Recent Progress in Cancer Research

By JOHN R. HELLER, JR., M.D.

THE MANY recent advances in cancer research make possible the cure of more cancers today than 20 years ago. Unless the cancer is far advanced, modern surgery or radiation, or a combination of the two, now offers the patient a greater opportunity for survival. There is also a better outlook for patients with advanced cancer who may be beyond the hope of permanent cure. New palliative measures have been developed which may prolong lives in comfort and increase their usefulness. All of this is possible even though knowledge of the etiology of cancer is slight, and an all-purpose cure for cancer's many forms is lacking.

The fact that one can regard cancer in such an encouraging light is highly significant, for the concerted attack against it is relatively new. Modern cancer research goes back about 50 years, but only since the end of World War II have significant sums of money been available for this purpose. Support and coordination of research are now being provided on an unprecedented scale, and many of the ablest investigators in the Nation are teamed in an effort to conquer cancer.

Nonetheless, cancer poses a dilemma which few other diseases can match. It is a complex public health problem because in cancer we are dealing not with a single disease, but with many diseases. The more data that are accumulated in the research laboratories, the more there appears to be learned about the cancerous process, its growth, and its control. The multitude of new approaches that have come to light seem to branch out into an almost infinite number of ideas. There appears to be an endless amount of knowledge which can be accumulated about cancer.

The vastness and diversity of cancer research can be illustrated by reviewing some of the many approaches employed by cancer investigators.

Basic Research

A large part of cancer research is devoted to basic studies which increase understanding of the carcinogenic process and tumor development. Advances in basic research come slowly and seldom make headlines, but they are vital to the search for better methods in diagnosis, control, and therapy. The advances noted here by no means cover the entire field of basic research, but rather illustrate the kind of original work being done in laboratories of this country.

Among the advances in the basic biological sciences are those which have emerged from tissue culture laboratories. An important contribution which will make possible more effective use of tissue culture in the study of both normal and cancer cells is the three-dimensional tissue culture technique developed by Earle and his associates at the Public Health Service's National Cancer Institute (*1*). These scientists have grown massive cultures of tissue cells in the interstices of three-dimensional masses made up of thousands of glass rings. Many

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applications for this technique are foreseeable. Already it has been applied in collaborative studies with the Naval Medical Research Institute to obtain large cultures of human epithelial cells for skin grafting purposes.

A new technique for growing cancer cells outside the body in the form of recognizable tissues has been developed by Leighton of the National Cancer Institute (*2*). His sponge matrix method for tissue culture employs an ordinary cellulose sponge as the skeleton on which the cancer cells are grown. Cells grown in this way form organized aggregates which frequently resemble the tissue pattern present in the living animal. This method has been used to grow many animal tumors and at least two human tumors, a malignant melanoma and a chondrosarcoma. The melanoma grew very well and produced new pigment within the sponge. The sponge-grown tissue can be sectioned, stained, and studied with the same methods used in examining tissues from the body. This technique for tissue culture might be used to study the direct effects of drugs, hormones, or radiations on neoplastic tissues or to study the factors, and perhaps the patterns, involved in tumor growth and metastases.

A valuable tool for the study of carcinogenesis, tumor development, and related problems has been developed at Yale University by Greene, who has transplanted human tumors to the brains of mice and guinea pigs (*3*). With the exception of brain neoplasms, however, only tumors which had metastasized were transplantable. Human tumors were grown in mice for 70 to 90 days before the mice died. In guinea pigs the tumors grew for as long as 90 to 100 days.

A new medium for the growth of malignant tumor tissue which conceivably may be applied to problems of human cancer has been discovered by Lutz at Boston University (*4*). He has used the cheek pouch of the hamster as a site for the growth of neoplastic tissue, both homologous and heterologous, under conditions in which frequent observation and exact measurements can be carried on for long periods. Human tumors and tumors from the rat, mouse, guinea pig, and frog have been grown by this means.

