

Tales abound about both of these pioneer tissue culture masters. For Earle, his life was full of "little folk" that interfered with his investigations. One such incident involved the inexplicable film of oil on his most precious glassware, no matter how rigorously washed in all sorts of corrosive acids. The phenomenon was finally traced to a night watchman who warmed his cheese sandwiches in the constant-temperature incubator in which the glassware was kept. This led to the installation (in duplicate) of 24-hour temperature-monitoring devices.

Years later, Dr. Harry Eagle (*83*) became Scientific Director of the NCI and quickly converted the complex in vitro procedures, with their expensive equipment and appropriate magical incantations, into a simplified technology. The definition of the basic media so that they could be prepared commercially completed the conversion of the exclusive techniques of Earle and of Gey into procedures within reach of all reasonably functional laboratories.

Voegtlin's group, with its special predilection for Hopkins graduates, did not discriminate against women. Mary E. Maver (1891–1975), a biochemist from the University of Chicago, contributed a long series of studies on enzymatic characteristics of tissues and tumors, with special interest in a group of proteolytic enzymes, the cathepsins, which unfortunately correlated best with the amount of necrosis (*84*). Helen M. Dyer (1895–) joined the pharmacology division as a young technician, returned to George Washington University to obtain a doctorate in biochemistry, and rejoined the NCI. She contributed to the metabolism studies

PHOTO 7.—Tissue culture, cytology group, 1944. *Left to right:* J. H. Daniel, H. W. Chalkley, W. R. Earle, and G. H. Algire.

of the azo and fluorene carcinogens (*85*) and to the studies of the physiologic factors in gastric function and compiled an early index of chemicals that had been tested experimentally as chemotherapeutic agents against cancer (*86*).

Dr. Roscoe R. Spencer (1888-   ) was a commissioned officer member of the pharmacology group, who became the assistant chief of the NCI under Voegtlin and the second chief upon Voegtlin's retirement in 1943. He was a Virginian and obtained his doctorate from Johns Hopkins.

Spenny, as he was called by his associates, was a bona fide medical hero, who had participated in the development of a successful tick vaccine against Rocky Mountain spotted fever (*87*). His interests in cancer were primarily at a philosophical level, with cancer as an example of species adaptation in a multicellular organism. He studied the effects of carcinogens and environmental factors such as temperature on small, free-living organisms (*88, 89*). The observations were devoid of tests for genetic changes or biochemical markers and have left no impress.

A pleasant man with a brush moustache and smiling face, Spenny was not an administrator. He tried his best to hold together a group of individualists during wartime conditions, with indifferent results. The *Journal of the National Cancer Institute* (JNCI), established by Voegtlin in 1940, was beginning to atrophy from diminishing contributions, in part because he could not bear to continue his predecessor's edict of exclusive outlet from the staff. Finally a committee of the staff gently relieved him of his duties as editor.

After the war, disaster struck Spencer when he testified before a Congressional Appropriations Committee that he did not think that an expanded budget for the NCI was justified. For a government official to intimate that more money is not essential is to reserve for himself a place at a lower rung of bureaucratic Hades. Spencer was promptly replaced. His testimony was quickly corrected as an early example of misspokenness—what had been meant was that such budgetary increases had to be long term in nature and in commitment, with adequate preparatory training and new facilities, etc.

No description of Voegtlin's pharmacology group and the early days of the NCI would be complete without the inclusion of Miss Ora Marshino, chief administrative officer. She was a lawyer who held the chief's office in complete and absolute sway. It was a sin for a secretary to light a cigarette in the office; any staff member, of any rank, who deviated from the chief's orders or wishes had her to answer to. But Ora never was the dragon she appeared to be. She was a meticulous, knowledgeable, and irreplaceable administrative assistant for the National Advisory Cancer Council and for the NCI and an archivist who, long after her retirement, compiled histories of the NCI (*3*) and its Research Fellows (*90*). She was invaluable to the chief and to everyone else in the place, but it took a long time to appreciate this.

C. The Third Group: Research Fellows

And so it came to pass that the ground for the NCI building was broken with appropriate ceremonies on October 3, 1938. The Georgian three-story structure of redbrick (photo 8) was carefully set peripherally to the main complement of the National Institute of Health. The traditional Institute was a symmetrical five-building arrangement with the administrative building in the center. The central building boasted large white columns for its front, giving it a southern plantation look.

The new activity, cancer, was tolerated but not completely accepted by the microbe fighters who were the elite of the new campus. It was only after World War II that the National Cancer Institute Act was replicated for a series of new institutes, on heart, neurological diseases, and other disease categories. The National Institute of Health then became the plural National Institutes of Health. For years, however, the title above the administration building just had the "s" added to the word Institute, where it stood out like a corrected typographical error—testimony to astute economy that was presumably being practiced therein.

The NCI building was completed by January 1940. The Boston group, however, moved in before the onset of inclement weather, during the previous October. Loaded on trucks, every piece of equipment, including some trash cans filled with trash, reached the new home, although some cages of animals were spilled on the way and a few experiments were ruined. Many of the laboratory attendants rode post, since the government by long custom paid for the travel of only those best able to pay and not of the lowlier employees. Only a few dieners and the secretaries remained behind, and even fewer eventually returned to Boston. It was a tightly knit group.

The Washington contingent, of course, had fewer prob-

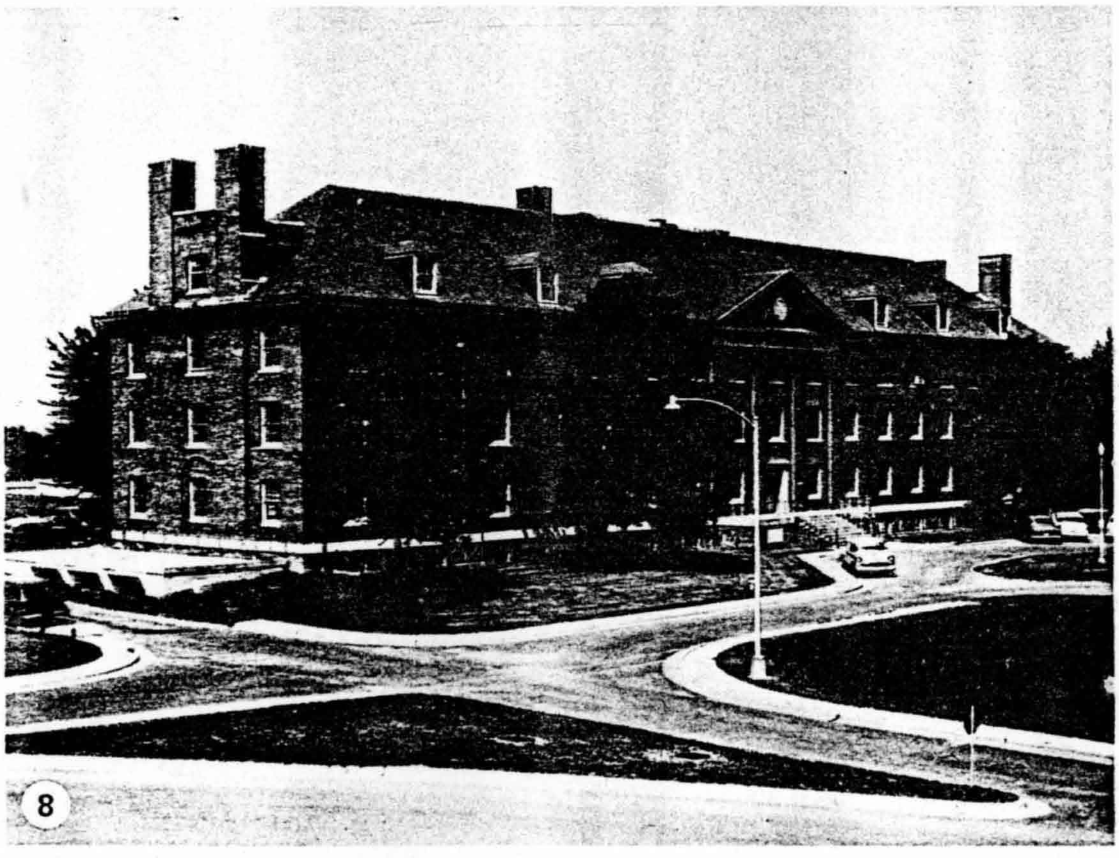


PHOTO 8.—The NCI building, Bethesda, Md., around 1955.

averse to moving, especially since all already were residents of the area. They moved by stages, as the inside of the building was finished. By January 1940, all were in place.

Voegtlin expanded the staff by another cadre, recruited under the authority of research fellowships. Thirteen were appointed during 1938 and assigned to Boston, Bar Harbor, or retained at their institution. Fifteen more were required during 1939 and 1940. Of the total of 28, 17 were assigned or transferred to Bethesda and two more to the clinical facility at Baltimore.

The third group of Research Fellows included some of the leading figures of the subsequent two decades of the Institute.

Among the original Research Fellows, Dr. Jesse P. Greenstein (1902-59) stands out (*91*). He was a workaholic biochemist, who began his career in New York even before obtaining his doctorate from Brown University in 1930. An intense but traumatic tutelage at Harvard, Germany, and Berkeley followed. This period left a mark on Greenstein, who found how difficult it was at that time for a Jew to get a permanent position despite his arduous work and undoubted contributions to protein chemistry. An addition to his family resulted in a rebuke rather than an increase in his beggarly stipend. The opening at the NCI represented a haven, where he could continue his driving interests in amino acids, yet fulfill his obligations to cancer research.

The truth was that Greenstein was but peripherally interested in cancer, for which he dramatically overcompensated, to the benefit of cancer. The first four volumes of the JNCI contain 32 papers by Greenstein. The culmination was his classic *Biochemistry of Cancer* (*92, 93*) of 1948 and 1954, the best synthesis of the subject since the contributions of Dr. Otto Warburg in the 1920's.

Greenstein would set up procedures for the measurement of enzymes, from acylase to zymohexase, train a technician to run the procedure, and have it done on a spectrum of transplanted tumors and comparable normal tissues that were harvested for him by Dr. J. W. Thompson and others assigned to the task. One of the more interesting findings was the reduction of liver catalase activity in tumor-bearing animals (*94*). Greenstein reached a generalization that tumors as a class converged biochemically in their enzymatic characteristics, a generalization that was made on established transplanted tumors and that was not as clear when spontaneous neoplasms were examined. There was a rapid flow of publications, often completed over the weekend following the experiments. The main talents of Greenstein and his associates in the meanwhile were applied to the isolation, synthesis, and biochemical study of amino acids, from which came many honored recognitions from his peers.

Greenstein was a driving, driven man, and his sudden death by stroke at the early age of 57 deprived cancer research of what by 1959 was its commanding figure in the field of biochemistry. Many younger men thrived under his wing, but older associates who preferred different approaches or a more moderate pace were discarded or sought refuge elsewhere. In fact, another laboratory was eventually created for many of such refugees.

Greenstein's position and reputation were soon so high that his voice became important in administrative as well as scientific policies of the NCI. The reorganization of the NCI effected by Scheele with the post-war expansion had the blueprint of Greenstein for the intramural laboratory portion of the plan. Greenstein may have become the Director of the NCI, but preferred to retain his hands on his retorts rather than to get involved in the paper problems of others. Had he accepted, the intramural program may have emerged much more structurally centralized and directed than it became under the benevolent laissez-faire of Dr. John R. Heller.

PHOTO 9.—J. P. Greenstein, about 1944.

During the 1930's there was considerable interest in nutrition and cancer. This interest has been a recurrent one in cancer research, with papers of supposition and postulations going back to the 19th century. The 1930 interest was stimulated by the demonstration that the growth of rodents was inhibited by large amounts of carcinogenic hydrocarbons, especially if the diet was low in its content of sulfur-containing amino acids. This led to the investigation of low-cystine diets in carcinogenesis. Leukemia elicited by percutaneous applications of 3-methylcholanthrene, hepatomas induced by azo dyes, and spontaneous mammary cancers indeed could be inhibited by the placement of the animals on low-cystine diets. However, the animals were a sorry-looking lot, thin, hairless, and shaky, and the conclusion was that the effect was a nonspecific one. Obviously, tissues possessing necessary nutritional factors were required for carcinogenesis as well as for normal growth (*95, 96*).

A similar conclusion followed studies on the effect of vitamins on tumor growth. Deficiency in pantothenic acid or riboflavin inhibited tumor growth, but at levels that seriously interfered with the host's nutrition (*97*). The primary investigators in this area were Dr. Julius White, a Research Fellow, and Dr. Harold P. Morris, a civil service scientist from the Department of Agriculture.

Interest in nutritional factors in cancer subsided to a low ebb by 1950, after the careful work of Dr. Albert Tannenbaum in Chicago showed that tumor initiation and growth in mice were related nonspecifically to the total caloric intake. White became chief of the Laboratory of Physiology and found a full-time occupation in its administration. Morris specialized in developing in rats stable transplantable hepatomas, which varied from aggressive, anaplastic types to growths that were hard to distinguish morphologically or biochemically from normal hepatic tissue, the so-called minimal deviation tumors. These tumors became a favored material for biochemists throughout the world and led to literally hundreds of publications, many with Morris as coauthor (*98*). This work showed that the neoplastic state was a reversion of the tissue toward its embryonic undifferentiation, reiterating in biochemical terms observations recorded by the histologists of the previous century.

A biochemist trained in tissue metabolism techniques, Dr. Dean Burk was transferred from his post at Cornell University, where he investigated a wide variety of tumors (*99*). For reasons best known to himself, Burk became a proponent of irregular methods of cancer treatment and an embarrassment to the administrators. Other biochemical talents were represented by Drs. Richard J. Winzler (1914-72), W. vB. Robertson, and J. Shack (*100-102*).

PHOTO 10.—H. P. Morris and C. Dubnik, about 1944, preparing experimental diet for rats.

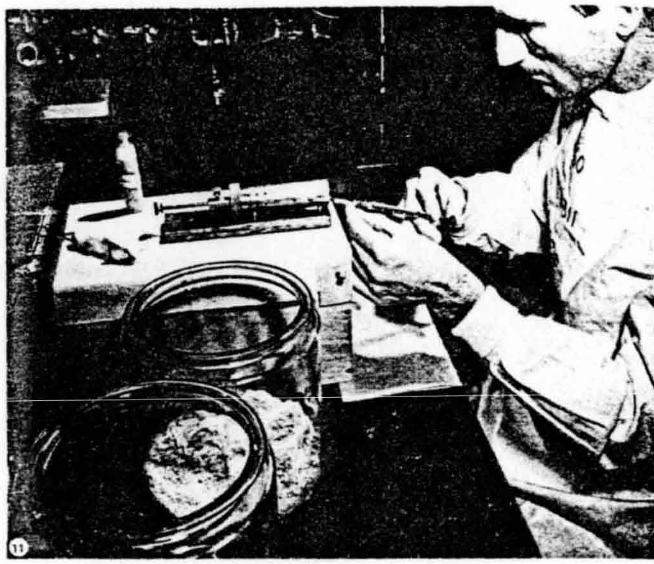


PHOTO 11.—W. E. Heston, about 1944, giving iv injections to mice.

The research program of the NCI was also strengthened by the addition of more formally trained geneticists and pathologists than were represented by the incumbents.

Dr. Walter E. Heston was moved from his temporary assignment at The Jackson Laboratory in Bar Harbor, Maine, the center of mammalian cancer genetics developed by Little. Heston continued and expanded his studies on pulmonary tumors and heredity in mice; he attempted to localize tumor susceptibility to specific genes (*103, 104*). Later, experimental genetics was further enriched by the addition of Dr. Margaret K. Deringer to the staff.

Dr. W. Ray Bryan (1905-75) was transferred from his association with Dr. J. W. Beard at Duke University. His interests were in viruses, a controversial area of cancer research in 1940. The august Advisory Committee, headed by Murphy, that outlined approaches to fundamental cancer research (*105*) for the NCI concluded that: "The very exhaustive study of mammalian cancer has disclosed a complete lack of evidence of its infectious nature"; this included viruses but presumably excluded chickens. And that was that, although by 1940 the milk factor in the etiology of mammary cancer in mice had been demonstrated by the geneticists of The Jackson Laboratory, and Dr. R. E. Shope of Rockefeller had further revived mammalian viral oncology with his discoveries of the papilloma-carcinoma growths of the rabbit. Shope's discoveries also stimulated the re-entry of Rous into cancer research.

Andervont, Bryan, and I at this point joined hands for an attack on the mammary tumor of the mouse. We took on the biologic-genetic, viral, and endocrinologic areas for individual emphasis. There were no formal protocols, as such arrangements eventually became known. The group met practically daily, usually at the brown-bag lunch period, and it was of an ideal size for intimate and constant interactions. With the collaboration of other members of the staff, the work culminated in the first monograph that emanated from the NCI, *A Symposium on Mammary Tumors in Mice* (106). It contained the first evidence for the antigenic property of the milk factor, obvious implication of its viral nature, and exhaustive data on the endocrinologic, genetic, nutritional, and other factors that influenced the appearance of the neoplasms.

The problem of mammary tumors in mice and the milk-transmitted virus that was involved in its etiology was impractically slow for virologists and biochemists, since the assay of samples depended on the appearance of tumors, which took some 12 months to emerge even in the more susceptible strains. Bryan somehow convinced Voegtlin that the Rous and Shope viruses, with which he had worked previously at Duke (*107*), could be considered chemical agents with peculiar characteristics. Part of the attic became a chicken yard, and Bryan initiated his now classic quantitative bioassay studies on the Rous agent (*108*). Before that, however, he prepared himself with an analysis of quantitative dose-response data with polycyclic hydrocarbons. Such quantitation was a late comer to chemical carcinogenesis, starting at the behest of Fieser during the last year of the Boston group (*109*).

Much later, in the 1950's, Bryan became one of the pioneers of the extensive viral cancer program, but his talents lay in his own work and not in administrative arrangements between diverse and often competing research workers who sought support under the program. Burdened by a sick wife, Bryan was semiretired to a honorific post until he died in 1976, a victim of emphysema caused by the cigarettes he continually smoked (*110*).

Hartwell continued to compile data on chemicals that had been tested for carcinogenic activity. The original volume appeared in mimeograph form and listed 696 compounds, of which 169 were said to have elicited cancer in experimental animals. A decade later, in 1951, data had accumulated on 1,329 compounds, of which 322 were reported as positive (*111*). Today the listing is in the thousands, and subsequent volumes were made possible only by use of computers. Hartwell soon went to other involvements, including exploration of botanicals for carcinostatic sources, after working with Shear on podophyllotoxin as one example.

