Some Advances in Clinical Practice

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It is indeed a pleasure to be here on this auspicious occasion and to speak on the clinical aspects of the cancer program. I think one might begin by saying that five years is the conventional period required to evaluate any program in cancer, and it is not quite five years since passage of the act. It is in the nature of biomedical research that the fruits we recognize today have many of their roots much more than five years ago. Nevertheless, there have been a number of significant changes in clinical practice and clinical viewpoints during the past five years, and collectively I do not think these can be divorced from the National Cancer Program under the 1971 legislation. Indeed, it is reasonable to feel that without this federal support many, and probably most of them, would have been further delayed.

One of the anomalies of the cancer program is that the focus of treatment is still surgery, yet most of the research is going forward in the nonsurgical fields. Probably the fastest moving field in recent years has been chemotherapy. Five years ago the treatment of acute lymphatic leukemia in children was already well advanced through the efforts of Sidney Farber and many others. Methotrexate had been demonstrated to be curative in a large percentage of patients with chorionepithelioma and had been tried successfully in Burkitt's lymphoma in Africa.

The treatment of Hodgkin's disease was advancing but much of the experience with the modern methods developed and emphasized, particularly by Dr. Henry Kaplan at Stanford, has gone forward during the past five years. We now know that the results of combined therapy in Hodgkin's disease are incomparably better than anything we knew about at the time I received my medical education and for many years thereafter. Just how good these are remains to be determined because of the long follow-up necessary. It would appear that with combined therapy the vast majority of Hodgkin's patients will live over five years and there is reason to believe that many of them can be kept in health for a major part of their life expectancy, if not all of it.

Combined therapy has played an ever increasing role in Wilm's tumor, with increases in five year survival from the 30 to 40 percent with surgery alone, to the 50 or 60 percent with surgery plus radiation, and to the 70 to 80 percent with surgery, radiation plus chemotherapy.

The results in neuroblastoma are closely related to the age of onset; the earlier the age, the better the results. Some good results have been obtained with surgery alone, but again combined therapy has improved them. A more recent triumph has been in osteogenic sarcoma, where high doses of methotrexate with citrovorum rescue as advocated by Djerassi and demonstrated by Frei and his colleagues at the Sidney
Farber Center have paid off. It is still too soon to know exactly what percentage of people suffering from this condition will survive five years, or what their ultimate fate will be. Multiple myeloma and rhabdomyosarcoma have likewise been responsive and more recently granulocytic leukemia has begun to respond.

All of these conditions are by and large highly cellular, rapidly growing tumors and most of them have in the past brought early death, commonly within a year or two.

Turning to the field of radiology, we have a few advances in therapy. Some years ago Churchill Davidson in England put special stress on the low oxygen concentration at the center of tumors and emphasized the degree to which this impaired the effect of radiation. He applied hyperbaric oxygenation in the belief that he could soak the tissues in oxygen sufficiently to increase the sensitivity of the malignant cells to radiation. He was so convinced of this thesis that he felt it unjustifiable to run a control series. Had a randomized series been done, his results might have been far more convincing.

Another approach to the radiation treatment of cells at low oxygen tension is the use of fast neutrons. Their effect is less influenced by oxygen tension than is the effect of x-rays. Fast neutrons have been generated by cyclotrons, a number of which are available from earlier experiments in high energy physics. They can also be generated by the deuterium tritium technique advocated and developed by Dr. James T. Brennan at the University of Pennsylvania. The latter technique requires much less expensive apparatus, but generates only one degree of intensity of radiation (about 14 megavolts). Dr. Brennan was able to increase the number of neutrons generated by using a double source of ions beamed on a common target. In this way the intensity of the beam was sufficient to keep the treatments within acceptable time limits.

Those generators which depend on cyclotrons are more versatile in that they can be adjusted to produce rays of varying degrees of intensity and, depending on the size of the cyclotron, the flux can be varied more widely also. In spite of the promising leads, fast neutron radiation has not come into wide use. Perhaps its best known trial has been at Hammersmith under the direction of Dr. Mary Catterall. She has applied it especially to tumors of the head and neck, and certainly a number of her results have been impressive. Her current randomized series had not run long enough to draw definitive conclusions when last I heard her report.

Radiology has contributed more in diagnosis, perhaps, than in therapy. Here again, we are dealing with a steady advance, rather than with anything that began in 1971. In 1963, David Kuhl published [1,2] his studies on the application of computer technology to tomography. He had entered into conversations with a manufacturer of X-ray equipment to produce the apparatus commercially, but the final decision of that company was negative. In 1972 Godfrey Hounsfield [3], a British engineer, persuaded the EMI organization in Great Britain to build such an apparatus, which resulted in the EMI scanner. This new method for diagnosis of intracranial lesions, including tumors, has swept the civilized world.

The enlargement of this apparatus to accommodate the whole body has followed rapidly and several such units are now in place in various major cities in the United States. They produce a series of sections through the body showing the relative density of different tissues, including bone, and the relations of these shadows to each other. Computerized axial tomography is a major advance in radiologic diagnosis. Dr. Kuhl has worked on the application of computer technology to the analysis of signals from radioactive isotopes and further developments may be expected.