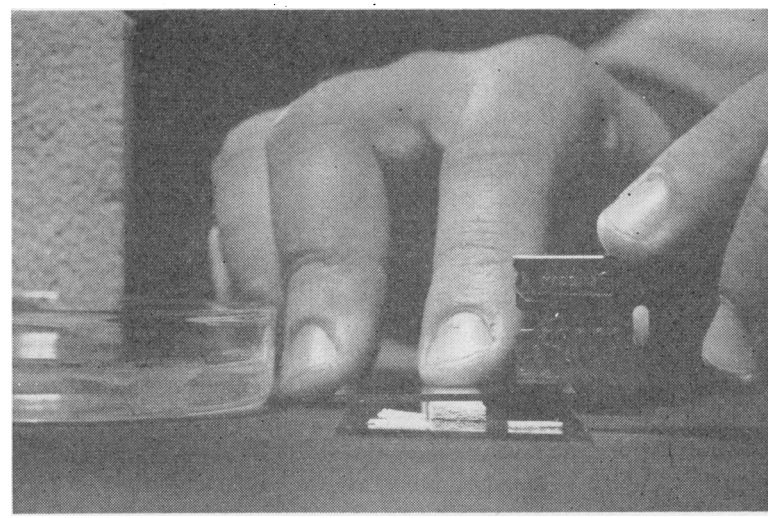
Among the recent basic studies relating cancer to prolonged hormonal imbalance are those of Morris and his associates at the National Cancer Institute. These investigators have recently developed transplantable cancers of the thyroid gland of mice following the ingestion of thiouracil, a goiter-producing drug which inhibits the secretion of thyroxin (*5*). These cancers, when growing in normal animals, provide valuable material for experimental research dealing with problems of thyroid cancer and hormonal imbalances, and aid in the search for improved methods of using radioactive iodine in the treatment of thyroid cancer in man.

Tools for the development of cancer therapeutic measures have been provided by the chemical-screening projects conducted at the Memorial Hospital for Cancer and Allied Diseases, the National Cancer Institute, and other laboratories. Shear and his associates at the National Cancer Institute have tested more than 3,000 chemicals for tumor-damaging ability (*6*). About 500 have been found to damage sarcoma, 37 in mice following a single injection of a near-lethal dose. It must be emphasized that these compounds are not yet clinically useful, but they provide a stockpile from which it may be possible to develop drugs to treat cancers of man. It is essential that chemicals with some potential ability to affect the growth of cancer be tested thoroughly on experimental animals before they are made available for clinical trial. Screening itself is only the beginning of a chemotherapy program; it must be followed by systematic and extensive pharmacological research.

Clinical Research

In addition to advances in basic research, cancer investigators have reported encouraging progress in the search for improved methods in treatment and diagnosis.

The treatment of cancer, once limited to the use of surgery and radiation, has been expanded to include anticancer drugs, hormones, and radioactive isotopes (*7*). Although the cure of cancer still remains with surgery and radiation, these new agents are valuable additions to the therapeutic program. Perhaps progress should not be measured entirely by cure, as Steiner of the University of Chicago has pointed out, for this criterion fails to give credit to palliation



The first step in the sponge matrix method for tissue culture, developed at the National Cancer Institute. With an ordinary razor blade, thin slices are cut from narrow strips of sponge; then the slices are washed, sterilized, and placed in test tubes to receive implantations of tissue.

(*8*). In his words, "Enormous and gratifying progress has been made in prolonging life in usefulness and comfort by chemotherapeutic, endocrinological, surgical, and radiological palliative measures," and "research that results in better palliation is significant because of the possibility that by becoming very slightly more effective it will be curative."

Surgery

In the field of surgery there has been a remarkable series of refinements and improvements. Radical surgery has emerged as an important development. Knowledge of the physiological limits of surgery has become more exact. As a result, a great variety of cases that were hitherto considered inoperable and hopeless may now undergo surgery with good chances of survival.

One example of the concept of more radical surgery is seen in a review of the old and the new techniques employed in breast cancer. Previously, the mastectomy removed little more than the breast and the armpit lymph nodes. The surgical concept was enlarged because in numerous instances it was seen that the cancerous lesion spread after surgery. Following extensive research, which revealed that the lymph nodes under the ribs frequently harbor cancer cells, breast surgery began to involve the removal of more bony structure and the lymph nodes under the ribs in properly selected cases.