Dr. Harold F. Blum, with long experience in photodynamic processes and reactions to ultraviolet radiation, initiated exact, quantitative studies on ultraviolet carcinogenesis in mice (*112, 113*). Dr. Paul S. Henshaw expanded research in radiobiology.

The pathology group added several young associates. Dr. G. Burroughs Mider (*114*) conducted investigations on induced skin tumors and leukemia in mice. He refused to buckle under Stewart's hegemony over pathology and left the NCI after 3 years, later to return as its Associate Director in Charge of Research and thence to Associate Director of the National Institutes of Health in 1955. Dr. Jesse E. Edwards (*115*) was interested in induced hepatomas and found that carbon tetrachloride was a hepatocarcinogen in mice. After a couple of years he departed for the Mayo Clinic and made a prominent name for himself in the pathology of the heart. Dr. Albert J. Dalton, a cytologist, remained with the NCI for his whole career. He emerged as an authority in electron microscopy (*116*).

D. NCI Takes Shape

By mid-1940, the NCI was a going concern, in a building proudly proclaiming its name for its intramural laboratories and for regular meetings of the National Advisory Cancer Council to set policy and to recommend the disbursement of grant funds. It also had a clinical facility in Baltimore and a publication of its own.

Writers and photographers from *Life*, the weekly illustrated member of the *Time-Life* empire, came to call, probably by carefully stimulated invitation rather than spontaneously. The NCI and cancer research were described in the June 17, 1940, issue of *Life*. The article included a dramatic photograph of a posed staff meeting (photo 12).

Voegtlin was in complete charge over the activity and was, in effect, also the executive officer for the extramural grant program. The extramural activities were under direct control of the National Advisory Cancer Council (at that time, the advice was to the Surgeon General). There was an executive secretary of the Council, originally Dr. Ludwig Hektoen, retired professor of pathology from Chicago who was brought over from his post with the National Research Council. Hektoen, a pleasant, soft-spoken man long past his prime, spent a few days at the NCI before and after the meetings of the Council. The detailed work fell upon Ora Marshino in keeping records and in translating the actions of the Council, as approved by the Surgeon General, by guiding fund allocations through the bureaucracy.

The National Institute of Health, with the NCI as its component, had two personnel systems. The top administrative posts were carefully guarded preserves of the commissioned corps of the PHS. The other system was the Federal civil service. Voegtlin, a civil service employee as head of the Division of Pharmacology, was admitted to the corps on his designation as Director of NCI. During the war he proudly wore his four-stripe uniform.

Most of the scientific staff were under civil service, and the Research Fellows after variable periods were absorbed into the civil service ranks, with a few of the M.D.'s opting for the commissioned corps. The duality of personnel systems led to problems, of course; it certainly was not a tidy arrangement welcomed by business managers. Yet it had its advantages, providing more than one way of doing things. For one thing, officers were considered mobile and could be transferred more easily than the civil servants.

The officer-civil service differences were exploited as status symbols by some of the staff and their wives, especially those known in the army as guardhouse lawyers. They took great delight in comparing various real and imagined advantages and disadvantages of one group over the other. NCI seemed singularly free of this diversion and, for that matter, of all group social affairs. Voegtlin and his wife were not socializers, and all other groupings, around the usual games or dances, were spontaneous or informal, or mostly nonexistent. The Andervonts, Andy and Letha, held annual New Year's Eve shindigs, with piano playing by Mary Shimkin and the singing of nostalgic songs, on and off key, and enough alcohol to remember the next day. The usual womanizing, at the level permitted or ignored in those days, of course went on, and a few romances even led to marriages. Alcoholism, compulsive gambling, and other social

PHOTO 12.—Staff of the NCI, 1940. Reproduced from *Life*, June 17, 1940, through Herbert Gehr, Life Magazine copyright Time Inc. *Left to right:* M. B. Shimkin, H. Kahler, M. J. Shear, M. B. Melroy, H. L. Chalkley, R. R. Spencer, M. E. Maver, P. S. Henshaw, H. L. Stewart, E. Lorenz, F. C. Turner, and W. R. Earle.

vices were kept underground, and the few divorces that occurred awaited the more permissive post-war period. The NCI staff of 1940 by 1976 standards would be considered staid and certainly not with-it, but it did not consider itself bored, deprived, or depraved.

Voegtlin reported to the Director of the National Institute of Health, and Dr. Lewis R. Thompson was an easy rider for such a smooth, no-wave activity as the NCI under Voegtlin. It was not wise for any staff member to go out of channels regarding anything that had to do with cancer or the NCI.

The policy, that elusive phantom used to enforce personal wishes, was one of iron-clad separation of the intramural staff and the extramural affairs of the NCI. The meetings of the Council, held four times a year and chaired by the Surgeon General, were closed, confidential, and confined. Voegtlin wanted no help from the outside with his direction and, at the same time, wanted no criticisms that the intramural personnel would profit from intimate knowledge of grant requests from scientists from other institutions. This sharp separation persisted and was considered sacrosanct until the arrival of the contract mechanism of supporting research during the 1950's, which eventually required participation of intramural scientists as legal project officers. The questions of confidentiality of grant requests and the public right to know about the deliberations of advisory bodies to the government were to come up even later.

The designed isolation of the intramural staff from the extramural activities of the cancer program was further abetted by complete control over travel and reviews of all manuscripts and memoranda going beyond its walls by the Director's office—meaning the Director himself—unless it could be stopped by his administrative assistant.

Voegtlin did not have a firm organizational pattern for his intramural staff, preferring to designate his senior scientists as temporary chairmen of activities. He visualized a series of interdisciplinary groups working on specific problems but hoped that these would arise with a minimum of help and persuasion on his part. He did issue indirect orders, or suggestions, enforced by the allocation of funds, that biochemical characterization of tumor tissue, nutritional factors in tumor origin and growth, carcinogenesis in tissue culture, and studies of gastric cancer had high priority. Some of the older biochemists from his pharmacology group were assigned to act as property managers and suppliers of animals and tissues to the more active researchers.

The whole intramural activity was sufficiently small to have direct guidance from the chief. About 100 people formed the staff, which included everyone from the janitors to the front office. All were housed in one building, which had six floors—the three official stories, an attic, a basement, and a sub-basement. The first floor, on the left of the entrance, had the Director's suite, including conference rooms and a cubbyhole for the Managing Editor of the JNCI. On the right side of the first floor were the biologists, with Andervont's personally handled mouse strains occupying the rear half of the area. This, and a few other animal areas, were the only air-conditioned spaces in the building. In 1940, summer in Washington, or even in the more fortunate Bethesda, which was at a higher elevation from the swamps upon which the Capitol was built, was not conducive to labor. When the temperature reached 90 and humidity went over 100, the personnel were dismissed to continue sweating at home. Actually, a better rule would have been the point at which the chair stuck to one's bottom when one attempted to rise. Mice did poorly under such conditions, and they had first call for preservation.

The second floor was allocated primarily to biochemistry, with Greenstein holding sway on the right and Shear on the left. The third floor was for the pathologists and the tissue culture suite of Earle. Biophysics and the heavy equipment, such as ultracentrifuges and electron microscopes that were coming to the fore, were housed in the basement and the sub-basement, along with more animal rooms, with mice, rats, and guinea pigs being almost exclusively the material. Except for the stocks of the geneticists, the animals were imported by purchase from the few breeding laboratories that existed at the time. The animal facilities of the National Institutes of Health were yet to be developed, and there was a permanent disagreement about the quality of mice from various sources. Problems of quarantine and uniformity of diet were constantly being discussed. Cancer research was one of the earliest of scientific fields to recognize and accept the need for genetically defined, environmentally uniform animals for their work, which included standard diets and knowledge of the disease spectrum that always lurked in the background. To other scientists, even at the National Institutes of Health, inbred, homozygous animals seemed abnormal and not representative, and the questions of uniform diet seemed almost unreasonable pickiness. Perhaps the fact that total life-time studies were often required in cancer research, whereas for much other research the time span was much shorter, was involved in the lack of understanding.

The sub-basement also housed radiologic equipment and some radium. Lorenz, not a tidy investigator by any definition, so contaminated the area with radioactivity that some rooms had to be sealed off for years after his demise.

The attic was the storeroom and eventually also the chicken yard for Bryan's work on the Rous tumor viruses.

Voegtlin was insistent upon having a periodical publication for the NCI. In 1938, the only cancer journal in the United States, the *American Journal of Cancer,* was going under financially, and the AACR, for which it was the house organ, was attempting to continue it under a new title, *Cancer Research.* Both *Cancer Research* and the JNCI appeared in 1940, the former as a monthly, the latter as six issues per year (*117*).

The orders to the intramural staff were that all papers by them were to appear in the new publication of the NCI. The only exceptions, granted individually by the chief, were some papers on the chemical isolation of amino acids by Greenstein. This makes the contents of the first few volumes of the JNCI a good record of the NCI research (*118*).

Volume 1, 1940-41, of the JNCI consisted of 863 pages, of which 61 were devoted to the proceedings of a conference on gastric cancer. There were 44 original research papers, five scientific reviews, and three administrative reports, all by 53 authors. At that time, multiple authorships were not common; the average number of authors per paper was two. Division of the scientific staff into three groups shows that 29 papers were by the ex-Boston contingent, 16 by the ex-Washington people, and 21 were by the new infusion of Research Fellows. Voegtlin was the editor, selecting his consultants on an ad hoc individual basis as and when he felt such consultation was needed; except in pathology, it seldom was.

As to the eventual fate of the members of the original staff, Spencer became the next Director of the NCI, serving from 1943 to 1947. He was replaced by Scheele, who was the Director for less than a year before being designated the Surgeon General. Scheele's connections with cancer research were administrative, and he was not identified as one of the boys. He led the NCI into one of its expansions, put it in the hands of Heller, and left for bigger arenas, leaving no publications to record his views or contributions.

When the organization of the NCI was formally divided into sections, which were then promoted to branches, and eventually to laboratories, five became headed by alumni of the Boston group and two by previous Research Fellows. Mider reached the highest administrative levels upon his return to the NCI as its Scientific Director under Heller. Perhaps as another indication of either relative ability or aggressiveness of the three groups, four of the Boston contingent eventually were elected to the presidency of the AACR. From the Washington group, only Voegtlin reached this august post; indeed, he was the only Director of the NCI to do so.

The staff assembled once a month, or on the call of the chief, for scientific conferences, at which the results of research or plans were discussed as selected by the chief, who chaired the meetings. Occasionally a prominent visitor would be invited. Leo Loeb, the grand old man of cancer research from St. Louis, was the first such speaker, and his carefully edited remarks were published in the JNCI.

The chief did not welcome technical assistants at the meetings nor their representation on publications. Their presence was limited to those specifically involved in the work to be presented, and their listing on publications required vigorous defense.

There was full discussion at the staff meetings, which were restricted to research. Administrative matters were the exclusive province of the chief, to be discussed with individual members on an ad hoc basis, if at all.

The format and course of the meetings soon became established, in line with the personalities involved. The more aggressive younger or ambitious individuals could be depended on to be heard from, to attract attention, or to get a dig at a senior adversary. Two or three of the latter were guaranteed to speak their piece, no matter what the topic, reinforcing the audience with their wisdom and experience. The alumni of the Washington group were characteristically a silent lot, tending to sit on the back rows and to become involved in introspection. In the days before air conditioning, it was pleasant to drowse under the large, sunny windows.

No minutes were kept of these informal sessions, which were always firmly controlled and terminated strictly on time. The real interactions between the scientists occurred in daily contacts, consultations, and bull sessions, usually at lunch or toward the end of the day. The brown-baggers assembled: the biologists around Andervont, the pathologists around Stewart, and the biochemists around Greenstein. Administratively more ambitious individuals made it a point to walk to the central building where, in line or in the cafeteria, they could see, hear, be seen, and even be heard.

The first formal conference was on gastric cancer, organized with great care by the chief. The conference was held in the largest auditorium on the top floor of the administration building of the National Institutes of Health. A memorandum to the staff announced that their attendance was welcome, but that they were to sit back of the roped-off section of the auditorium and that they were not to enter into the discussions unless specifically invited to do so. Except for the few on the program, no one from the staff appeared at the meeting.

The gastric conferences were repeated in New York in 1944 (*119*) and in 1946 (*120*) and represented an early attempt at a programmatic approach to cancer. Intramurally, investments on attempts to produce experimental cancer in mice (*121*) and rats (*122*) were unsuccessful. Dr. Morris K. Barrett (1900-67), who emerged as a surgeon during the war (*123*), did write a scholarly review (*124*) on approaches to the problem, but by then the interests had dissipated.

E. The Outlanders

The 1937 National Cancer Act was broadly coached, its purposes being stated as ". . . conducting researches, investigations, experiments and studies relating to the cause, diagnosis, and treatment of cancer." It would require a lawyer to explain the subtle differences between researches, investigations, experiments, and studies, but the goal of prevention, diagnosis, and treatment of cancer is clear here as well as through other provisions of the Act. Certainly clinical activities, statistics, epidemiology, and what became known as cancer control were implicitly included in the interpretative, if not the spelled-out directions to be taken.

The original formulation of the NCI, intramurally as well as extramurally, included these activities, but they were less evident than the more visible laboratory studies. They also tended to be forgotten even more quickly.

As far as statistics of cancer are concerned, the analyses of mortality data by Schereschewsky (*25*) in the mid-1920's were expanded and updated by a series of publications by Gover (*125*). These were issued between 1939 and 1941 from the Division of Public Health Methods, on funds allocated from the NCI. Gover is identified as an associate statistician, which is about all that is known about her.

Dr. Harold F. Dorn (1906-63), a senior member of the Division of Public Health Methods, undertook a pioneer survey of the incidence of cancer in ten metropolitan areas of the United States. The basic data were gathered between 1937 and 1939, but the final report appeared in 1944 (*126*). Approximately a decade later, 1948-49, the survey was repeated in the same areas and in more extensive form. These surveys are benchmarks in the field of cancer statistics and epidemiology (*127*).

Dorn was an economist by training and specialized in studies involving large populations. He was for two decades the chief statistician not only for the NCI but for the whole National Institutes of Health. Dorn was a quiet, reserved person who avoided arguments, kept his own counsel, and achieved what he was after by dogged pursuit. Following World War II he became increasingly more involved in international studies and affairs; he held the office of Secretary-General of the International Union Against Cancer until his untimely death from carcinoma of the kidney. Dorn realized that the true dimensions of research in epidemiology had to involve the whole world and that the United States alone was too homogenized and too limited for such endeavors.

Cancer epidemiology at the NCI in 1939-40 was allocated to one room near the chief's office. From there, two activities eventually surfaced. One was a survey of radiation protection in hospitals, in connection with the program of radium loans. Cowie and Scheele (*128*) found, as is almost inevitable in such surveys, that there was much to be desired in the safety compliances. The other activity was an evaluation of breast cancer therapy (*129*) based on records gleaned from nine large cancer hospitals by Dr. James Hawkins (1909-72). The prevailing view was that, until the prevention of cancer became practical on a public health scale, the control of the disease was dependent on cancer therapy.

In 1940 there was mighty little to deploy in cancer prevention. The Papanicolaou vaginal smear procedure emerged with a 1941 publication, but it was years before it became broadly accepted among clinicians and pathologists. The public education campaigns of the ASCC emphasized awareness of symptoms and the allay of fear. Breast self-examination was being cautiously discussed in committees, with the usual alarms against the fanning of cancerophobia.

Until the conclusion of the war and the post-war expansion, epidemiology at the NCI was practically restricted to public health statistics. Epidemiology as a research method in the search for causes was first represented by a study of Henshaw and Hawkins (*130*). By the simple device of counting deaths from leukemia among radiologists and among other physicians, these authors showed the higher risk among radiologists, which they attributed to exposure to ionizing radiation.

Cancer statistics as gathered and analyzed by Dorn also gave rise to some hypotheses of cause. The predominant one, and the most obvious, was the geographic distribution of skin cancer, related to exposure to sunlight. This relationship, of course, was known for at least two decades and suggested by dermatologists of the 19th century.

In regard to therapy, surgery held full sway, with radiation considered only as an ancillary method. The NCI purchased 9.5 g radium for loans to over 50 approved hospitals; by 1943, some 7,000 patients had received treatments with the loaned radium. But modern radiotherapy, as developed in France, became a significant feature of cancer treatment in the United States only following World War II.

Clinical activities of the NCI were developed at the Marine Hospital (subsequently renamed U.S. Public Health Service Hospital) in Baltimore, about 50 miles north of Bethesda. Dr. John E. Wirth (1905-65), a surgeon trained at Memorial Hospital in New York and working at the Swedish Hospital in Seattle, Washington, was given the task of organizing a 100-bed tumor clinic. It was equipped with two 250-kV radiation units and a facility for the storage of radium and production of radon seeds. The latter, including design of a deep well for immediate use in case of an air raid or other disaster, was the work of a shy physicist, Dr. John E. Rose (*131*). He and Wirth were initially employed as Research Fellows.

The tumor clinic was supposed to receive all cancer patients admitted to PHS facilities east of the Mississippi. Such referral was ordered by an official memorandum from the Surgeon General. Compliance, however, was something else, since surgeons of the system were not about to forego their most interesting cases elsewhere. Radiotherapy candidates were usually available, particularly for recurrences after unsuccessful surgery.

The tumor clinic added Dr. Juan A. del Regato, a French-trained Cuban physician, as the radiotherapist. There began a long debate concerning the proper role of radiation in the treatment of cancer. The Memorial Hospital training looked upon radiation as an adjunct under order by cancer surgeons. del Regato exemplified the modern view of radiotherapy and radiobiology as specialties, with primary treatment of some forms of cancer as its responsibility. The war interrupted further developments. When Wirth returned from his wartime duties, he found that he was not to assume charge of the clinical cancer facilities planned for Bethesda and went into private practice in California. del Regato transferred to the cancer hospital at Columbia, Missouri, and there wrote with Dr. Lauren Ackerman one of the best one-volume treatises of cancer, which has gone through four editions and has been translated into Spanish and Polish (*132*).

The tumor clinic had a laboratory that was supposed to develop a research program as well as to do the necessary pathology and other specialized procedures. Interactions between the laboratories in Bethesda and the tumor clinic in Baltimore were minimal. On occasion, a biochemist would express interest in tumor tissue of human origin, usually after stimulation by the chief, or Wirth would come to Bethesda for periodic visits with the chief and suggest some collaborative endeavor. Arrangements would be made to deliver specimens but would soon falter from lack of real interest or various difficulties and misunderstandings. Laboratory scientists tend to consider clinicians as conveniences, not to be included in the original plans or the eventual publications, unless they happen to think of mentioning them in a footnote of acknowledgment. Clinicians with an idea of performing some determinations on human tissue reciprocally consider the laboratory workers as handy technicians who should be delighted to do such work. These divergent attitudes provided ample room for misunderstandings in both directions.

The period of 1940 was a decade or more before biometrically designed clinical trials were medically accepted. It was even before retrospective studies were part of the experience of clinicians, or even before standardized definitions and analyses of therapeutic results. There was, of course, little to test or to analyze other than surgical procedures. In 1941, however, Dr. Charles Huggins of Chicago opened the modern era of cancer chemotherapy with his observations on the ameliorative effect of diethylstilbestrol in advanced cancer of the prostate. A modest trial of sc implanted diethylstilbestrol pellets was undertaken at the tumor clinic in Baltimore (*133*). The chief reason for the procedure was that the patients there could not be relied upon to take the medication orally.

F. Other Parts of the Forest

The period around 1940 had no unifying or predominant scientific hypothesis regarding the cause or cure of cancer. There were proponents of the Warburg concept of cancer as a cellular adjustment to anoxia, becoming manifested as anaerobic glycolysis in tumor tissue. The concept of a common-denominator endogenous carcinogen based upon cholesterol lost proponents with the introduction of azo dyes into the field of chemical carcinogens.

Cancer research around 1940 was also laboring under some premature and unfounded conclusions that were voiced by many of the leading investigators of the day. One was that cancer was not an infection and that virus research in cancer was a waste of time, despite the examples of the fowl sarcomas, mammary tumors in mice, and rabbit papillomas. This negative attitude was to be overcompensated two decades later, when virus research was going to solve the problem of neoplasia. Another premature consensus was that neoplastic growth, other than transplanted tumors, exerted no immunologic reactions in the host. Dr. William Woglom (*134*), a scholar of cancer and a writer of thoroughly documented, lucid papers, labeled immunologic research on cancer as an unpromising area by his review of 1929. A similar attitude existed against chemotherapy. In a famous statement, Woglom (*135*) likened the search for systemic agents against cancer with a search for chemicals that would dissolve the left ear and leave the other ear in place. Being a cautious scientist, he left a small loophole in his analogy by saying that it was "almost, but not quite" appropriate.

Indeed, many scientists of the time considered research on cancer a waste of time and a graveyard for scientific reputations. There was an example of this, too, in the only Nobel Prize to be given for cancer research up to 1966. This was in 1926, when it was awarded to Dr. Johannes Fibiger of Denmark, for his intriguing investigations in rats of gastric cancer which he related to an organism transmitted by cockroaches that the rats ingested. This work could not be duplicated by others and is still an enigma—for everyone accepts that Fibiger was a thoroughly honest, astute, and capable pathologist. The prize probably should have gone, or at least have been divided with, Yamagiwa of Japan, who introduced the induced tar tumor into cancer research (*136*). Then, as now, such prizes place higher value on novelty, elegance, and complexity of procedure than on simplicity or utility.

In the environment of 1940, a single, general direction to cancer research was neither wise nor possible. Retrospectively, the leitmotifs were in chemical carcinogenesis, biochemical, primarily enzymatic searches for differences between normal and cancer tissues, and the effects of nutrition on tumor growth and its host.

It is easy to fall into chauvinism and to overevaluate the importance of one's own institution. The NCI, however, was important from its beginning. Cancer research even on an international scale in 1940 was such a modest endeavor that the entry of the NCI did produce a quantum-jump expansion.

The national scope of the cancer research activities is well reflected by the size of the AACR, our oldest professional cancer society, which goes back to 1907 (*137*). In 1940 it had about 200 members. Its annual meeting that year, in Pittsburgh, was held conveniently in one large room. There were 40 papers on the program and plenty of time for discussions.

The 1940 meeting of the AACR in Pittsburgh saw a rebellion of the younger members against the older poobahs who since 1907 had considered the organization as a private club with self-perpetuating officers and directors. Over the unbelieving, cataleptic rage of the old guard, the constitution was rewritten to allow all members to vote for the board of directors and to introduce a greater measure of democratic procedure in the selection of its members and programs. The AACR then began steady growth toward becoming the most prestigious professional organization in cancer research in the world. Gradually, the NCI and the American Cancer Society (ACS) accepted supportive roles and underwrote the AACR publication, *Cancer Research,* as an outlet for research reports for which they had made fiscal allocations. Of course, fiscal aid implies some control, but in this relationship, with constant vigil, control and interference were minimized. There are definite advantages to having officers of a professional organization also serve as counselors to the agencies that disburse funds.

The Federal budget for cancer under the National Cancer Act did not shut off or reduce private or State funds for cancer, despite the fears expressed by those who view any incursion of the government with alarm. Rather, the national program primed the pump. In New York, Alfred P. Sloan and Charles Kettering donated funds from their General Motors profits to found the Sloan-Kettering Institute as the research arm of the Memorial Hospital. In Wisconsin, the McArdle endowment served as the basis for a cancer laboratory there. In Texas, the M. D. Anderson money performed a similar function for the University of Texas at Houston. These were the seeds from which arose the largest and the most eminent cancer institutes in the United States. Each was assisted by funds from the national allocations for cancer. Each trained and developed scores of scientists and clinicians who were to expand the research attack against cancer in the years to follow. These developments, of course, had to await the conclusion of World War II.

Internationally, England and Germany were in the forefront of cancer research in 1937, the latter country already being intellectually disemboweled by the Nazis. In Germany, Warburg was still the doyen of biochemistry, and the *Zeitschrift für Krebsforschung* still a leading cancer research journal. In England, the Kennaway group in London set the pattern and pace of chemical research in cancer. The older Imperial Cancer Research Fund was in the doldrums, because its Director, Gey, espoused the viral etiology of cancer—prematurely and on inadequate evidence. In Japan, research on cancer, originally grouped around the great Yamagiwa, oriented itself around T. Yoshida and azo dye carcinogenesis. One of his associates, R. Kinosita, in a tour of the United States just before the war, spread the word and made hepatomas in rats a favorite material for biochemists. The liver was a better control for hepatoma than most tumor-normal tissue pairs and also provided such interesting variants as fetal liver, regenerating liver, and liver damaged by noncarcinogenic toxins.

The Fourth International Cancer Congress was scheduled to be held in 1939 in Atlantic City. By then, few investigators could come from Europe, although the lights were not being dimmed as yet in the United States. This was the last one for the duration.

At the NCI the war made its inevitable impact; its effects began to be felt with the reorientation of the national posture and the universal draft. Although most of the professional staff were beyond the age of service, there were members of the reserves, younger technical assistants, and the pull toward enlistment in a war with a popular cause. Thus the NCI had but a year of the initial structure visualized by Voegtlin before it had to batten down its hatches for the duration.

Voegtlin and the responsible administrators of the PHS retained biomedical research activities as viably as possible. For this, some defense-oriented work that seemed also to bear on cancer was located. Perhaps the most important of such research was in radiation, as part of the Manhattan Project that culminated in the atomic bomb. Active plans for a post-war expansion also were pursued without interruption.

It was the best of times, and not the worst of times. The virtues of smallness are often exaggerated, but even in 1940 the older alumni of the original Boston and Washington groups were sighing nostalgically for the good old days of less than a decade before.

They had not seen anything yet!

IV. WAR AND CONSEQUENCES, 1942–48

World War II divides the history of the 20th century scientifically as well as politically. It marks the rise of the United States to preeminence in biomedical sciences, in part due to the contributions by American scientists and in part due to the destruction of European scientific institutions.

Cancer research and the NCI reflected the changes during this period. Thus a description of the national movements in biomedical science is necessary to understand and place oncology in proper perspective within the broader area of biomedical research.

A. National Attitudes

At no time during the involvement of the United States in World War II was there any but the most optimistic view of its outcome. Military defeats were but temporary setbacks, and the destruction and horror of war never touched the homeland. As a consequence, even during the depths of the war, thinking, planning, and preparation for the post-war recovery and expansion were being actively pursued.

Science and its yields loomed large and obvious. The explosion of the atomic bomb, first in the desert of New Mexico and tragically next over Japan, was perhaps the most dramatic and important event in contemporary history. The American public was quickly acquainted with the scientific genius that released this new form of energy and cataclysmic destruction.

The American public also became acquainted with the miracles of medicine that were being offered to our fighting men, miracles of surgery made possible by blood replacement, control of shock, and the antibiotics and miracles of preventive medicine that controlled epidemics. For the first time in history, disease produced less casualties than the trauma of combat.

The willing drafting of science for the war effort was effected by President Roosevelt by the creation of the Office of Scientific Research and Development (OSRD), under Dr. Vannevar Bush. In this organization, medical affairs were under the chairmanship of Dr. A. N. Richards, pharmacologist from the University of Pennsylvania. OSRD, in one capacity or another, involved the total potential of science, and, in its functions, academicians were indistinguishable from their colleagues in uniform. In its councils and by its products, the organization demonstrated the power of science, a power that could be applied to peacetime purposes as to those of war. Bush, in his 1945 report, "Science—the Endless Frontier," outlined the vistas, and Dr. John R. Steelman, in his report of 1947, developed the thesis.

OSRD was a wartime agency, and its replacement by a National Science Foundation was blocked by President Truman because its directorate as initially proposed was removed from sufficient governmental controls. Also, it was visualized that biomedical research would be transferred to an expanded National Institute of Health rather than to the new science agency, which would be concerned with the so-called basic sciences (*5, 138*).

While these issues were being contested in Washington, a seminal development was taking place in New York. There the wealthy advertisement magnate, Albert Lasker, and his wife Mary became interested in biomedical research. The affliction of their cook with cancer was a trigger of this interest, and it was accentuated some years later when Albert Lasker developed a fatal cancer of the large intestine.

The Lasker fortune could have established a research institution along the format of the Rockefeller Institute for Medical Research. But Albert Lasker thought in bigger terms, of involving the national treasury through appropriations. And the way to that goal was to organize a lobby for biomedical research that would persuade Congress to make such allocations (*139, 140*).

Among the Lasker expansions was into the ACS, which in 1944 was founded as a reorganization of the ASCC. The Society represented a ready-made lobby group that already extended into the National Advisory Cancer Council of the NCI.

Mary Lasker occupies and will be remembered for a commanding role in biomedical research in the United States. She followed the tactical plan laid out by her husband, not only for cancer but also for mental and cardiac diseases, the three most prominent causes of disability and death. The plan involved a small, effective group of professional and governmental people at key points: in the voluntary organizations such as the ACS, in government, and well-placed money and educational materials where they would count. The latter included slick prints of the problem and its solution to be placed on the desks of all Congressmen and not simply mailed and thus forgotten. Generous support, then quite legal, was made available for election campaigns of a few well-selected converts, especially Lister Hill in the Senate and John E. Fogarty in the House. Membership on councils that recommended the distribution of subsequent funds closed the circle. Direct access to the White House and the reward of research scientists by prizes and statuettes of the Victory of Samothrace were useful reinforcements and excellent public relations for biomedical sciences as well as for the Lasker Foundation. It was an effective extrapolation to its logical extremes of the advertising-mercantile culture of the United States, applied to goals considered worthy by the medical-scientific community.

B. The PHS

Surgeon General Parran and his lieutenants, especially Dr. Joseph Mountin, continued to remake the PHS in accord with their views of the future. The laws applying to the PHS were rewritten in 1944, which included wider authority for research, grants, and training at the National Institute of Health and for a clinical center. The authorizations were activated by appropriation of funds in 1947. Shortly thereafter a half-dozen categorical institutes were created in the model of the NCI, and the National Institute of Health became plural.

The personnel requirements for the programs continued to be met by three systems of employment: the commissioned officers corps of the PHS, the Federal civil service, and research fellowships. The commissioned corps was the elite leadership group of public health generalists. Parran recognized that the training of medical officers recruited to the corps was deficient in public health, and provisions for such training were developed through the venereal disease program, the special baby of Parran in which he first made his mark while on assignment to New York State and the coterie of Franklin Roosevelt. The training ground was Johns Hopkins.

It was, therefore, no accident that following the war many top positions in the PHS became occupied by officers trained in venereal disease control. The prevailing view, which culminated at its apogee during Nixon's presidency, was that management was a specialty in itself, somehow independent of the subjects it manages. During the 1940's, however, venereal disease training programs were the only ones available, and they certainly were useful in molding a leadership cadre for the PHS. The decline of the commissioned corps experienced later was attributable to the lack of systematic recruitment for outstanding medical graduates during the war, because the PHS was made part of the military forces only by courtesy late in the war and was not in a position, or desired, to compete with the army and navy for personnel. This, plus the disappearance of systematic training programs for its younger officers, inevitably led to deteriorations, the effects of which became evident much later.

During the mid-1940's, it was still the policy to head divisions and institutes of the PHS by commissioned officers. And so it came to pass that in 1946, when Scheele returned from the war as a public health officer with the Supreme Headquarters of the European Theater, he was assigned to be assistant chief of the NCI, now a formal division of the National Institutes of Health. By that time R. E. Dyer had lost whatever confidence he had in the administrative abilities of Spencer, so de facto Scheele became the head of NCI.

Scheele had had training in cancer matters at the Memorial Hospital before the war, but his interests were in public health and in administration rather than research. Upon Spencer's retirement in 1947, Scheele's elevation to directorship, and coincident with an expanded appropriation, the NCI was reorganized and expanded.

In this new turn of events, some differences of opinion had to be resolved. The two major areas here involved the scope of the clinical center and the growth of the NCI at Bethesda in contrast with the establishment of colonies elsewhere in the country.

C. War Assignments and Colonies

The NCI professional staff by 1942 was well represented by persons beyond the early draft age. Also, decisions at higher levels were to disturb research as little as possible. These factors, as well as the successful progress of the war, served to preserve the main activities of the NIH throughout the war.

Among those who served in the armed forces were Dr. Harold L. Stewart as pathologist at Letterman General Hospital in San Francisco and White, Barrett, Scheele, and myself in the European Theater.

Vacancies were more evident among the younger technical and attendant staff. Many of them later took the educational advantages under the G.I. Bill of Rights and joined professional ranks upon the completion of their duties.

The vacancies on the staff were filled during the 1942-46 period by commissioned officers, such as Drs. A. B. Eschenbrenner and A. Nettleship in pathology, and by Research Fellows. Of the eight hired as Research Fellows during 1942-46, six were women; during the previous 4 years, 1938-41, only one of 34 Research Fellows was a woman.

Spencer, trying to hold the place together during this time, was apparently sold on the idea of creating colonies of direct operations at a distance from Bethesda. The idea was taken up by three commissioned officers. Dr. James Hawkins wanted to develop epidemiology in Boston, in association with the clinical cancer facility organized by Dr. Sidney Farber. Dr. Roy Hertz, brought in for studies in endocrinologic physiology, was given a green light to have a clinical research unit at George Washington University, while retaining his laboratories at the NCI. I was permitted to begin a combined laboratory-clinical unit in conjunction with the University of California Medical School in San Francisco (*12*).

It is not known what concurrence, if any, Spencer had for the colonies from the Director of the National Institute of Health, but the San Francisco unit was approved and backed by Surgeon General Parran. Nevertheless, the decision to create a clinical center at Bethesda and the new directorate of the NCI were not compatible with decentralization, at least at that particular time. In the clear light of retrospect the life-span of the "colonies" was finite at the beginning. Of course, Hertz merely transferred his patients when the Clinical Center opened in 1954. Hawkins became involved in training in surgery and in the early tests of antifolic acid compounds. A visit with the new scientific director led to a disagreement that culminated in a resignation by Hawkins, who returned to private clinical practice in Idaho. The California unit, the Laboratory of Experimental Oncology, existed for 7 years, 1947-54, and was then terminated. Ostensibly, 15 clinical research beds in San Francisco could not be defended while 500 were available in Bethesda.

Scheele's short directorship of the NCI of less than 1 year preceded his elevation to Surgeon General. He quickly formalized the internal organization into a research branch with six sections of biology, biochemistry, biophysics, chemotherapy, endocrinology, and pathology in Bethesda and a seventh section in San Francisco. A research grants branch and a cancer control branch were also established in Bethesda; each was headed by a commissioned officer. The research branch was placed under Dr. Harry Eagle, another officer, brought in from his venereal disease laboratory at Johns Hopkins.

Eagle was ordered to take the assignment and had a frustrating 2 years before resigning to return full time to his own research. He decided that the cancer program needed many changes but found the organization too solidly entrenched. Also, he insisted in continuing his own work on media for spirochetes and then devised semidefined media for mammalian cells in tissue culture. For Eagle's work, half the first floor of the NCI building was converted to laboratories.

The new grants branch was initially headed by a young officer, Dr. David Price, who specialized in public health administration and soon rose to higher posts. He was succeeded by Dr. Ralph G. Meader, who was recruited from his position as executive secretary of the Childs Fund at Yale (*22*). This activity became the administrative arm of the National Advisory Cancer Council, especially after the embarrassment of 1948, when its executive secretary, Dr. A. C. Ivy, became involved with Krebiozen.

The cancer control activities were placed under Dr. Austin V. Deibert, who in 1951 was succeeded by Dr. Raymond F. Kaiser (*141*). This branch had its own grants-review mechanism and remained semi-independent of the intramural and grant programs until transferred to another division of the PHS in 1960. It never overcame its image of being an orphan in the research environment of the NCI.

D. The Bench Workers

Cancer research intramurally continued without serious interruption during the war period, although the number of contributions, as represented by publications, declined sharply.

Some research lines initiated and pursued during the war were noteworthy. None, of course, solved the cancer problem, but all advanced knowledge that inevitably would be usefully applied to further investigation.