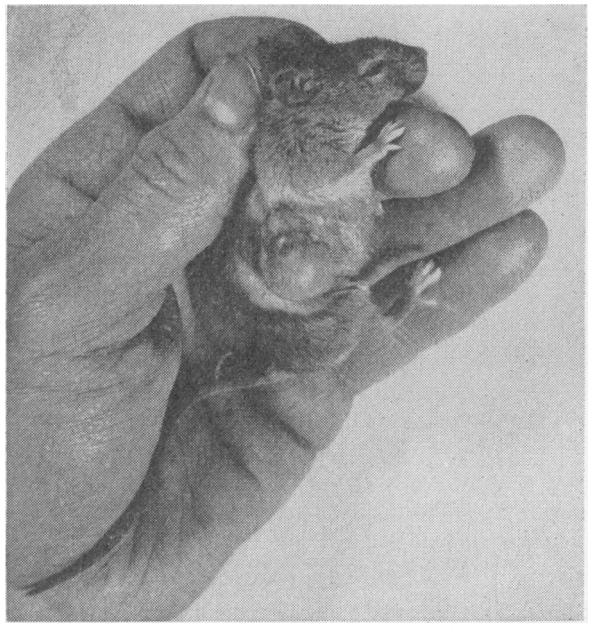
Many factors other than better operative techniques are also contributing to the continuing improvements in cancer surgery. Among these are better preoperative and postoperative care, better anesthesia, control of infection by antibiotics and chemotherapy, and control of shock by transfusions.

Radiation

In recent years the comparative advantages of surgery and radiation have been under intensive study, and the question of when to operate and when to irradiate is now better understood. At the same time, numerous technical advances have been made in radiation therapy. In addition to radium, radon, and medium voltage X-ray machines, the radiologist has at his disposal supervoltage X-ray generators, new types of radiation from the betatron and the cyclotron, and a number of new radioactive substances for use in treatment.

Among other advances in the field of radiation, progress has been made in controlling or avoiding radiation burns and radiation sickness. Investigating the problem of radiation sickness, scientists at a number of laboratories are seeking ways to modify lethal irradiation injuries. In collaborative studies with the Argonne National Laboratory of the University of Chicago, Lorenz and his associates at the National Cancer Institute have discovered that intravenous or intraperitoneal injections of bone marrow into mice and guinea pigs enable from 70 to 100 percent of the animals to survive acute lethal doses of irradiation (*9*). These discoveries may prove valuable in the irradia-

The large tumor on the mouse's flank is a transplant from one of a number of thyroid cancers produced experimentally in mice. The transplantable thyroid cancers provide a valuable new tool for cancer research.



tion treatment of cancer and in improving survival chances following lethal amounts of irradiation, as in atomic warfare.

In the treatment of cancer, the byproducts of atomic research called radioisotopes continue to exhibit increasing utility. Radioactive iodine has been used with good results in some cases of inoperable cancer of the thyroid. Phosphorus and sodium are used in whole body radiation; gallium, in bone tumors. Radioactive phosphorus is used in the treatment of polycythemia vera and certain chronic leukemias; gold is used in cancer and peritoneal and pleural carcinomatosis, and bromine in bladder tumors.

The use of most of these radioactive isotopes requires further experimentation. Better means must be found for localizing many of the isotopes within the cancerous areas, and more effort must be expended in developing radioactive compounds with a high degree of tumor specificity.

Radioactive cobalt appears to show some promise as a substitute for radium. More abundant than radium, radioactive cobalt is relatively inexpensive and will be available through the Atomic Energy Commission to both general practitioners and specialists who meet AEC standards. Cobalt can be handled more easily than radium and can be fashioned into various pliable shapes, thereby permitting the radiologist greater flexibility in applying dosages.

It must be emphasized that radium therapy is not going out of use. Radium still plays a tremendously important role in cancer therapy throughout the world. Through the radium loan program of the National Cancer Institute alone, 56 hospitals (in 29 States and the District of Columbia) are employing this type of therapy. Early in 1952, Roosevelt Hospital in New York City unveiled a new converging beam projector radium therapy unit. The projector, weighing 5 tons and using 50 grams of radium, has the power of a 20-million-volt X-ray machine. Radium therapy units such as this and the high voltage X-ray machines now in use offer hope for the cancer patient. With these, it is possible to reach cancers which are not amenable to other radiation therapy or for which surgery offers a low cure rate. Such units are designed to increase the effect of radiation therapy on deep-seated tumors.

Anticancer Drugs

Although their present clinical importance should not be overemphasized, one of the most encouraging aspects of cancer therapy is the rapid development of new chemical agents. None has achieved the status of a cancer cure. But it can now be said, in contrast to the dismal outlook of 15 or 20 years ago, that chemotherapy has been established as a valuable and sound adjunct to surgery and radiation.

Some anticancer drugs have had wide clinical trial. Nitrogen mustards given intravenously have produced temporary remissions in patients with Hodgkin's disease, lymphosarcoma, chronic leukemias, and mycosis fungoids. Triethylene melamine, a newer agent, has produced similar effects in Hodgkin's disease, lymphosarcoma, chronic leukemias, and neuroblastoma when administered by mouth. A drug formerly used as an anesthetic for laboratory animals, urethane (ethyl carbamate) has been found useful in the treatment of some chronic leukemias and multiple myelomas. In the treatment of acute leukemia in children, the

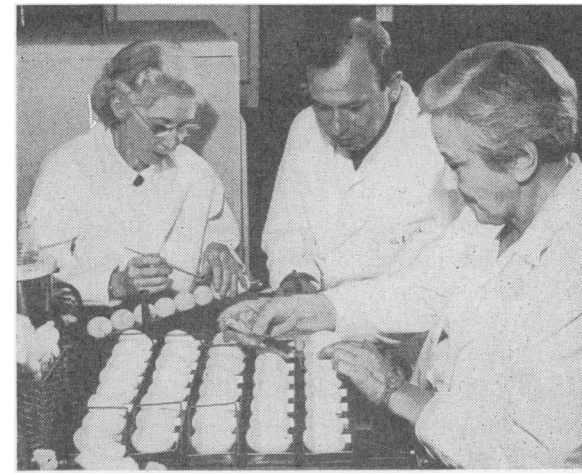
folic acid antagonists, notably aminopterin and amethopterin, have caused temporary clinical improvements. Among other drugs showing promise in the treatment of leukemia, there is a new compound, GT–41 or 1,4-dimethyl sulfonyl butane. Temporary remissions in chronic myelogenous leukemia have been obtained through the use of GT–41, Dr. Alexander Haddow of the Chester Beatty Research Institute, London, reported at the Second National Cancer Conference in Cincinnati during March 1952.

A technique for intra-arterial chemotherapy which may become a valuable auxiliary to surgery and radiation in treating cancer has been developed by Bierman at the National Cancer Institute's Laboratory of Experimental Oncology, San Francisco, and by Klopp at George Washington University, Washington, D. C. This technique uses specially designed catheters to inject drugs into close contact with the cancers, lessening damage to normal tissues (*10*). Administration of agents by the intra-arterial route appears to be quicker and to produce results of longer duration than intravenous injections. Recently there have been successful attempts to employ chemotherapeutic measures to prepare apparently inoperable cancer patients for surgery. Klopp and his collaborators have reported that aureomycin given intra-arterially or intravenously permitted surgery on several cancer patients whose lesions could ordinarily be considered inoperable.

Hormones

Huggins of the University of Chicago was among the first to demonstrate that induced imbalances of hormones might have marked effects on some types of neoplastic disease. He observed remissions in the growth of prostatic cancer following castration and administration of estrogenic substances. Correlative work on carcinoma of the breast by many investigators in the United States and in foreign countries has indicated that the general principles developed by Huggins may obtain in certain cases of mammary cancer. Unfortunately, the beneficial effects of hormones seem to be temporary to the majority of subjects, but there is hope that present studies will lay the groundwork for hormonal cure of certain specific cancers.

Measuring the toxicity of tumor-damaging drugs by injecting them into eggs and observing the effect on chick embryos, one of the early steps in the development of possible anticancer drugs.



Hertz and Cromer have used hormones to prepare patients for surgery (*11*). Observing the effect of progesterone on carcinoma of the cervix, they found that regressive alterations of the tumor occurred in 11 of 17 cases and that only one patient showed actual tumor progression while under progesterone therapy. More recently, Hertz has been giving intensive doses of a water-soluble form of estrogen to persons with breast and prostatic cancer. Administered intravenously and subcutaneously, these large doses are well tolerated by the body and are reported to be highly effective in activating estrogen therapy. This new technique is under study to see whether it may be more useful than other types of estrogen therapy.

Research on Diagnosis

Because the curability of cancer is closely related to early diagnosis, the problem of finding a good screening test is an urgent one. An ideal solution would be the development of a blood test like the Wassermann—a test which can be applied on a mass basis at reasonable cost and which is specific enough to identify a high percentage of cancer cases at an early stage. At present there is no such general cancer test. Many new tests have been developed and evaluated, but as yet none has been found which is sufficiently sensitive and specific to be practicable.

However, the approach seems hopeful. It is known, for instance, that there are changes in the body chemistry of cancer patients. For example, in some patients with prostatic cancer the acid phosphatase level is increased. Much effort is being expended in this area of research. Among the approaches are physical and chemical analyses of the body fluids, development of certain immunological reactions and many enzymological procedures, and the use of radioactive tracers.