In the biology of cancer, Andervont plugged along. He explored the response of different strains of mice to chemical carcinogens and factors that affected the appearance of various spontaneous tumors. During 1943-46, some 21 papers included his name as author or coauthor. He established a milk factor-positive line of BALB/c mice (*142*); Andervont and Bryan (*30*) showed that the milk factor was antigenic and that passive immunization to it could be demonstrated. I (*143, 144*) induced interstitial cell tumors of the testes in BALB/c mice given implants of diethylstilbestrol-cholesterol pellets and showed that adrenalectomy as well as ovariectomy reduced the appearance of mammary tumors in mice. Heston and Deringer (*145*) demonstrated a relationship between the lethal yellow gene of the mouse and susceptibility to spontaneous pulmonary tumors.

The biochemistry group under Greenstein was the champion in turning out papers. No less than 58 reports under Greenstein's name were published in 4 years. In 1948 appeared his *Biochemistry of Cancer* (*92*), a synthesis of studies on the biochemical characteristics of tumor tissue and cancer research in general. The research group, including Dr. Alton Meister (*146*) and Dr. Vincent E. Price, also continued work on the isolation of proteins and amino acids.

Radiobiology was a target of research, and contracts from the national endeavors eventually were identified with the Manhattan Project. The long-term effects of low doses of radiation on several species were exhaustively studied, with the result that the accepted tolerance dose was revised downward (*147*). Dr. Henry S. Kaplan, after working with Dr. Jacob Furth, joined the group and continued his studies on radiation-induced leukemia in mice (*148*). At the same time, Henshaw and Nettleship were also engaged in radiobiology and accidentally discovered that urethan was a carcinogen. Urethan was employed as an anesthetic for mice to immobilize them while they received radiation, and at autopsy the animals were found to have multiple lung tumors (*149*).

Eschenbrenner, who was placed in charge of pathology during Harold Stewart's absence, investigated the hepatomagenic effects of carbon tetrachloride and chloroform in mice (*150*). He and Dr. Eliza Miller (*151*) applied quantitative techniques devised by Chalkley to histologic studies and obtained important results. They dissociated cirrhosis from neoplasia in the induction of liver tumors and showed that these are separate and not sequential reactions. The purported hyperplastic effect of radiation on the interstitial cells of the testes was shown to be a relative change due to the atrophy of the spermatic elements (*152*). Eschenbrenner was involved in the planning of the clinical cancer center before the full dimensions of the center were decided, and his separation from the NCI was traumatic and unfortunate. The quantitative approach to histology remained an underdeveloped field.

PHOTO 13.—H. L. Meyer, around 1944, setting up mice for radiation exposure investigations by A. Nettleship and P. Henshaw. Urethan carcinogenesis was discovered in the course of these experiments.

Earle, with Dr. E. L. Schilling, Dr. Virginia J. Evans, and, later, Dr. Katherine K. Sanford, in 1944 began publishing their meticulous, truly long-term attempts to transform normal cells to cancer in vitro. The contributions of the techniques developed by the group are yet unexploited. The growth of single isolated tumor cells from which the clones could be grown (*153*), the role of a cellophane substrate (*154*), and eventual fluid-suspension cultures that allowed the production of large volumes of cells (*155*) were among such contributions. Earle continued to develop chemically defined media for tissue culture without serum or embryo juice.

Interest in the nutritional aspects of cancer induction and growth somehow abated. White was in Europe, and his wife, Florence, continued his studies (*156*). Morris, with Dunn and Dubnik, became interested in propagating hepatomas in rats (*157*), which led to the establishment of a wide variety of transplantable liver tumors that became favorite materials for biochemists throughout the world.

Dr. C. Donald Larsen (1905-75), a biochemist from Rochester who was supposed to work on lipid problems in cancer, lost interest in lipids but initiated the study of a series of carbamic acid esters (*158, 159*) following the demonstration of urethan as a carcinogen. An important contribution from these studies was the discovery of a transplacental carcinogenic effect of urethan (*160*). After the war, Larsen transferred from his laboratory to research grant administration.

Shear's group had completed its studies on chemical carcinogenesis by 1942 and reoriented toward chemotherapy. The main thrust was to isolate the fraction from *S. marcescens* that produced hemorrhage in transplanted tumors (*161*). Hartwell (*162*) studied the reactions of nitrogen mustard with proteins and amino acids, but no extended attention was placed on these agents.

E. The American Cancer Society

In the complex, confusing societal ecology of the United States, the dividing line between governmental and nongovernmental activities is fuzzy. This is also true, of course, of cancer. The affairs of the NCI, including its budget, cannot be understood without knowledge of the professional and public pressures and judgments that are being constantly made of it and its achievements. In turn, one of the roles of the NCI is to maintain a balance with the unofficial domain, which in cancer is primarily represented by the ACS.

The ACS was organized in 1944 as a reorganization of the ASCC, which was founded in 1913. The Woman's Field Army was organized in 1933 as an arm for its public education campaigns. But the involvement of such scientists as Drs. J. B. Murphy, Francis Carter Wood, and—above all—C. C. Little in its programs increasingly highlighted the importance of gaining new knowledge through research. With the stimulus given by the Laskers to raise their sights in organization and in funding and with the post-war role of the NCI not being clear, the ACS was frankly designed to take over the cancer affairs of the country. It is not incidental that the leaders of the group were more at ease and more dedicated to private sources of funds than to governmental allocations.

In the national expansion of the ACS, the governing group encountered the problem and the dangers of conflict of interest. Members of the group were among the best qualified to develop the cancer program and thus accept funds for such purposes. Could they then also sit in judgment of the allocations? In 1944, the question was resolved by having an outside group act in the review capacity. Little approached the National Research Council, who set up with ACS money a review mechanism called the Committee on Growth (COG). The name was an indication of the "basic" research approach as the appropriate one: Cancer was seen as an aberration of growth which had to be understood if cancer were to be understood and, through such understanding, conquered or controlled.

The Executive Committee of COG was a blue-ribbon group of biomedical scientists, with Dr. Cornelius P. Rhoads as chairman. It included no government employees, although these were placed on many of the discipline panels that reviewed research applications. Its advice was forwarded to the ACS, but the funds available for allocation were known and divided to panels by executive judgment of research priorities.

The same problem, real or possible conflict of interests, exists in governmental review processes and probably is impossible to resolve. The most knowledgeable to judge are also the most competent to be supported. Probably the best empirical approximation is the "sunshine" principle, in which business is conducted in the open and not in closed-door executive sessions.

The ACS also became the public lobby for cancer before Congress. This function was honed to perfection by Mrs. Lasker and her small, professional advisory coterie, on which Farber of Boston was the cancer champion. The proposed budget of the NCI was slipped to the group, and a cooperative member of the Congressional Appropriations Committee would ask the right question, about the much larger budget that really was needed to continue the battle against cancer. The process became as formalized and as stately as the mating dance of the whooping crane.

The balance between NCI and ACS tended to keep both "honest"; various working arrangements were made to act in concert. Thus figures on incidence and mortality were "coordinated," and it was agreed that ACS should get the lion's share of publicity at conjoint meetings.

F. Other Cancer Institutes

The immediate post-war period saw the rise of four institutions devoted to cancer to commanding positions they have retained since. Inflation affects titles as much as currency. During the first two decades of this century, specialized cancer research institutions were known as laboratories; by 1950, the appropriate titles were institutes; now, they are centers, comprehensive or otherwise.

The expansions of the post-war years were closely associated with the personalities of the directors whose influences, of course, extended far beyond their own institutions.

Cornelius Packard Rhoads (1898–1959), a hematologist at the Rockefeller Institute, became Director of the Memorial Hospital for Cancer and Allied Diseases in New York in 1940. His research program originally was oriented around nutritional factors and physiology of cancer but, after wartime experience with nitrogen mustard gases, his emphasis shifted to chemotherapy. Rhoads was a driving man, for whom there were two cardinal sins: One was to believe that the problem of cancer would not be solved and the other was that the solution would be found anywhere but at his creation, the Sloan-Kettering Institute.

In 1946, Sidney Farber (1903–73), a professor of pathology at Harvard, established the Children's Cancer Research Foundation in Boston, now the Sidney Farber Cancer Center. His research program centered around the treatment of leukemia in children, and it was here that the folic antimetabolites were discovered. A large, impressive man with a silky voice, Farber was a key adviser to legislators, philanthropists, and medical organizations. His advice was softly given but best not disregarded.

A Texas surgeon, Dr. Randolph Lee Clark, became Director of the M. D. Anderson Hospital for Cancer Research in Houston in 1946. Under Clark's aggressive leadership, which has continued for 30 years without interruption, this component of the University of Texas became one of the largest and most important cancer centers in the nation. Among its specialties are many publications and meetings.

Dr. Harold P. Rusch, born and educated in Wisconsin, has devoted his professional life to oncology. He became Director of the McArdle Laboratory for Cancer Research at the University of Wisconsin in 1946 and has led its continued growth ever since. He could be counted on to represent the bench workers at high-policy councils. The Wisconsin group has been a prime contributor to biochemical research on cancer.

The oldest cancer research laboratory, at Buffalo, New York, had to wait until 1952 for expansion into the Roswell Park Memorial Institute, under the guidance of Dr. George E. Moore.

The directors of these institutes are prominently represented on the National Advisory Cancer Councils and on many other panels and policy advisory boards of the NCI. As such, they determined the course of events more than most of the intramural staff. Such determinations often had the consequence of additional funds for their own institutions and programs.

G. Meetings and Conferences

Meetings and conferences of scientists are a necessary component of their lives if they are to remain viable and current, even if some such meetings may be scheduled at vacation spots.

During World War II there was a natural reduction of such meetings of cancer specialists, but some memorable ones were held. The meetings were noteworthy because they represented benchmarks of exchange and consensus of opinions that were influential in determining the future course of research.

A conference in endocrinologic aspects in cancer, for example, was held at Atlantic City in June 1942. Dr. Charles Huggins presented his results of endocrine ablation in prostate cancer, Dr. Konrad Dobriner talked of his studies on steroid excretion in cancer, Dr. Ira T. Nathanson gave a paper on steroid treatment in breast cancer, and there was a series of reports on the endocrine factors in experimental carcinogenesis (*163*).

Two important meetings were held at Gibson Island, Maryland, in 1944 and 1945. They were on research approaches to cancer, and the second one was seminal in the development of concepts and acceptance of chemotherapy as a justified field of research. The proceedings of both conferences were published (*164, 165*) in full after careful editing by Dr. Dean Burk and his program committees. The Gibson Island conferences were eventually replaced by the annual Gordon Research Conferences. The proceedings are not published—a luxury to the participants and a loss to the great majority who cannot attend.

The AACR discontinued its annual meetings for 3 years, 1943-45. Its official publication, *Cancer Research*, which replaced the bankrupt *American Journal of Cancer* in 1940, appeared regularly, although often late. The foreign cancer journals (in Germany, France, and Japan) disappeared temporarily as war casualties. Only the laboratories in England continued to exist and to perform their work. As did many other American laboratories, soon after the war NCI welcomed some prominent European visiting scientists. They included Dr. Otto Warburg of Germany, Dr. Isaac Berenblum of Israel, and Dr. Leslie Foulds of England.

The first post-war meeting of the International Union Against Cancer was held in St. Louis, Missouri, in 1947, under the chairmanship of Dr. Vincent Cowdry. The United States had to provide travel and living expenses for all European participants. They were a sad, tired lot, but not too tired to shout their displeasure at the appearance of a German collaborator on the speaker's podium. The wounds were still open and they would take time to heal.

V. NCI COMES OF AGE: 1948-57

The two decades between the late 1940's and the late 1960's were a golden age for biomedical research in the United States. The image of science was as a source of limitless bounty, and no problems of sickness and death were beyond its solution, given enough money and publicity. Even the animalistic Joe McCarthy period that so affected the national and international politics did not permeate to biomedical research. Given enough time and impetus, however, it would have, and plans were made to meet it with such fire-breaks as the Peters case, in which a consultantship was withheld because of the political views of the recipient (*166*). An NCI staff member was transferred to a more distant institution to obscure his crime of having belonged to a suspect maritime union. The Senator did himself in before the situation became too serious for the biomedical area.

The predominant feature for research during this period was the growth of the budget. At the NCI, the budget grew from $14 million in 1948 to $48 million in 1957. Of course, the great bulk of the money was for extramural research and other cancer activities. Intramurally, the largest determinants affecting the programs were the opening of the Clinical Center in 1953 and the creation of the National Cancer Chemotherapy Program in 1955. The first oriented a large component of activities toward clinical research. The second dissolved the sharp distinction between intramural and extramural activities. The pristine ivory towers of laboratory research were breeched forever, and the NCI lost its innocence.

The contract mechanism for support of research, borrowed from the Department of Defense for the needs of the chemotherapy program, led to far-reaching effects that were still evolving two decades later. Contracts for research support activities were and remain controversial. Contracts required specifications and details that seemed foreign to research delving into the unknown.

The requirement for government-employed "project officers" to be responsible for contracts involved intramural scientists in management. Many scientists were not trained for such duties, and management functions hampered their own research. Some scientist-managers exploited the situation by directing large funds toward their own scientific interests.

One reason for the introduction of the contract mechanism was to involve commercial concerns that were considered ineligible for grants. Commercial participation was necessary and beneficial, but could have been achieved by the modification of the grant guidelines.

Another reason for the contract mechanism was that it was to be faster and simpler than the grant procedures. But complexities of review and approval of contracts grew, and commitments became increasingly shorter, progress reports and project site visits more frequent, and plans and requests for proposals (RFP) ever more detailed.

Thus, as in so many other human affairs, the problems and limitations of the grant-in-aid and the direct-operation systems were replaced by the contract system, rather than remedied by it. But perhaps the biggest single problem was bigness itself. A research program that expanded from a few million to many hundred million dollars inevitably reached a new level of visibility and accountability, of public and political interest.

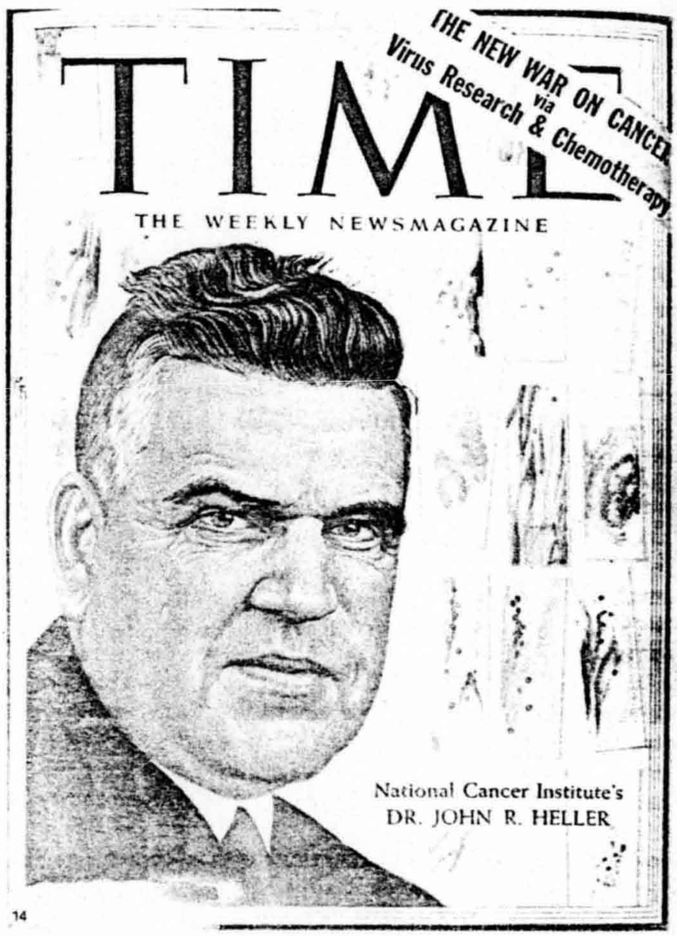
A. New Leadership

The reorganization and expansion of the NCI required more room than was available in Building 6, the original home of the NCI. The Office of the Director, cancer control, and related activities were moved to T6, a long, two-story building that was the temporary structure for the PHS during the war, it in turn having been ousted by the Combined Chiefs of Staff from the PHS building on Constitution Avenue. Another area for NCI expansion was into a flat-top brick structure between Buildings 2 and 3, which soon got a reputation for having uncontrollable heat and poor ventilation. The activities around the Director were shifted to a series of buildings, some off campus and as far as Silver Spring, and never did get together in one place again.

A number of events in 1948 again changed the directorate of the NCI. Surgeon General Parran resigned precipitously or was fired by the Administrator of the Federal Security Agency, the predecessor of the U.S. Department of Health, Education, and Welfare. His successor was Scheele, and Scheele selected Heller as the next Director of the NCI. The reasons for the appointment are no clearer now than they were in 1948, to Heller no more than to the workers at NCI. The new Director, a North Carolina gentleman, had spent his career as a venereal disease control officer and had risen to head the activity. With Eagle, another alumnus of venereal disease, as the Scientific Director, the more facetious members of the NCI felt that it should be renamed the National Cancer and Clap Institute.

Heller never did develop a deep interest in cancer. He was an administrator, pure but not simple, who knew human behavior and liked people. During his 12 years as Director of the NCI, the longest tenure so far, it is hard to recall any scientific decision, report, or controversial opinion that emanated from him on cancer or any other substantive topic. Heller will always be remembered by many staff members whom he protected, even when they were in error. It is in a way fitting that he was the only Director or member of the NCI to grace the cover of *Time*, on its July 27, 1959, issue. He was also the first individual institute director to be elevated to Assistant Surgeon General. In 1960 he became president of the Memorial Hospital-Sloan-Kettering Institute in New York, a position that required more administrative ruthlessness than a gentleman like Heller could muster. He sustained an incapacitating stroke, from which he was rehabilitated by his devoted wife, and returned to NCI as a special assistant for foreign relations.

NCI in 1948 was joined by four other categorical institutes at the now-plural National Institutes of Health. The National Institutes of Health directorate also became of more



14

PHOTO 14.—J. R. Heller, from the cover of *Time*, July 27, 1959.

intimate concern to cancer affairs. Grants in cancer, except for those in cancer control, were now reviewed by panels of an overall National Institutes of Health Division of Research Grants. Upon Dr. R. E. Dyer's retirement as Director of the National Institutes of Health in 1950, his crown prince, Dr. Norman Topping, was bypassed for Dr. William Sebrell, a careful and conservative nutritionist who was ill at ease in a large administrative post. During the national imbroglio about the poliomyelitis vaccine in 1955, Sebrell became ill and Dr. James Shannon made his mark before the television audience with the Secretary of the U.S. Department of Health, Education, and Welfare cowering in the background. Shannon's directorship lasted from 1955 to 1968 and reflected his imaginative, hard-driving, hard-drinking characteristics. NCI had more than its share of the ever-increasing budgets, planned programs, and the new mechanism of research by contract.

At the NCI, the post of Scientific Director remained vacant from 1949 to 1952, when Mider was recruited to return. The business of research and other activities went on without visible or definable differences; this suggested that some of the directorate positions were of more value as table-of-organization box fillers than as actual functions. A suggestion was made, when the title of Associate Director in Charge of Research was changed to Scientific Director, that the immediate administrative superior be named the Unscientific Director.

B. The Director's Office

The Office of the Director continued to encompass the usual administrative and service units and a few activities that did not fit readily elsewhere. Thus the editorial office of the JNCI, now expanded to a respectable working staff, was administratively in the Director's office, although it actually operated rather independently. The JNCI was rehabilitated from its nadir of size and appearance by Dr. Ross C. MacArdle (1901-64) (*167*), who also selected its format, including the blue cover that acquired the appellation of MacArdle-pants blue, for obvious reasons. The editorial board of the JNCI also reviewed all papers for publication emanating from NCI, whether submitted to the JNCI or to other publications. The procedure was a policy dictated from on high, resented by many who considered the review as unnecessary and demeaning under the academic-type visage for which the National Institutes of Health strove. The editorial board did not like it either, and most reviews of papers not destined for the JNCI were rather pro forma.

The Research Grants Branch had particularly intimate relationships with the Director's office since it processed the bulk of budgetary allocations and served as the administrative arm of the National Advisory Cancer Council, which had to recommend all grants for payment after they had been reviewed by the study sections of the all-National Institutes of Health Division of Research Grants. Dr. Ralph G. Meader, a hard-working Yankee with a hair-shirt for a conscience, was in charge. After the dissolution of the COG, its executive officer, Dr. O. Malcolm Ray, became Meader's deputy. Meader protected the grant system with all his might and was thoroughly opposed to the eventual contracts as another mechanism to support research.

The National Advisory Cancer Council, originally visualized as advisory to the Surgeon General and as a technical body of experts, was evolving into a more general policy group. As the budgets increased and cancer became increasingly more visible nationally, membership to it was reviewed by ever higher levels, eventually reaching the White House. By 1957, it included public members who were selected for political as well as other reasons.

Traditionally, its advisory functions did not include the intramural affairs of NCI. To meet requirements for review and advisory bodies for the intramural areas, a special visiting committee of counselors was organized. A proliferation of similar bodies for other activities quickly occurred, producing more problems than were resolved.

C. Cancer Control

It can be logically defended that all activities in cancer are directed at its control. But in a public health service environment, control is a narrower field that excludes research and clinical care and emphasizes the preventive measures and statistics, thus making the denominator population its main concern. These are the distinctions between schools of medicine and schools of public health and between medical centers and departments of health. In the United States, with the hyperdevelopment of therapeutic medicine and the atrophy of preventive medicine, these do not mix comfortably, as they should, but present an area for disagreements based on different viewpoints.

Should public health activities be at the National Institutes of Health or at administrative bureaus related to State functions? Is the proximity of such activities to research desirable, wishfully thus being able to translate the findings of research to practical application with least delay? What are the differences and similarities between research grants and control grants?

These and many related problems were encountered by the expanded Cancer Control Branch of the NCI which was initiated in 1947, abolished through transfer by 1960, and resurrected in the National Cancer Plan of 1971.

During the decade 1948-57, the cancer control activities were well understood and accepted by Scheele and Heller but were foreign and suspect to the intramural staff. The branch was administratively responsible for cancer grants to State health agencies, radium loans to hospitals, grants to medical and dental schools for cancer teaching programs, and nursing activities (*141*). In support of these functions, educational materials were developed under joint sponsorship of the ACS.

Among the direct functions of the branch was a national attempt to promulgate exfoliative cytology for the diagnosis of cancer of the uterine cervix. NCI and PHS were specifically prohibited to practice civilian medicine or otherwise to endanger the sacred precincts of the private practice of medicine. Thus such programs had to have specific approval of the local medical societies and were allowed only if they were for demonstration. Full expenses, of course, were to be borne by the government.

The Exfoliative Cytology Program was begun in earnest in 1951 at the University of Tennessee Medical School, and the observations made in Memphis still remain among the most impressive; it demonstrated the value of the procedure in the detection of truly early cervical cancer, thus reducing mortality from the disease (*168*). The program was organized before appropriate controls for field studies became accepted, as they were a decade later when X-ray mammography was being evaluated.

By 1957, there were seven field programs in cervical cytology, from Washington, D.C., to San Diego, California. Analyses of data from Memphis and from San Diego, particularly by Dr. John E. Dunn (*169*), were important in delineating the usefulness of the procedure, as well as providing information on the natural history of cervical cancer. Much of the data from other centers, necessary for administrative control during the programs, yielded nothing more than the grossest of approximations to the frequency of abnormal findings in undefined populations. The final recommendation for the disposition of the reports was to bury them deep during the first moonless night.

Statistics and epidemiology became legitimate scientific disciplines during the 1950's and were first incubated in the Cancer Control Branch. Dorn, who had conducted the first national cancer incidence studies in 1938, returned from his wartime duties with the army and quickly organized a repeat survey of the same ten city areas in 1948-49. He recruited statisticians being released by the armed forces and soon gathered a group with talents equalled only to those of the British school of Dr. A. Bradford Hill. This group included Drs. Jerome Cornfield, William Haenszel, Nathan Mantel, Marvin Schneiderman, and Sidney J. Cutler, who were to make important biometric contributions not only to cancer but also to other fields. Dorn and Cutler (*170*) finished the final report on the 1948-49 survey in 1959, and it remains one of the benchmarks in the statistics and epidemiology of cancer. Biometry was made into a separate branch in 1951. Dorn became the chief statistician for the National Institutes of Health. He took Cornfield with him and was increasingly involved in international studies and affairs in his role as Secretary-General of the International Union Against Cancer.

Epidemiology also found an initial home with the Cancer Control Branch. This activity was headed by Dr. Alexander G. Gilliam (1904-63), a careful, canny Scotsman who was at his best at finding methodologic inadequacies (*171*). Dr. R. L. Smith published analyses of mortality from cancer among oriental and other ethnic groups in the United States (*172*).

The Cancer Control Branch also undertook studies on environmental cancer. For this, in 1949 Dr. Wilhelm C. Hueper joined the staff, first having his laboratories at Georgetown Medical School and then moving to the Clinical Center 3 years later, becoming part of the research staff under Mider.

Hueper, educated in Germany as a pathologist, was a renowned expert in occupational cancer and the author of the definitive text he published in 1942 (*173*). His own work was prodigious (*174*), but his strong views regarding industrial hazards soon got him into difficulties. He earlier had been discharged by DuPont for pointing out their deficiencies, and when he became a Federal employee, he insisted on extending his criticisms to other industries. Although undoubtedly many of his criticisms were justified, his activities were terminated by complaints from industrial concerns. The Surgeon General finally ordered that Hueper was not to make field trips, in order to preserve Federal programs in industrial hygiene more general than carcinogenic hazards. It left Hueper embittered, and he intermittently lashed out against any authority closest at hand, communicating his unhappiness to such unlikely outlets as the *Police Gazette*. Hueper at a meeting was asked for his criteria of tumor malignancy. His reply was characteristic, "Ven I say it's malignant, it's malignant!" Protected by successive NCI Directors whom he upbraided, Hueper retired at the mandatory age of 70, with a World Health Organization medal shared with Dr. L. M. Shabad of Moscow for their contributions to environmental carcinogenesis.

Hueper was involved in the organization of the survey program of uranium miners in the Colorado-Utah plateau. Continued annually by Wagoner et al. (*175*), this program has clearly demonstrated the increased hazard of developing lung cancer among these uranium miners. An ecologic study organized in Hagerstown, Maryland, was less productive since its design was void of specific hypotheses and based on an inadequate population.

An early responsibility of the Cancer Control Branch was the evaluation of diagnostic tests for cancer, in which Dr. Andrew Peacock, Dr. Eli Nadel, and others reached repeatedly negative conclusions. Perhaps the most important yield was the development of the biometric considerations that were relevant to testing the tests (*176*).

D. Clinical Research

The Clinical Center opened its doors in 1953. The first patients to be admitted were those of Hertz, who were transferred from his clinical facilities at George Washington University. One of them promptly died, contrary to the policy established by the National Institutes of Health Director, who wished not to admit patients with short life expectancies.

The clinical services in cancer were organized into three branches—medicine, surgery, and endocrinology—and the two supporting branches of radiology and pathology, the latter serving other institutes as well.

Dr. Charles G. Zubrod, of Boston and St. Louis, an associate of Shannon during the antimalarial program for the armed forces, was placed in charge of the Medicine Branch. Among his young associates were Dr. Emil Frei III, who headed the leukemia service, and Dr. Nathaniel I. Berlin, who headed the metabolism service.

Dr. Robert R. Smith, a commissioned officer trained at the Baltimore Tumor Clinic and the Memorial Hospital, was appointed chief surgeon. Among the early investigations emanating from this branch was the effect of adenoviruses injected into cervical carcinoma for cytolytic effects (*177*), as a segment of then-current interest in the possible antineoplastic properties of viruses. The major program was in supraradical surgery for neoplasms of the head and neck and the pelvis. Another current interest, that of tumor cells in the blood and wound washings, culminated in the conclusion that the presence of such cells had no influence on prognosis (*178*).

The medical research programs were directed to chemotherapy, especially of pediatric acute leukemia with antifolates, following the leads developed by Farber in

PHOTO 15.—The Clinical Center of the National Institutes of Health, opened in 1953.

Photo 16.—E. Frei III getting acquainted with a little patient with leukemia, about 1957.

Boston. However, biometric design and contratest concepts were immediately accepted and developed, even to the extent of including the chief biometrician, Schneiderman, as one of the authors on clinical papers (*179*).

In contrast to Zubrod's group, Hertz's group refused to accept biometrically controlled clinical studies. Hertz subscribed to the views of some of the older, most respected clinicians, such as Farber and Dr. Alfred Gellhorn. It was in Hertz's group that the most impressive result in cancer chemotherapy was discovered, the curative effect of disseminated choriocarcinoma in women by methotrexate (*180, 181*).

The priority for the discovery is shared by a young Chinese associate, Dr. Min Chiu Li, who observed as a Research Fellow at Memorial Hospital a sharp drop in gonadotropic hormone output in a patient with a testicular tumor who was given methotrexate. The observation was confirmed and extended on Hertz's service at the Clinical Center, where previous animal studies showed the need for folic acid during pregnancy.

For 4 years, the Endocrinology Branch included Dr. Delbert M. Bergenstal (1917-59) (*182*) as the assistant chief. As an associate of Huggins in Chicago, he participated in the development of adrenalectomy for advanced hormone-dependent cancers. He and his associates introduced o,p'-DDD for adrenocortical cancer (*183*). His premature death was a loss to biomedical science.

E. Cancer Chemotherapy Program

The first large engineered and directed national program in cancer, aimed at the discovery of effective systemic chemical agents, was formed in 1955 (*184, 185*). Its origin was 2 years before when, following appropriate preparations and testimony, Congress instructed NCI to launch a program in the chemotherapy of acute leukemia. A stimulating factor, as so often is the case, is that a neighborhood child of a staff member of an influential Congressman had died of leukemia.

NCI organized a committee, started a newsletter, an annotated bibliography, and a series of seminars and symposia and promised favorable consideration of worthy grant requests. These orthodox steps were considered inadequate by the Lasker-Farber sponsors, and the sights were raised beyond the usual patterns. To translate the plans into action, an expert on government facilitations, organizations, and stimulations was assigned from the Division of Research Grants. He was Dr. Kenneth M. Endicott, originally from Colorado, a pathologist, a commissioned officer, a driver, and an expeditor wise in the ways of making things go. In double-time, a Cancer Chemotherapy National Service Center (CCNSC) was organized to include other governmental and public agencies, a series of advisory committees headed by Farber, and the authority to support its activities by contract, a mechanism patterned to that evolved at the Pentagon. The program was laid out from the acquisition of chemicals to be tested, through bioassay, pharmacology, and chemical trials. For the dimensions of the program, new sources of animals had to be developed, because it required more mice than were available for all of cancer research at that time.

Endicott knew that a drug development program could not succeed without the participation of the pharmaceutical industry. For a while the industry was wary and refused to accept contracts, but Pfizer finally did and other companies soon followed. Relationships with industry were eased by the enticement of Dr. Robert Coghill, one of the founders of the deep-fermentation process for penicillin production, to the activity as deputy for industrial research.

One area excluded from the contract formula was clinical aspects. The lawyers intimated that NCI could be held responsible for malpractice and other legal problems under contracts more readily than under grants, which were conditioned gifts and further removed from direct operations. Endicott had over his desk a framed quotation from Shakespeare's *Henry VI, Part 2* (IV, ii. 86), ". . . the first thing we do, let's kill all the lawyers," but he had to go along with the warning. Clinical testing groups, therefore, were funded by grants, which produced a whole series of other problems. Review of grants was through study sections of a National Institutes of Health division for grants, and the section to which the clinical group studies were designated for review had a chairman unsympathetic to biometrically designed trials and an executive secretary who interpreted his duties so rigorously that liaison essential for program development was impossible. To add to the complications,

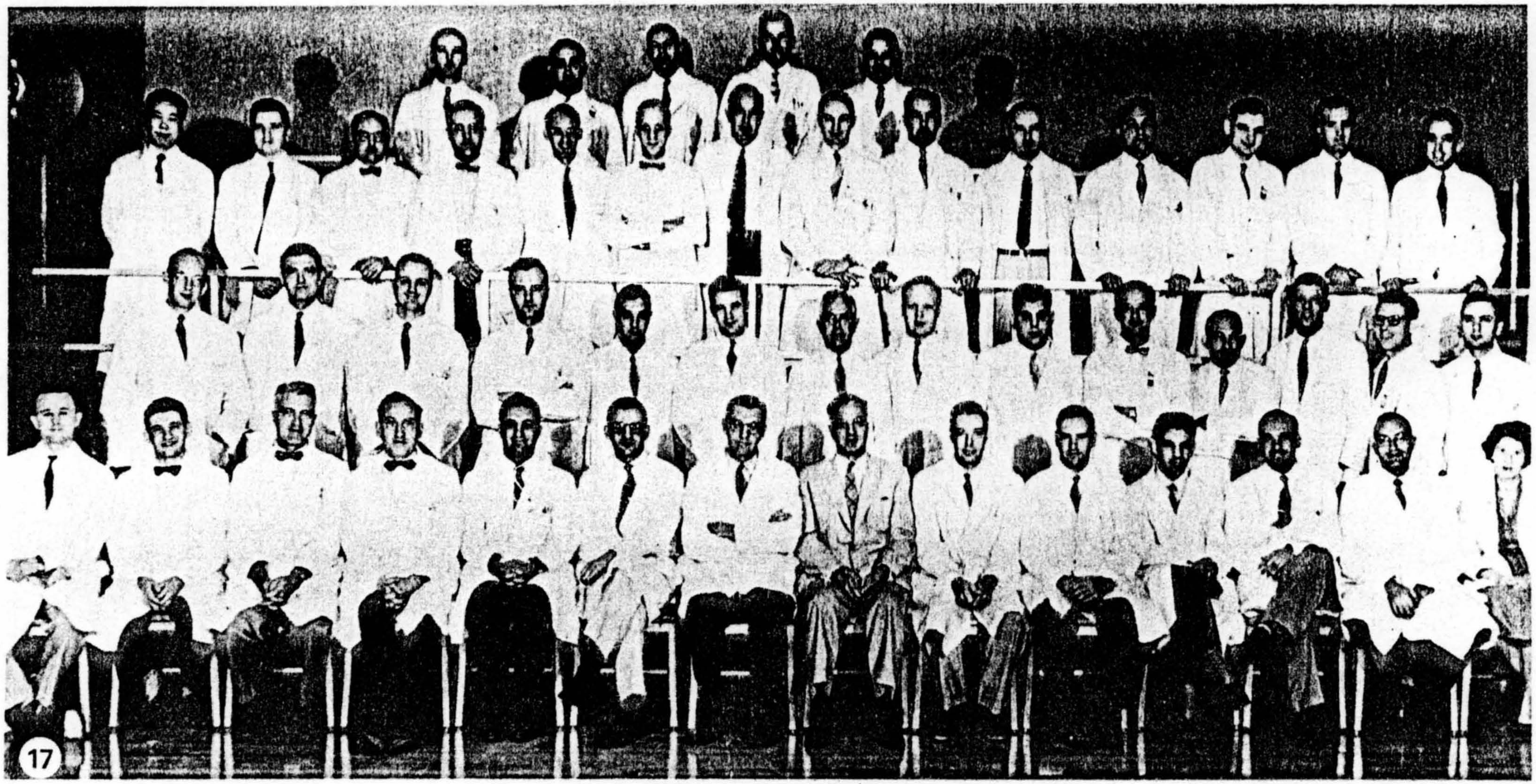


PHOTO 17.—The NCI clinical staff, 1957. *First row, left to right*: R. Reinertson, W. E. Schatten, R. R. Smith, R. Hertz, P. Rubin, A. L. Flick, C. G. Zubrod, G. B. Mider, D. P. Tschudy, M. Schick, J. L. Steinfeld, H. Herbsman, A. Ship, and J. Shohl. *Second row, left to right:* A. Garceau, R. D. Fritz, W. J. Pieper, E. J. Freireich, A. H. Levy, H. A. Lubs, Jr., J. R. Andrews, J. L. Fahey, B. R. Landau, J. Stengle, H. R. Engel, J. Stabenau, R. R. Paton, and R. Mendelsohn. *Third row, left to right:* M. C. Li, R. G. Crounse, D. Nathans, G. Goldin, N. I. Berlin, M. E. Liebling, C. O. Brindley, J. R. Jude, C. Z. Haverback, J. F. Potter, E. J. Van Scott, S. M. Weissman, H. J. Levine, and T. A. Waldmann. *Fourth row, left to right:* P. T. Condit, R. A. Milch, J. Laszlo, P. D. Olch, and W. Kramer.

the grants chief for NCI was antagonistic to the contracts mechanism, and the Scientific Director was opposed to having intramural personnel involved either in contracts or in the chemotherapy organization.