Although a useful general test appears to be still in the future, some of the specific tests show definite promise. One of the most useful is the cytologic examination developed by Papanicolaou of Cornell University Medical College. Briefly, this test consists of collecting exfoliated cells—by aspiration or scraping—from a hollow part of the body; then placing the cells on a glass slide and examining them for possible cancer. The method is particularly useful as an aid to the diagnosis of cancer of the uterine cervix. In the past few years many qualified persons have been trained in the techniques of this test and the interpretation of its results, and at the present time some practitioners are routinely employing this screening procedure in cervical cancer diagnoses.

Although this test is theoretically applicable to any of the body excretions, further experimentation is necessary to determine its general use. From the standpoint of accuracy, the method is applied at present with greatest success in the diagnosis of cancer of the uterine cervix and the lung.

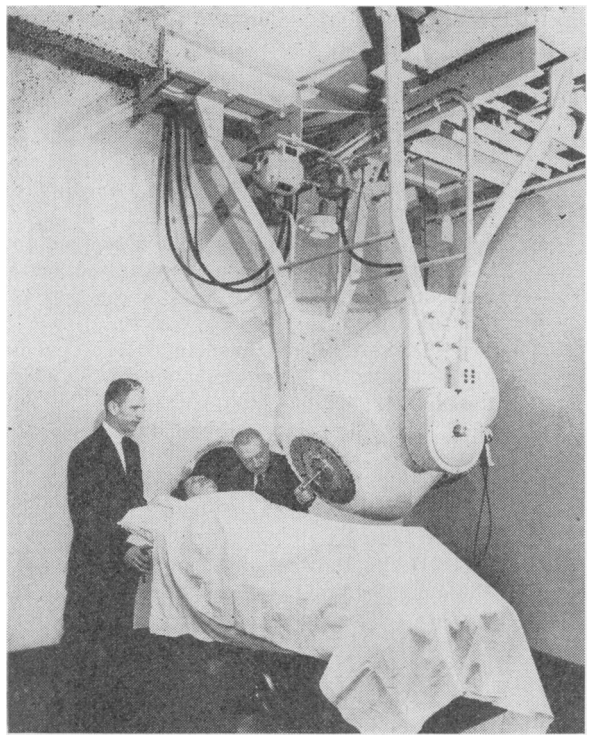
Cancer of the uterine cervix is of great clinical importance. The uterus is the second most frequent site of cancer in the female, and in that organ the disease occurs most frequently in the cervix. Cancer of the uterine cervix is reported to be 75 percent curable in the early stage and 15 percent when moderately well advanced. To determine the case-finding possibilities of the cytologic method in cancer of the uterine cervix, a 3-year study is under way in Memphis and Shelby County, Tenn., in which all women 20 years of age and older will be given an opportunity to have cytologic examinations for uterine cancer at yearly intervals. Supported by grants-in-aid from the National Cancer Institute, this project is being conducted with the cooperation of the Memphis and Shelby County Medical Society, the Memphis and Shelby County Health Department, the Department of Obstetrics and Gynecology and the Institute of Pathology of the University of Tennessee College of Medicine, and the Memphis Division of the American Cancer Society. (See *Public Health Reports*, June 1952, frontispiece.) Further studies in this field will be done in the cytology laboratory which the National Cancer Institute will operate in the Public Health Service's new Clinical Center at the National Institutes of Health, Bethesda, Md.

Variations of the original cytologic technique have been developed for the diagnosis of cancer of other sites. An abrasive balloon technique has been used with some success in the detection of gastric carcinoma. In this technique the balloon, covered by a fine, silk mesh, is inserted in the stomach, inflated, deflated, and withdrawn. The stomach debris which clings to the mesh of the balloon is examined with a microscope for cancer cells. Although this new diagnostic tool shows considerable promise when used in conjunction with X-ray, it requires further evaluation.