The resolution of the impasse could not be reached through compromise and casualties were inevitable. The study section was "modified" and the executive secretary "transferred." The Scientific Director was only partly mollified, threatened to resign, and later was promoted to a higher post at the National Institutes of Health. The organization of clinical study groups proceeded under the clinical panel headed by Dr. I. S. Ravdin of Philadelphia. The pioneer group was based on the Medicine Branch of NCI headed by Zubrod and differentiated into a leadership position as the Eastern Study Group, which included Frei, Dr. Emil Freireich, and Dr. James Holland. The Memorial Hospital clinical interests, under Dr. J. Burchenal, were organized as a Leukemia Group. There was considerably more difficulty in having this group accept rigid biometric design. The institution under Farber, in Boston, never did accept such controls, despite Farber's chairmanship and sponsorship of the program. Apparently controls were something for other people.

The clinical area of CCNSC also developed the plan for the use of chemotherapeutic agents as adjuvants following surgery performed with curative intent (*186*). This plan was originated not only to test chemotherapeutic agents under the most favorable conditions, when the residual tumor load was at the minimum, but also to get surgeons and radiologists involved in the program.

The clinical trials of chemotherapeutic agents did provide scientific answers to the indications and limitations of their use. But even more important, the groups organized for the trials were the training ground for a new generation of clinicians who learned and accepted the need for biometric design and statistical analysis in clinical studies as the methods by which the anecdotal "art of medicine" could be reinforced by a demonstrable science of medicine. The importance of this contribution extended well beyond the field of oncology, which itself evolved into a recognized specialty.

It was inevitable that a little bureaucracy arose, consisting not only of the staff but also of many other organizations funded by Endicott under the program, with complicated review and approval mechanisms and constant uneasy scrutiny from established bureaucracies of the National Institutes of Health and outside bodies. Getting around program inhibitors was a major activity in itself. Publication by government is a jealously guarded prerogative of the GPO, which reports to Congress. To launch a rapid, informal communications medium, *Cancer Chemotherapy Reports*, under a contract circumventing GPO, had to carry a reminder that it really was not a publication. And soon its review processes took as long as those for most other journals.

Reviews of new programs became increasingly more complicated, particularly when the problems related to investigations on human beings, i.e., informed consent, gained public visibility. Activities began to acquire stately dignity and a glacial pace of forward movement.

Some programs of the CCNSC, however, arose on the spur of the moment. A $5 million endeavor on hormones in cancer was simply added to one budget, apparently because a friend spoke to a friend in the Senate. A more modest program, on the analysis of end results in cancer (*187*), began when there was a windfall that had to be allocated within days or be returned, and there was a statistician interested in taking it on. Very little systematic planning was built into these activities; perhaps they can be considered results of administrative serendipity.

There can be no doubt that the imaginative, hard-hitting drug development program in cancer has borne fruit. Whether all the effort and expense were commensurate with the results, of course, remained a subject of debate in which proponents and opponents expounded rather than listened. The influence of the cancer chemotherapy program extended beyond the United States, to Europe and to Japan. The campaign against cancer was increasingly a worldwide involvement.

F. Back at the Laboratories

The NCI sections of 1948 grew and expanded into branches and laboratories, but not at the rate of the new programs. Most scientists play a one- or two-string lute embellishing the same primary melody over their careers. Reshuffling the same personnel does no more than exchange chairs, and only new, younger additions to the staff, plus judicious retirements and attritions, lead to real programmatic changes.

In the Laboratory of Biology, Andervont continued to hold his easy sway and perform his own neat work. His inbred strains of mice, handled personally as usual, were studied for skin tumors following applications of 3-methylcholanthrene (*188*) or for interstitial cell tumors following implantation of diethylstilbestrol pellets (*189*). Heston continued to cross different strains for various induced and spontaneous tumors (*190*). Heston and Dunn (*191*) published an ingenious experiment to demonstrate that the characteristic for lung tumors resided at the tissue level. They showed that lung tumors were induced in lung tissue from susceptible strains and not in that of resistant strains transplanted to the cross of the two strains. Dr. Lloyd W. Law (*192*) continued his studies on factors modifying leukemia in mice.

Leukemia in mice was added to the mouse mammary tumor as being of viral origin in 1951, by the now classical research of Dr. Ludwik Gross (*193*). The demonstration was dependent on the use of young animals, in which the concept of vertical transmission was developed. In 1953, Gross also observed that filterable extracts from leukemic mice also induced parotid gland and other tumors and that the inducing agent was distinct from the leukemia virus. Dr. Sarah E. Stewart (1906-76), then working at the PHS hospital in Baltimore, reproduced these results during the same year (*194*). Extension of the work in collaboration with Dr. Bernice E. Eddy showed the oncogenic versatility of the leukemia-associated filterable agent following its growth in tissue culture, both in terms of the variety of neoplasms produced and of crossing species barriers by being oncogenic in hamsters, rats, and other rodents as well as in mice (*195*). The agent was named the polyoma virus and has led to some tussling for priority. It is not inappropriate to note that the results published by both Gross and Stewart at this time gained considerably in being accepted by the cancer research community through confirmatory work by Law (*196*), recognized as a most careful and critical experimenter. In retrospect, there is ample credit to be shared by all, but the preeminent role of Gross has been amply recognized.

Virus research on mice and chickens became well accepted. In 1958 Bryan became head of the newly created Virus Oncology Section, which blossomed into another programmed research endeavor by 1960. Bryan's collaborative work on the Rous virus extended to Rutgers. In 1956, a paper was published on the use of chick brains as a host virus system, in which a young man, Dr. Frank J. Rauscher, Jr., appeared as coauthor (*197*).

The tissue culture group under Earle continued its fine work (*198*). Algire's in vivo chambers in mice provided more information on vascularization (*199*). And Dr. Richmond T. Prehn contributed one of the early papers marking the rebirth of immunology in cancer. He showed that some immunity to 3-methylcholanthrene-induced sarcomas could be elicited in homozygous mice (*200*).

The Laboratory of Biochemistry continued to be dominated by Greenstein. Maver compared DNA and RNA extracted from normal and tumor tissue (*201*). Dr. Benton B. Westfall extended his biochemical work to glutamine in tissue culture (*202*). A husband-and-wife team, Drs. John and Elizabeth Weisburger, began their studies on the metabolites of *N*-2-fluorenylacetamide (*203*).

In 1948, the biochemical group was joined by Dr. George U. Hogeboom (1913–56), who had worked at Rockefeller Institute with Dr. Albert Claude on cell fractionation and identification of functions of subcellular components. This led to a fertile 8 years of work on mitochondria and other cell components of normal liver and hepatomas, with Dr. W. C. Schneider as co-worker. It was established that mitochondria were the center of respiration and energy production in the cell and that a key enzyme, diphosphopyridine nucleotide, was synthesized exclusively in the nucleus (*204, 205*). It was an irreparable loss when Hogeboom died suddenly from a pulmonary embolus following minor surgery.

PHOTO 18.—W. R. Bryan and V. Riley injecting Rous sarcoma virus into a chicken, about 1950.

The Laboratory of Chemical Pharmacology continued work on the polysaccharide isolated from *S. marcescens* that produced hemorrhage in tumors. It was eventually used clinically in a few cases but did not maintain interest. A plant material, podophyllin, became another focus of investigation (*206*). Shear's role in the chemotherapy program under the CCNSC was that of a self-imposed elder consultant. However, his young associates, Dr. Abraham Goldin and Dr. J. M. Venditti, with the statistical help of Mantel began investigation of the effects of schedules on experimental therapy, which later led to considerations of the optimum doses and schedules in treatment with the use of two or more drugs (*207*). These considerations were applicable to clinical situations, especially when multiple-drug schedules became a preoccupation.

The Laboratory of Pathology, with the responsibilities of providing pathology services for the Clinical Center, also was the source of consideration for pathologic morphology generated in the research areas. Individual pathologists, particularly Dunn, were well represented in papers from other laboratories of the NCI. Centralized services for histologic sections were provided, and compilations of transplantable tumors in animals were prepared (*48*). Among the talented younger pathologists who began to make their mark in research were Dr. Joseph Leighton, Dr. Clyde J. Dawe, and Dr. Alan S. Rabson.

G. The Broader Picture

The explosive expansion of biomedical research during the 1950's was not limited to cancer or to the National Institutes of Health. The same expansion was occurring among the voluntary health agencies, universities, and special research institutes of the nation. Funds from Federal sources were more than matched by State and private allocations. New buildings rose to accommodate the new activities, and old facilities were rehabilitated. New scientific and educational media were launched, such as *Cancer* and *Ca* by the ACS and the *Cancer Bulletin* by the M. D. Anderson Hospital in Houston.

The ACS became firmly established as one of the foremost voluntary health agencies of the country. One-third of its annually collected funds were allocated to research and distributed according to the recommendation of the COG. The 11 reports from COG during its existence are able summaries of the state of the art and the conventional technical wisdom concerning cancer (*208*). In 1955, Dr. Harry Weaver, who had engineered the polio program for the National Foundation that led to the introduction of the killed virus type of vaccine of Dr. Jonas Salk, was substituted for Dr. Charles Cameron as senior vice-president for research. The contract with COG was terminated, the decision being that the ACS would organize its own advisory groups (*209*). The program that evolved now included target-area research, e.g., on lung cancer, as well as the classical orientation by scientific disciplines as defined by academicians.

One reason behind this reorientation was the belief that in some areas of cancer there was need for programmatic emphasis. The ACS had become involved in direct operations and the epidemiologic studies of lung cancer were done by its statisticians, Dr. E. Cuyler Hammond and Dr. D. Horn. Preliminary data fully confirmed the findings from England by Dr. R. Doll and Dr. A. B. Hill that smoking of cigarettes was associated with decreased longevity and increased risk of lung cancer. Planned research and applications on diagnosis and prevention of lung cancer appeared to be justified and timely.

Public and professional education in cancer was expanded at the ACS and, by concurrence with the NCI, in this area ACS was accorded primary position. A series of quadriannual professional meetings, the National Cancer Conferences, were begun in 1948, and the published proceedings represent valuable summaries, particularly in clinical cancer. An innovative idea for public information was developed by Mr. Pat McGrady of the ACS, by science-writer tours to cancer laboratories; after 2 years, the tours were replaced by more manageable annual seminars for science writers.

The chief centers for cancer research in the United States by the mid-1950's were: the Memorial Hospital-Sloan-Kettering Institute in New York City; the M. D. Anderson Hospital for Cancer Research in Houston, Texas; the McArdle Laboratory for Cancer Research in Madison, Wisconsin; the Children's Cancer Foundation in Boston, Massachusetts; and the rehabilitated Roswell Park Institute in Buffalo, New York. Programs in cancer research were developing at several universities, including Columbia, Pennsylvania, Missouri, Chicago, and California. With the growth of Federal funding, a whole series of problems arose regarding the appropriate role and extent of research in educational institutions. Research monies, in direct and indirect ways, including those for traineeship and fellowship, subsidized postgraduate education and began to extend even deeper with such programs as teaching subsidies for cancer. The overhead to the institutions rose steadily. One solution to the resultant problems that was uniformly not taken was to turn down the Federal dollars.

The boundaries of NCI were no longer defined by one building on the campus of the National Institutes of Health. Even on the campus, laboratories and sections spilled all over Bethesda and extended to Silver Spring, although distant colonies were a remembrance of the past. Many members of the intramural staff participated in contracts, study sections, and various review and advisory bodies of the ACS and other institutes.

The primary scientific society in cancer research, the AACR, now had important representation from the NCI, and in 1955 Andervont was elected its president, the first from NCI since Voegtlin held the office in 1941. The publication of the AACR, *Cancer Research,* grew in size and importance and received generous subsidy from ACS, NCI, and a number of private foundations.

In international affairs on cancer, the International Union Against Cancer reflected the post-war recovery and growth. Its quadriannual congresses were resumed, with the locations being Paris in 1950, São Paulo, Brazil, in 1954, and London in 1958. Dorn became its Secretary-General in 1953, extending the influence of the United States. From the NCI, Harold L. Stewart and Shear were particularly active and influential in its affairs.

H. The Smoking Controversy

It is obvious that, during the first 20 years of its existence, NCI had a large place in the ever-expanding knowledge regarding neoplastic diseases. Its efforts and the efforts of scientists throughout the world, however, had not led to major "breakthroughs" in treatment or in the understanding of the pathogenic processes that converted normal cells into malignant counterparts.

A major advance in the prevention of one important cancer entity, lung cancer, had been made by 1957. The definition of tobacco smoking as a major health hazard in the Western world ranks with the discovery in the last century of the dangers of contaminated water supplies. The discovery was made primarily by cancer research workers with epidemiologic methods. Yet the discovery was rejected by many laboratory scientists, obfuscated by the vested interests of the tobacco industry, and remains unapplied by people in the face of ever-rising mortality from lung cancer.

Dorn (*210*) contributed a prospective study on 250,000 veterans of World War II, which added evidence of the role of smoking in lung cancer. This study could have preceded the Hammond-Horn survey for the ACS; however, there were delays in obtaining clearance for questioning veterans and printing the questionnaire forms. The results were published late and modestly, and Dorn contented himself to saying that a statistical relationship had been demonstrated; he was a careful man.

The evidence for the conclusion that tobacco smoking is a major health hazard was finally collated and presented officially to the nation in 1964 as a report on "Smoking and Health" (*211*) by a committee appointed by the Surgeon General, at that time Dr. Luther L. Terry. This was but a terminal step in a long chain of events, studies, and reports recognized as conclusive in 1957 by a special committee of the NCI, the National Heart Institute, the ACS, and the American Heart Association (*212*).

The reaction to the developments by scientists at the NCI and elsewhere was interesting and instructive. Little, one of the true giants of research in genetics of cancer and perennial Director of the ACS, became scientific director for the tobacco interests. Dr. Stanley Reimann, founder of the cancer institute in Philadelphia, scoffed at the whole idea. At the NCI, Heller, one of the organizers of the interagency committee, could get no consensus from his stable of researchers. Harold Stewart and Shear especially raised various reservations and doubts; Stewart's negative assessment was particularly devastating because his reactions were accepted by his friends in pathology at other governmental agencies and other scientific organizations. Even Hueper, seeing a competition between industrial hazards and smoking, assumed a moralistic position that, after all, the latter was an individual option whereas industry had to be controlled. Andervont, a hearty smoker and old friend of Little, joined the tobacco advisory council.

Even in retrospect, it is inexplicable why this should have occurred. Many scientists have hypertrophied supersensitive egos and consider administrators their natural enemies. But to deny the obvious seemed to lie in deeper psychological levels than could be rationalized by overt behavior. The single greatest discovery in cancer during the first 20 years of existence of the NCI remained rejected, for Heller was not about to exert his position of leadership, and the Surgeon General was not about to expose his flanks to the inevitable attacks from the political and economic forces from the tobacco-growing States.

All of this demonstrates why few research scientists are in policy-making positions of public trust. Their training for detail produces tunnel vision, and men of broader perspective are required for useful application of scientific progress.

VI. A STOPPING PLACE

The 1957 history of the first 20 years of the NCI (*213*) is a convenient marker and the stopping place for this essay.

The NCI of 1957 was quite different from what it was in 1937 and what it was to be in 1977. The NCI even by 1957 could not be described as a single, definable institution, but as a national—and, indeed, a truly international—endeavor. The boundaries between cancer institutes, university-based research, and the Federal and the private sectors were becoming less defined. From mice as its major biologic material, patients with cancer became the focus of much of the research. From a budget of under $1 million, the annual investment was approaching $1 billion.

The problem of cancer, however, remained implacable, and the research forays remained unfocused. Since the early years of the 20th century, it had been clear that the cancerous transformation of cells was transferred to the daughter cells, thus probably involving the genetic directorate of the cell. The mechanism for this transformation was ascribed to somatic imitation by Dr. T. Boveri and his school and to virus infestation by Dr. A. Borrel and other proponents of the viral theory of cancer.

By 1957, a scientific consensus was arising that the viral aspects of cancer were a fertile field for investigation, after being relegated out of the mainstream for some four decades. There were just too many animal tumors, in chickens and in rodents, in which viruses obviously played an etiologic role, to contend that the human species was an exception.

A practical reason for the return of virology in cancer research was the conquest of poliomyelitis. This programmed research, supported by a private foundation, left unemployed many important investigators in tissue culture and virology. Cancer research was an obvious and promising area to which these talents and materials could be applied.

The program in viral oncology, therefore, was becoming formulated by scientists and was to become the next programmatic development in the cancer endeavors. This development, along with its immunologic aspects, occurred during the 1960's.

The rise of molecular biology can be dated from the 1944 work of Dr. O. T. Avery and his young associates that DNA controls heredity, but an even better milepost was the announcement of the double helix structure of DNA by Dr. F. Crick and Dr. J. D. Watson in 1953. The biochemistry of cancer gradually revived from its doldrums, although the main stimulus came later from the immunologic demonstrations of fetal and tumor antigens.

It is fair to state that the engineered or managed program in chemotherapy never united the working scientists under its banner. The NCI's role was one of expansion rather than innovation. Cozy arrangements were developing between individual cancer institutes and commercial pharmaceutical houses, with closed-door arrangements for antifolics and other antimetabolites. The size and scope of the national program expanded the efforts, and the small individual arrangements were simply swamped out of existence.

By the mid-1950's, the surgical approach to cancer treatment had reached its apogee and radical radiation therapy was well on the way. The results, as measured by survival, indicated that the available methods could, at best, be extended to about 50%. The future for the remainder of the afflicted had to come through better understanding of the causes and the pathogenetic mechanisms that could be directed toward its prevention, or to improve diagnostic and therapeutic measures that, by definition, had to be systemic in their goals. Only time will tell when the penicillins for neoplastic disease will be discovered; the progress made in 20 years indicates that the question of "whether" is no longer valid. There is good reason to examine the pace and the dimensions of the efforts, which may have been faster and greater than justified. Plans of a national scope have an acceleration factor built into them, a factor further stimulated by the formal and informal bureaucracies and lobbies such plans create and nurture.

Thus in 1957, most of cancer research was phenomenologic, but its techniques were becoming increasingly sophisticated. Cancer research was no longer applying to its materials findings in genetics, biochemistry, and other scientific disciplines. Cancer now was providing findings that returned to and were extended by the more basic scientific disciplines. Cellular immunity, for example, arose in part on findings in cancer research, and the problems of virus-cell interactions provided clarifications from neoplastic disease.

And, as in any incompleted voyage, some of the routes have been circular. Thus there is recurrence of attention to environmental chemical carcinogens, from man-made and natural sources, and to nutritional factors in human carcinogenesis.

The National Cancer Act of 1971 raised by a quantum leap the investment being made toward the solution of the cancer problem (*204*). Cancer research, as it delves ever deeper into the cell, cell-virus interactions, genetic template, and process of differentiation, is now at the core of the most basic biomedical research. Recognition of the role of cancer in biomedical research is evident in the expanding number of its workers being elected to honorific academies and the award of Nobel prizes in 1966 and 1975.

Yet the real solution of the cancer problem, in terms of understanding its pathogenic mechanisms or preventing or reversing its inexorable consequences, still lies in the future.

The basic contention (*214*) remains: Cancer is a solvable problem, solvable by a human thought-and-action process we call scientific research, and within the capabilities of human intelligence with which we were endowed by our Creator.

REFERENCES

(*1*) Voegtlin C, Spencer RR: The Federal cancer control program. Natl Cancer Inst 1:1-19, 1940

(2) MARSHINO O: Administration of the National Cancer Institute Act, August 5, 1937, to June 30, 1943. J Natl Cancer Inst 4:429-443, 1944

(3) HELLER JR: The National Cancer Institute: A twenty year retrospect. J Natl Cancer Inst 19:147-190, 1957

(4) National Institutes of Health: NIH Factbook. Guide to National Institutes of Health Programs and Activities. Chicago: Marquis, 1976

(5) MIDER GB: The Federal impact in biomedical research. *In* Advances in American Medicine: Essays at the Bicentennial (Bowers JZ, Purcell EF, eds), vol 2. New York: Josiah Macy Jr. Foundation, 1976, pp 806-871

(6) MILES WD: Creation of the National Cancer Institute. Manuscript at National Library of Medicine, p 30

(7) SHIMKIN MB: Research activities of the National Cancer Institute. J Natl Cancer Inst 5:77-88, 1944

(8) MIDER GB: Research at the National Cancer Institute. J Natl Cancer Inst 19:191-223, 1957

(9) ANDERVONT HB: Problems before the Association (presidential address). Cancer Res 16:471-478, 1956

(10) STEWART HL: The cancer investigator (presidential address). Cancer Res 19:804-818, 1959

(11) DUNN TB: The value of animal research and the men who do this research (presidential address). Cancer Res 22:898-905, 1962

(12) SHIMKIN MB: Upon man and beast—adventures in cancer epidemiology (presidential address). Cancer Res 34:1525-1535, 1974

(13) ———: Neoplasia. *In* Advances in American Medicine: Essays at the Bicentennial (Bowers JZ, Purcell EF, eds), vol. 1. New York: Josiah Macy Jr. Foundation, 1976, pp 210-250

(14) TRIOLO VA: Nineteenth century foundations of cancer research. Origins of experimental research. Cancer Res 24:4-27, 1964

(15) ———: Nineteenth century foundations of cancer research, advances in tumor pathology, nomenclature, and theories of oncogenesis. J Natl Cancer Inst 25:75-106, 1975

(16) TRIOLO VA, SHIMKIN MB: The American Cancer Society and cancer research. Origins and organization: 1913-1943. Cancer Res 29:1615-1641, 1969

(17) LOMBARD HL: The Massachusetts cancer program. Boston: Multilithed, 1959, p 170

(18) SHRYOCK RH: American Medical Research Past and Present. New York: Commonwealth Fund, 1947

(19) MCCOY GW: A preliminary report on tumors found in wild rats. J Med Res 21:285-296, 1909

(20) U.S. Public Health Service and Marine Hospital Service: Annual Report of the Surgeon-General for the Fiscal Year 1910. 1911, p 37

(21) BAYNE-JONES S: Aspects of cancer research in the United States of America: A tribute to George Milton Smith (1879-1951). Tex Rep Biol Med 10:1084-1098, 1952

(22) MEADER RG, RAY OM, CHALKLEY DT: The Research Grants Branch of the National Cancer Institute. J Natl Cancer Inst 19:225-258, 1957

(23) FURMAN B: A profile of the United States Public Health Service, 1798-1948. Washington, D.C.: U.S. Govt Print Off, 1973

(24) ANDERVONT HB: J. W. Schereschewsky: An appreciation. J Natl Cancer Inst 19:331-333, 1957

(25) SCHERESCHEWSKY JW: The course of cancer mortality in the ten original registration States for the 21-year period, 1900-1920 (PHS Bull No. 155). Washington, D.C.: U.S. Govt Print Off, 1925

(26) Surgeon-General of the Public Health Service of the United States: Annual Report, 1928. Washington, D.C.: U.S. Govt Print Off, 1928, p 28

(27) SCHERESCHEWSKY JW: The prevention and control of cancer: A plan for nationwide organization. Public Health Rep 53:961-969, 1938

(28) SHIMKIN MB: Howard B. Andervont: An appreciation. J Natl Cancer Inst 40:xiii-xxv, June 1968

(29) ANDERVONT HB: Pulmonary tumors in mice. Public Health Rep 52:212-221, 1937, and 54:1529-1533, 1939

(30) ANDERVONT HB, BRYAN WR: Properties of the mouse mammary-tumor agent. J Natl Cancer Inst 5:143-149, 1944

(31) ANDERVONT HB: Influence of environment on mammary cancer in mice. J Natl Cancer Inst 4:579-581, 1944

(32) SHEAR MJ: Studies in carcinogenesis: Production of tumors in mice with hydrocarbons. Am J Cancer 26:322-332, 1936

(33) SHEAR MJ, STEWART HL, SELIGMAN AM: Studies in carcinogenesis. XIII. Tumors of the spleen and liver in mice following the introduction of hydrocarbons into these organs. J Natl Cancer Inst 1:291-302, 1940

(34) SHEAR MJ, LEITER J, PERRAULT A: Studies in carcinogenesis. XIV. 3-Substituted and 10-substituted derivatives of 1,2-benzanthracene. J Natl Cancer Inst 1:303-336, 1940

(35) ———: Studies in carcinogenesis. XV. Compounds related to 20-methylcholanthrene. J Natl Cancer Inst 2:99-113, 1941

(36) SHEAR MJ: Studies in carcinogenesis. XVI. Production of subcutaneous tumors in mice by miscellaneous polycyclic compounds. J Natl Cancer Inst 2:241-258, 1941

(37) ———: Studies on chemical treatment of tumors: Effect of disturbances in fluid exchange on transplanted mouse tumors. Am J Cancer 25:66-88, 1935

(38) SHEAR MJ, TURNER FC, PERRAULT A, et al: Chemical treatment of tumors. V. Isolation of hemorrhage-producing fraction from *Serratia marcescens* (*Bacillus prodigiosus*) culture filtrate. J Natl Cancer Inst 4:81-105, 1943

(39) HARTWELL JL, SHEAR MJ, ADAMS JR JR, et al: Chemical treatment of tumors. VII. Nature of the hemorrhage-producing fraction from *Serratia marcescens* (*Bacillus prodigiosus*) culture filtrate. J Natl Cancer Inst 4:107-122, 1943

(40) KAHLER H, SHEAR MJ, HARTWELL JL: Chemical treatment of tumors. VIII. Ultracentrifugal and electrophoretic analysis of the hemorrhage-producing fraction from *Serratia marcescens* (*Bacillus prodigiosus*) culture filtrate. J Natl Cancer Inst 4:123-129, 1943

(41) BARRETT MK: Anaphylaxis and hemorrhage in transplanted tumors. J Natl Cancer Inst 2:625-630, 1942

(42) SHIMKIN MB, ZON L: Role of thrombocytopenia in hemorrhage produced in sarcoma 37. J Natl Cancer Inst 3:379-382, 1943

(43) SHEAR MJ: Role of the chemotherapy research laboratory in clinical cancer research. J Natl Cancer Inst 12:569-581, 1951

(44) KAPLAN HS: Egon Lorenz, 1892-1954 (obit.). J Natl Cancer Inst 15:iii-xi, Feb. 1955

(45) LORENZ E, ANDERVONT HB: Incidence of induced pulmonary tumors in susceptible strains raised in dust-free air. Arch Pathol 29:484-493, 1940

(46) LORENZ E, JACOBSON LO, HESTON WE, et al: Effects of long-continued total-body gamma irradiation in mice, guinea pigs, and rabbits. *In* Biological Effects of External X and Gamma Radiation. National Nuclear Energy Series, Manhattan Project Technical Section (Zirkle RE, ed), vol 22B, part I. New York: McGraw-Hill, 1954

(47) LORENZ E, HOLLCROFT J, HUNSTIGER H: Effects of ionizing radiations on a transplanted lymphosarcoma. J Natl Cancer Inst 11:1-16, 1950

(48) STEWART HL, SNELL KC, DUNHAM LJ, et al: Transplantable and transmissible tumors of animals. *In* Atlas of Tumor Pathology, sect XII. Washington, D.C.: Armed Forces Inst Pathol, 1959

(49) DUNN TB: Normal and pathologic anatomy of the reticular tissue in laboratory mice, with a classification and discussion of neoplasms. J Natl Cancer Inst 14:1281-1433, 1954

(50) ———: The Unseen Fight Against Cancer. Charlottesville, Va.: Batt Bates & Co., 1975

(51) STEWART HL, LORENZ E: Induction of adenocarcinoma of the pyloric stomach in mice by methylcholanthrene. J Natl Cancer Inst 2:193-196, 1941

(52) ———: Adenocarcinoma of the pyloric stomach and other gastric neoplasms in mice induced with carcinogenic hydrocarbons. J Natl Cancer Inst 3:175-189, 1942

(53) MORRIS HP, WAGNER BP, RAY FE, et al: Comparative study of cancer and other lesions of rats fed *N,N'*-2,7-fluorenylenebisacetamide or *N*-2-fluorenylacetamide. Natl Cancer Inst Monogr 5:1-53, 1961

(54) SNELL KC, STEWART HL, MORRIS HP, et al: Atrophy, proliferative lesions, and tumors of the salivary glands of rat ingesting *N*-2-fluorenylacetamide or *N,N'*-2,7-fluorenylenebisacetamide. Natl Cancer Inst Monogr 5:55-83, 1961

(55) ———: Intracranial neurilemmoma and medulloblastoma induced in rats by the dietary administration of *N,N'*-2,7-fluorenylenebisacetamide. Natl Cancer Inst Monogr 5:85-103, 1961

(56) STEWART HL, SNELL KC, MORRIS HP, et al: Carcinoma of the

glandular stomach of rats ingesting *N,N'*-2,7-fluorenylenebisacetamide. Natl Cancer Inst Monogr 5:105-139, 1961

(*57*) SUGIMURA T, FUJIMURA S: Tumour production in glandular stomach of rat by *N*-methyl-*N'*-nitro-*N*-nitrosoguanidine. Nature 216: 943-944, 1967

(*58*) MARSHINO O: Dr. Floyd C. Turner, 1889-1960 (obit.). J Natl Cancer Inst 24:1239-1240, 1960

(*59*) TURNER FC: Experimental chemotherapy of tumors in mice. J Natl Cancer Inst 4:265-270, 1943

(*60*) ———: Sarcomas at sites of subcutaneously implanted bakelite disks in rats. J Natl Cancer Inst 2:81-83, 1941

(*61*) LEITER J, SHIMKIN MB, SHEAR MJ: Production of subcutaneous sarcomas in mice with tars extracted from atmospheric dusts. J Natl Cancer Inst 3:155-166, 1942

(*62*) SHIMKIN MB: Pulmonary tumors in experimental animals. Adv Cancer Res 3:223-267, 1955

(*63*) GRADY HG, STEWART HL: Histogenesis of induced pulmonary tumors in strain A mice. Am J Pathol 16:417-432, 1940

(*64*) STEWART HL: Roger W. O'Gara, 1915-1971 (obit.). J Natl Cancer Inst 46:vii-x, June 1971

(*65*) Anonymous: Carl Voegtlin, 1879-1960 (obit.). J Natl Cancer Inst 25:v-xv, Oct. 1960

(*66*) VOEGTLIN C, JOHNSON JM, DYER HA: Quantitative estimation of the reducing power of normal and cancer tissue. J Pharmacol Exp Ther 24:305-334, 1924

(*67*) VOEGTLIN C, THOMPSON JW: Glutathione content of tumor animals. J Biol Chem 70:801-806, 1926

(*68*) Donner Foundation: Index to the Literature of Experimental Cancer Research 1900-1935. Lancaster, Pa.: Wickersham Printing Co., 1948

(*69*) JOHNSON JM: Glutamic acid from normal and cancerous tissue. J Natl Cancer Inst 1:113-117, 1940

(*70*) CHALKLEY HW: Method for the quantitative morphologic analysis of tissues. J Natl Cancer Inst 4:47-53, 1943

(*71*) EARLE WR: Glenn Horner Algire, 1907-1958 (obit.). J Natl Cancer Inst 21:iii-vi, Sept. 1958

(*72*) ALGIRE GH, CHALKLEY HW: Vascular reactions of normal and malignant tissues in vitro. I. Vascular reactions of mice to wounds and to normal and neoplastic transplants. J Natl Cancer Inst 6:73-85, 1945

(*73*) CHALKLEY HW: Herbert Kahler, 1896-1962 (obit.). J Natl Cancer Inst 29:v-viii, Aug. 1962

(*74*) KAHLER H: Apparatus for milking mice. J Natl Cancer Inst 2:457-458, 1942

(*75*) KAHLER H, BRYAN WR: Ultracentrifugal studies of some complexes obtained from mouse milk, mammary tumor, and other tissues. J Natl Cancer Inst 4:37-45, 1943

(*76*) HETHERINGTON DC: Wilton Robinson Earle, 1902-1964 (obit.). J Natl Cancer Inst 35:iii-xiii, Sept. 1965

(*77*) EARLE WR: Production of malignancy in vitro. I. Method of cleaning glass ware. J Natl Cancer Inst 4:131-133, 1943

(*78*) ———: Production of malignancy in vitro. II. Photomicrographic equipment. J Natl Cancer Inst 4:135-145, 1943

(*79*) ———: Production of malignancy in vitro. III. Microcinematographic equipment. J Natl Cancer Inst 4:147-164, 1943

(*80*) ———: Production of malignancy in vitro. IV. The mouse fibroblast cultures and changes seen in the living cells. J Natl Cancer Inst 4:165-212, 1943

(*81*) EARLE WR, NETTLESHIP A: Production of malignancy in vitro. V. Results of injections of cultures into mice. J Natl Cancer Inst 4:213-248, 1943

(*82*) EARLE WR, SHELTON E, SCHILLING EL: Production of malignancy in vitro. XI. Further results from reinjection of in vitro cell strains into strain C3H mice. J Natl Cancer Inst 10:1105-1113, 1950

(*83*) EAGLE H: Metabolic studies with normal and malignant human cells in culture. Harvey Lect 54:156-175, 1958

(*84*) MAVER ME, DUNN TB: Catheptic activities of neoplasms and of the tissues of normal and tumor-bearing mice correlated with histologic changes. J Natl Cancer Inst 6:49-60, 1945

(*85*) DYER HM: Comparison of the patterns of excretion and the carcinogenicity in the rat of 2-acetylaminofluorene and related compounds. J Natl Cancer Inst 16:11-30, 1955

(*86*) ———: An Index of Tumor Chemotherapy. Washington, D.C.: Public Health Service, March 1949

(*87*) DEKRUIF P: Men Against Death. New York: Curtis Publishing Co., 1927

(*88*) SPENCER RR, MELROY MB: Effect of carcinogens on small free-living organisms. I. *Eberthella typhi*. J Natl Cancer Inst 1:129-134, 1940

(*89*) ———: Effect of carcinogens on small organisms. IV. Exposure of bacteria to high temperatures. J Natl Cancer Inst 3:1-5, 1942

(*90*) MARSHINO O: Research Fellows of the National Cancer Institute, Jan. 1, 1938-April 1, 1958 (Public Health Serv Publ No. 658). Washington, D.C.: U.S. Govt Print Off, 1959

(*91*) WINITZ M, SOBER HA, PRICE VE, et al: Jesse Philip Greenstein, 1902-1959 (obit.). J Natl Cancer Inst 24:vii-xxx, Jan. 1960

(*92*) GREENSTEIN JP: Biochemistry of Cancer, 1st ed. New York: Academic Press, 1948

(*93*) ———: Biochemistry of Cancer, 2d ed. New York: Academic Press, 1954

(*94*) GREENSTEIN JP, JENRETTE WV, WHITE J: The liver catalase activity of tumor-bearing rats and the effect of extirpation of the tumors. J Natl Cancer Inst 2:283-291, 1941

(*95*) WHITE J, MIDER GB, HESTON WE: Effect of amino acids on the induction of leukemia in mice. J Natl Cancer Inst 4:409-411, 1944

(*96*) WHITE J, ANDERVONT HB: Effect of a diet relatively low in cystine on the production of spontaneous mammary-gland tumors in strain C3H female mice. J Natl Cancer Inst 3:449-451, 1943

(*97*) MORRIS HP: Some nutritional factors influencing the origin and development of cancer. J Natl Cancer Inst 6:1-17, 1945

(*98*) ———: Development, biochemistry and biology of experimental hepatomas. Adv Cancer Res 9:227-302, 1965

(*99*) BURK D, SPRINCE H, SPANGLER JM, et al: The metabolism of chicken tumors. J Natl Cancer Inst 2:201-240, 1941

(*100*) WINZLER RJ, BURK D: Blood proteose and cancer. J Natl Cancer Inst 4:417-428, 1944

(*101*) ROBERTSON WVB: Ascorbic acid content of tumors and homologous normal tissues. J Natl Cancer Inst 4:321-328, 1943

(*102*) SHACK J: Cytochrome oxidase and *d*-amino acid oxidase in tumor tissue. J Natl Cancer Inst 3:389-395, 1942

(*103*) HESTON WE: Lung tumors and heredity. I. The susceptibility of four inbred strains of mice and their hybrids to pulmonary tumors induced by subcutaneous injection. J Natl Cancer Inst 1:105-111, 1940