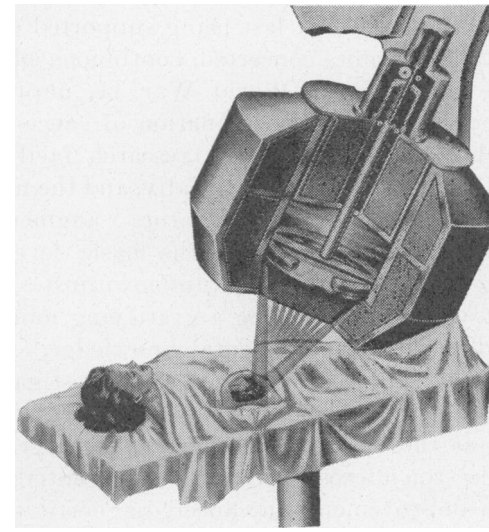
Gastric cancer is the first-ranking cause of cancer deaths among men. The development of a good diagnostic procedure for this type of cancer is essential since conventional methods discover only about one-fifth of the cases at an early stage. Toward this end, Traut and Rosenthal of the University of California have developed another new technique. It consists of washing the patient's stomach with a solution of papain, an enzyme which dissolves the mucus on the stomach lining and thereby frees cancer cells trapped by the mucus.

In the X-ray field at least two tools have been developed which aid the early detection of gastric cancer. Morgan at Johns Hopkins University has adapted the Schmidt camera to photofluorography for mass screening to discover gastric cancer. Moon at the University of Chicago has developed a device which combines X-ray and television equipment to give sharp, clear pictures of the dense parts of a patient's body.

Atomic energy research has provided still another approach to cancer diagnosis, that is, the use of radioisotopes as tracers to localize tumorous tissues. The use of isotopes in can-



The new converging beam projector radium therapy unit at the Roosevelt Hospital in New York City.



cer diagnosis rests upon the fact that certain abnormal body tissues concentrate large amounts of specific compounds above that of normal tissues. When these compounds are tagged with radioisotopes, the tissues which require the greatest amount of the compounds can be located with the aid of a Geiger or scintillation counter. Several isotopes appear to be of value in diagnosing cancers of various sites. Of the radioactive isotopes which have been used in their elementary form as diagnostic tracers, the best known is radioactive iodine for the diagnosis of metastatic cancers of the thyroid. Diiodofluorescein dye tagged with iodine has been used successfully in the localization of brain tumors, as has human serum albumin tagged with iodine. Phosphorus has been used with limited success in the diagnosis of cancers of the brain, breast, and testicle.

Cancer Morbidity Studies

The search for a diagnostic test has received much assistance from the rapidly developing field of cancer epidemiology. A number of studies and surveys relating to cancer morbidity and mortality have been conducted which may provide the answers to such questions as: How many people have cancer? How many can expect to get cancer? What sites in the body are most frequently attacked by cancer? How are age, sex, and race associated with specific cancer sites?

Dorn and his associates at the National Cancer Institute have prepared a series of cancer morbidity studies based on data for 1947–48 and covering 10 major metropolitan areas: Atlanta, New Orleans, Birmingham, Dallas, San Francisco, Denver, Detroit, Chicago, Pittsburgh, and Philadelphia. These studies are particularly valuable since they present comparative data over a 10-year period, each of the areas having been surveyed in 1937–39. Following publication of reports on the individual areas, a United States summary will be prepared. This summary will contain geographic comparisons, interpretations of apparent national trends, and special analyses which are not feasible for individual areas. In general, the studies re-emphasize the importance of the varied programs directed toward achieving early diagnosis and treatment.

Summary of Progress

Cancer progress has many aspects. One is the drastic and wholesome change in public attitudes. Another important change is that cancer research is at last being supported on a scale that permits concerted, continuous effort. Since the close of World War II, unprecedented support and coordination of cancer research have been provided, research facilities have been increased substantially, and the number of research investigators augmented greatly. Investigation at the basic level is being pursued to an extent unknown just a few short years ago, yielding a gratifying number of advances in fundamental knowledge. The armamentarium of the research investigators has been strengthened by the addition of tools such as the cyclotron, the mass spectrograph, the electron microscope, and the ultracentrifuge. With improvements in cancer diagnostic techniques have come increases in cancer clinics and other facilities for diagnosis and treatment. Cancer surgery has been refined and improved, technical advances in radiation therapy have been achieved, and chemotherapy has been established as a sound adjunct to both. Research has added much information on carcinogens and carcinogenesis which may be useful in the prevention of cancer.

It is doubtful that anyone would venture to say how close we may be to solving the cancer problem. It is a complex and serious one and we must prepare for a long and costly effort. Although false hope must not be placed on preliminary reports and unsubstantiated claims, recent progress indicates that cancer can be regarded as a practical, scientific problem which science can solve—and will solve.

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