(*104*) ———: Genetics of cancer. Adv Genet 2:99-128, 1948

(*105*) Committee Appointed by the Surgeon-General: Report: Fundamental Cancer Research. Public Health Rep 53:2121-2130 and J Natl Cancer Inst 19:317-325, 1957

(*106*) National Cancer Institute Staff: A Symposium on Mammary Tumors in Mice. Washington, D.C: American Association for the Advancement of Science, 1945

(*107*) BRYAN WR, BEARD JW: Studies on the purification and properties of the rabbit papilloma-virus-protein. J Natl Cancer Inst 1:607-671, 1941

(*108*) BRYAN WR: Biological studies on the Rous sarcoma virus. J Natl Cancer Inst 16:285-335, 1955

(*109*) SHIMKIN MB, ANDERVONT HB: Comparative carcinogenicity of three carcinogenic hydrocarbons. J Natl Cancer Inst 1:57-62, 1940

(*110*) BEARD JW, GROUPÉ V, MOLONEY JB: William Ray Bryan, 1905-1976 (obit.). J Natl Cancer Inst 57:231-232, 1976

(*111*) HARTWELL JL: Survey of Compounds Which Have Been Tested for Carcinogenic Activity, 2d ed. Washington, D.C.: U.S. Public Health Service, 1951

(*112*) BLUM HF, KIRBY-SMITH JS, GRADY HG: Quantitative induction of tumors in mice with ultraviolet radiation. J Natl Cancer Inst 2:259-268, 1941

(*113*) BLUM HF: Carcinogenesis by Ultraviolet Light. Princeton: Princeton Univ Press, 1959

(*114*) MIDER GB, MORTON JJ: Relative importance of local and constitutional effects of methylcholanthrene in production of skin tumors in the mouse. J Natl Cancer Inst 1:41-44, 1940

(*115*) EDWARDS JE: Hepatomas in mice induced with carbon tetrachloride. J Natl Cancer Inst 2:197-199, 1941

(*116*) DALTON AJ, EDWARDS JE: Mitochondria and Golgi apparatus of induced and spontaneous hepatomas in the mouse. J Natl Cancer Inst 2:565-575, 1942

(*117*) CHANEY DM, MURPHY MK: Editorial history of the *Journal of the National Cancer Institute*. J Natl cancer Inst 26:785-799, 1961

(*118*) Journal of the National Cancer Institute: Cumulated Index 1940-1956, 1957

(*119*) RHOADS CP, chairman: Conference on gastric cancer. J Natl Cancer Inst 5:311-382, 1945
(*120*) BRUNSCHWIG A, chairman: Conference on gastric cancer. J Natl Cancer Inst 7:299-424, 1947
(*121*) DYER HM, KELLY M, DUNN TB: Effect of administration of hot water, acids, alkali, mecholyl chloride, or atropine sulfate upon the gastric mucosa of mice. J Natl Cancer Inst 7:67-70, 1946
(*122*) MORRIS HP, LARSEN CD, LIPPINCOTT SW: Effects of feeding heated lard to rats with a histologic description of the lesions observed. J Natl Cancer Inst 4:285-303, 1943
(*123*) BREYERE EJ: Morris Karlynn Barrett, 1900-1967 (obit.). J Natl Cancer Inst 40:iii-vii, April 1968
(*124*) BARRETT MK: Avenues of approach to the gastric cancer problem. J Natl Cancer Inst 7:127-157, 1946
(*125*) GOVER M: Cancer Mortality in the United States (PHS Bull No. 248, 252, 275). Washington, D.C.: U.S. Govt Print Off, 1939, 1940, 1941
(*126*) DORN HF: Illness from cancer in the United States. Public Health Rep 59:33-48, 1944
(*127*) HAENSZEL W: Harold F. Dorn, 1906-1963 (obit.). Natl Cancer Inst Monogr 19:vii-xi, 1966
(*128*) COWIE DB, SCHEELE LA: A survey of radiation protection in hospitals. J Natl Cancer Inst 1:767-787, 1941
(*129*) HAWKINS JW: Evaluation of breast cancer therapy as a guide to control programs. J Natl Cancer Inst 4:445-460, 1944
(*130*) HENSHAW PS, HAWKINS JW: Incidence of leukemia in physicians. J Natl Cancer Inst 4:339-346, 1944
(*131*) ROSE JE, SWAIN R: Remote-controlled radium emanation plant and automatic measuring apparatus for gold implants. J Natl Cancer Inst 10:605-623, 1949
(*132*) ACKERMAN LV, DEL REGATO JA: Cancer Diagnosis, Treatment, Prognosis. St. Louis: C.V. Mosby, 1947
(*133*) SHIMKIN MB, ZON L: Absorption of subcutaneously implanted pellets of diethylstilbestrol in man. J Natl Cancer Inst 3:367-370, 1943
(*134*) WOGLOM WH: Immunity to transplantable tumors. Cancer Rev 4:129-247, 1929
(*135*) ———: General review of cancer therapy. *In* Approaches to Tumor Chemotherapy (Moulton FR, ed). Washington, D.C.: American Association for the Advancement of Science, 1947
(*136*) HIRSCHEN F: Yamagiwa's tar cancer and its historical significance. Gann 59:447-451, 1968
(*137*) TRIOLO VA, RIEGEL IL: The American Association for Cancer Research, 1907-1940. Historical review. Cancer Res 21:137-167, 1595-1596, 1961
(*138*) SWAIN DC: The rise of a research empire: NIH, 1930 to 1950. Science 138:1233-1237, 1962
(*139*) DREW EB: The health syndicate—Washington's noble conspirators. Atlantic Monthly Dec:75-82, 1967
(*140*) SHAUGHNESSY DF: A history of the American Cancer Society. Thesis. New York: Columbia Univ, 1955
(*141*) KAISER RF, PETERSON RI: Activities of the Field Investigations and Demonstrations Branch. J Natl Cancer Inst 19:259-274, 1957
(*142*) ANDERVONT HB: Fate of the C3H milk influence in mice of strains C and C57 black. J Natl Cancer Inst 5:383-390, 1945
(*143*) SHIMKIN MB, GRADY HG, ANDERVONT HB: Induction of testicular tumors and other effects of stilbestrol-cholesterol pellets in strain C mice. J Natl Cancer Inst 2:65-80, 1941
(*144*) SHIMKIN MB, WYMAN RS: Effect of adrenalectomy and ovariectomy on mammary carcinogenesis in strain C3H mice. J Natl Cancer Inst 6:187-189, 1945
(*145*) HESTON WE, DERINGER MK: Relationship between the lethal yellow (A^y) gene of the mouse and susceptibility to spontaneous pulmonary tumors. J Natl Cancer Inst 7:463-465, 1947
(*146*) MEISTER A: Acylpyruvase activity of certain normal and neoplastic tissues. J Natl Cancer Inst 9:125-127, 1948
(*147*) LORENZ E, HESTON WE, ESCHENBRENNER HB, et al: Biological studies in the tolerance range. Radiology 49:274-285, 1947
(*148*) KAPLAN HS: Comparative susceptibility of the lymphoid tissues of strain C57 black mice to the induction of lymphoid tumors by irradiation. J Natl Cancer Inst 8:191-197, 1948
(*149*) NETTLESHIP A, HENSHAW PS: Induction of pulmonary tumors in mice with ethyl carbamate (urethan). J Natl Cancer Inst 4:309-319, 1943
(*150*) ESCHENBRENNER AB: Induction of hepatomas in mice by repeated oral administration of chloroform, with observations on sex differences. J Natl Cancer Inst 5:251-255, 1945
(*151*) ESCHENBRENNER AB, MILLER E: Liver necrosis and the induction of carbon tetrachloride hepatomas in strain A mice. J Natl Cancer Inst 6:325-341, 1946
(*152*) ———: Quantitative histologic analysis of the effect of X radiation on the interstitial tissue of the testes of LAF_2 mice. J Natl Cancer Inst 6:343-348, 1946
(*153*) SANFORD KK, EARLE WR, LIKELY GD: The growth in vitro of single isolated tissue cells. J Natl Cancer Inst 9:229-246, 1948
(*154*) EARLE WR, EVANS VJ, SCHILLING EL: Extension of cellophane substrate procedure to growth of in vitro cultures of large areas. J Natl Cancer Inst 10:943-967, 1950
(*155*) EARLE WR, SCHILLING EL, SHANNON JE JR: Growth of animal tissue cells on three-dimensional substrates. J Natl Cancer Inst 12:179-193, 1951
(*156*) WHITE FR, WHITE J: Effect of low lysine diet on mammary tumor formation in strain C3H mice. J Natl Cancer Inst 5:41-42, 1944
(*157*) MORRIS HP, DUNN TB, DUBNIK CS: Two transplantable rat carcinomas induced with *N*-acetyl-2-aminofluorene. J Natl Cancer Inst 9:225-228, 1948
(*158*) LARSEN CD: Survey of hypnotics in general with regard to pulmonary tumor induction in mice. J Natl Cancer Inst 7:5-8, 1946
(*159*) ———: Evaluation of the carcinogenicity of a series of esters of carbamic acid. J Natl Cancer Inst 8:99-101, 1947
(*160*) ———: Pulmonary tumor induction by transplacental exposure to methane. J Natl Cancer Inst 8:63-70, 1947
(*161*) SHEAR MJ, HARTWELL JL, PETERS VB, et al: Some aspects of a joint institutional research program on chemotherapy of cancer: Current laboratory and clinical experiments with bacterial polysaccharide and with synthetic organic compounds. *In* Approaches to Tumor Chemotherapy (Moulton FR, ed). Washington, D.C.: American Association for the Advancement of Science, 1947, pp 236-284
(*162*) HARTWELL JL: Reactions of bis (2-chloroethyl) sulfide (mustard gas) and some of its derivatives with proteins and amino acids. J Natl Cancer Inst 6:319-324, 1946
(*163*) Endocrine-Cancer Conference: Hotel Traymore, Atlantic City, June 5-6, 1942. Cancer Res 2:722-733, 1942
(*164*) MOULTON FR, ed: AAAS Research Conference on Cancer. Washington, D.C.: American Association for the Advancement of Science, 1945
(*165*) ———: Approaches to Tumor Chemotherapy. Washington, D.C.: American Association for the Advancement of Science, 1947
(*166*) Anonymous: Science 120: 1009-1010, 1954
(*167*) Laboratory of Pathology: Ross Clayton MacCardle, B.Sc., Ph.D., D.Sc. (Hon.), 1901-1964 (obit.). J Natl Cancer Inst 33:593-597, 1964
(*168*) KAISER RF, BOUSER MM, INGRAHAM SC, et al: Uterine cytology. Public Health Rep 75:423-427, 1960
(*169*) DUNN JE, SLATE TA, MERRITT JW, et al: Finding for uterine cancer from one or more cytologic examinations of 33,750 women. J Natl Cancer Inst 23:507-527, 1959
(*170*) DORN HF, CUTLER SJ: Morbidity from cancer in the United States. Public Health Monogr No. 56. Washington, D.C.: U.S. Govt Print Off, 1959
(*171*) GILLIAM AG: Note on evidence relating to the incidence of primary liver cancer among the Bantu. J Natl Cancer Inst 15:195-199, 1955
(*172*) SMITH RL: Recorded and expected mortality among the Japanese of the United States and Hawaii, with special reference to cancer. J Natl Cancer Inst 17:459-474, 1956
(*173*) HUEPER WC: Occupational Tumors and Allied Diseases. Springfield, Ill.: Thomas, 1942
(*174*) ———: Experimental studies in metal carcinogenesis. J Natl Cancer Inst 13:291-305, 1952; 15:113-129, 1954; 16:55-73, 1955; 16:447-467, 1955
(*175*) WAGONER JK, ANDLER VI, CARROLL BE, et al: Cancer mortality patterns among U.S. uranium miners and millers, 1950 through 1962. J Natl Cancer Inst 32:787-801, 1964
(*176*) Anonymous: Evaluation of cancer diagnostic tests. J Natl Cancer Inst 18:269-339, 1957
(*177*) SMITH RR, HUEBNER RJ, ROWE WP, et al: Studies on the use of viruses in the treatment of carcinoma of the cervix. Cancer 9:1211-1218, 1956

(178) SMITH RR, HILBERG AW: Cancer cell seeding of operative wounds. J Natl Cancer Inst 16:645-657, 1955

(179) FREI E III, HOLLAND JF, SCHNEIDERMAN MA, et al: A comparative study of two regimens of combination chemotherapy in acute leukemia. Blood 13:1126-1148, 1958

(180) LI MC, HERTZ R, SPENCER DB: Effect of methotrexate therapy upon choriocarcinoma and chorioadenoma. Proc Soc Exp Biol Med 93:361-366, 1956

(181) HERTZ R, LEWIS J, LIPSETT MB: Five years' experience with the chemotherapy of metastatic choriocarcinoma and related trophoblastic tumors in woman. Am J Obstet Gynecol 82:631-640, 1961

(182) HUGGINS C: Delbert Mauritz Bergenstal, 1917-1959 (obit.). J Natl Cancer Inst 23:iii-vi, Nov. 1959

(183) BERGENSTAL DM, LIPSETT MB, MOY RH, et al: Regression of adrenal cancer and suppression of adrenal function in man by o, p'-DDD. Trans Assoc Am Physicians 2:341-350, 1959

(184) ENDICOTT KM: The chemotherapy program. J Natl Cancer Inst 19:275-294, 1957

(185) ZUBROD CG, SCHEPARTZ S, LESTER J, et al: The chemotherapy program at the National Cancer Institute—history, analysis, and plans. Cancer Chemother Rep 50:349-540, 1966

(186) SHIMKIN MB, MOORE GE: Adjuvant use of chemotherapy in the surgical treatment of cancer. JAMA 167:1710-1714, 1958

(187) SHIMKIN MB: End-results of cancer: Introductory remarks. *In* Proceedings of Third National Cancer Conference. Philadelphia: J. B. Lippincott, 1957

(188) ANDERVONT HB, EDGCOMB JH: Responses of seven inbred strains of mice to percutaneous applications of 3-methylcholanthrene. J Natl Cancer Inst 17:481-495, 1956

(189) ANDERVONT HB, SHIMKIN MB, CANTER HY: Effect of discontinued estrogenic stimulation upon the development and growth of testicular tumors in mice. J Natl Cancer Inst 18:1-25, 1957

(190) DUNN TB, HESTON WE, DERINGER MK: Subcutaneous fibrosarcomas in strains C3H and C57BL female mice, and F_1 and backcross hybrids of these strains. J Natl Cancer Inst 17:639-647, 1956

(191) HESTON WE, DUNN TB: Tumor development in susceptible strain A and resistant strain L lung transplants in LAF_1 hosts. J Natl Cancer Inst 11:1057-1071, 1951

(192) LAW LW: Effect of gonadectomy and adrenalectomy on the appearance and incidence of spontaneous lymphoid leukemia in C58 mice. J Natl Cancer Inst 8:157-159, 1947

(193) GROSS L: Oncogenic Viruses, 2d ed. New York: Pergamon, 1970

(194) STEWART SE: Neoplasms in mice inoculated with cell-free extracts or filtrates of leukemic mouse tissue. I. Neoplasms of the parotid and adrenal glands. J Natl Cancer Inst 15:1391-1415, 1955

(195) STEWART SE, EDDY BE: Tumor induction by SE polyoma virus and the inhibition of tumors by specific neutralizing antibodies. Am J Public Health 49:1493-1496, 1959

(196) LAW LW: Recent advances in experimental leukemia research. Cancer Res 14:695-709, 1954

(197) GROUPÉ V, RAUSCHER FJ JR, LEVINE AS, et al: The brain of newly hatched chicks as a host-virus system for biological studies on the Rous sarcoma virus (RSV). J Natl Cancer Inst 16:865-875, 1956

(198) PERRY VP, SANFORD KK, EVANS VJ, et al: Establishment of clones of epithelial cells from human skin. J Natl Cancer Inst 18:709-717, 1957

(199) MERWIN RM, ALGIRE GH: The role of graft and host vessels in the vascularization of grafts of normal and neoplastic tissues. J Natl Cancer Inst 17:23-31, 1956

(200) PREHN RT, MAIN JM: Immunity to methylcholanthrene-induced sarcomas. J Natl Cancer Inst 18:769-778, 1957

(201) MAVER ME, GRECO AE: The purification and properties of desoxyribonuclease and ribonuclease from normal and neoplastic tissues. J Natl Cancer Inst 17:503-516, 1956

(202) WESTFALL BB, EVANS VJ, PEPPERS EV, et al: Effect of gentamine on the growth and metabolism of liver cells in vitro. J Natl Cancer Inst 17:131-138, 1956

(203) WEISBURGER JH, WEISBURGER EK, MORRIS HP: Urinary metabolites of the carcinogen *N*-2-fluorenylacetamide. J Natl Cancer Inst 17:345-361, 1956

(204) HOGEBOOM GH, SCHNEIDER WC: Intracellular distribution of enzymes. VIII. The distribution of diphosphopyridine nucleotide-cytochrome C reductase in normal mouse liver and mouse hepatoma. J Natl Cancer Inst 10:983-987, 1950

(205) SCHNEIDER WC: George Hall Hogeboom, 1913-1956 (obit.). J Natl Cancer Inst 17:iii-ix, Nov. 1956

(206) KELLY MG, HARTWELL JL: The biological effects and the chemical composition of podophyllin. A review. J Natl Cancer Inst 14:967-1010, 1954

(207) GOLDIN A, VENDETTI JM, HUMPHREYS SR, et al: Modification of treatment schedules in the management of advanced mouse leukemia with amethopterin. J Natl Cancer Inst 17:203-212, 1956

(208) Committee on Growth, National Research Council: Annual Reports to American Cancer Society. New York: American Cancer Society, 1945-56

(209) WEAVER HM: Support of cancer research by the American Cancer Society. J Med Educ 31:4-31, 1956

(210) DORN HF: Tobacco consumption and mortality from cancer and other diseases. Public Health Rep 74:581-593, 1959

(211) Advisory Committee to the Surgeon General: Smoking and Health. Washington, D.C.: U.S. Govt Print Off, 1964

(212) STRONG FM, BING RJ, DYER RE, et al: Smoking and health. Joint report of the study group on smoking and health. Science 125:1129-1133, 1957

(213) Commemorative Symposium: J Natl Cancer Inst 19:133-349, 1957

(214) SHIMKIN MB: Science and Cancer, 2d rev. Washington, D.C.: U.S. Govt Print Off, 1973