During the past five years the use of radioactive isotopes in diagnosis has been extended. The use of the isotope Iodine$^{131}$ and also Iodine$^{125}$ in the diagnosis of goiter
is now widespread. Radioactive Gallium has been used both in the diagnosis of tumors and in the diagnosis of hidden abscesses. Strontium\(^{99}\) has been used in the study of bone tumors, including metastases, but now seems to be getting displaced a good deal by Technetium\(^{99}\).

The introduction of opaque media by differential arterial catheterization has advanced, and the interpretation of the angiographs obtained by these techniques has been further refined. This has been particularly useful in the pancreas where the best scanning material, radioactive selenomethionine, has proved to be a rather crude indicator of pancreatic tumors.

One of the fields in which X-ray has been used increasingly in diagnosis is mammography. Twenty-eight centers have been set up, supported in part by the National Cancer Institute and in part by the American Cancer Society, for the diagnosis of early breast cancer. This trial has been reasonably productive. A small, but definite percentage of patients examined has shown signs suggestive of carcinoma. This has led to a large number of biopsies, some 20% of which have revealed carcinoma. Of the carcinomas discovered in this way, less than 25% have had axillary metastases in those cases in which the axillary contents were removed and submitted for histologic examination. This compares with 50 to 55% of cases with positive axillary nodes in most previous series. Since there has been a high degree of correlation between negative axillary nodes and five-year survival, it is reasonable to believe that a considerable saving of life has been accomplished in this way.

In the course of these studies it was noted that the mammogram was much more useful in women over the age of 50 than in the younger age group and increasing concern has arisen regarding the possible carcinogenic influence of the radiation. Alarm in this matter was touched off by a long-term follow up of women who had had tuberculosis earlier in life treated by pneumothorax with radiologic control. In a group of such women it was found that the incidence of breast cancer was five or six times as high in the breast on the side where the pneumothorax had been as in the other breast. This difference was attributed to the increased radiation. In light of these data and other data, the National Cancer Institute withdrew its recommendation to continue regular screening mammography in asymptomatic women under 50 and is now concentrating on women over 50.

Another form of radiation which has been utilized to some extent by radiologists, and to some extent by surgeons, is heat. Radiation of heat from the body surface has been measured with accurate instruments and plotted. The principal application has been in the breast and the resulting plot has been described as a thermogram. In general, just as inflammation is accompanied by rubor and calor, so increased infrared radiation will be found not only around abscesses, areas of infection, but also around tumors. If one can exclude infection on clinical grounds, then concentrations of infrared radiation suggest tumor formation and particularly the formation of malignant tumors. In practice thermography has been quite confusing to the average clinician and in general, even the radiologists do not like to rely upon it as the sole indication for biopsy. Many of them, however, do use it as an indicator for earlier repetition of mammography.

My own attitude toward it is a rather negative one, though my good friend, Dr. Philip Hodes, when he was Chairman of the Department of Radiology at Jefferson Medical School, had a number of examples in which it had been helpful in diagnosis and at least one rather convincing one in which it appeared that the diagnosis would have been missed for a period of time without it. The phenomenon underlying it is an interesting one, namely the increased blood flow elicited by malignant tumors.
Dr. Dale Coman years ago while transplanting tumors in rodents, took infrared photographs and found that within two hours of such a transplant increased infrared radiation was commonly measurable. Indeed, if increased infrared radiation did not appear in a reasonably short time, the tumor implant generally did not take. This phenomenon has been studied in a much more detailed way in recent years by Dr. Judah Folkman, now the Chief of Surgery at the Boston Children's Hospital. He has observed the phenomenon in a number of different ways and has sought an agent which accounts for the increased ingrowth of capillaries which a malignant tumor seems able to command from the host. He observed that if the implant was simply transplanted into an isolated organ maintained by perfusion, the implant would only grow to a very small size (I believe 2 or 3 millimeters), and then remain stationary because there was no angiogenesis. The viability of the implant could be proved by transplanting it to an intact host, where it would elicit a vascular response and begin to grow. He has, of course, been seeking ways of inhibiting this vascular response in the hope that human tumors likewise could be kept stationary. To my knowledge this quest has not as yet resulted in methods which are useful in the clinical field.

While the margin of the tumors seems supplied with abundant blood vessels and it is common to see increased radiation from such areas, the reverse is the case in the center of the tumor where the vascular supply is commonly deficient. Dr. Harry LeVeen [4], of the Downstate Medical Center of the University of the State of New York, has taken advantage of this in the following way: he has generated heat in the tissues by the application of controlled electromagnetic waves at a rate which they can be carried off by the normal circulation. Thus, a sufficient flux to generate a temperature of 104°F Fahrenheit in normal tissues is at times accompanied by the generation of temperatures of 110°F to 118°F in the inside of tumor masses. Such temperatures maintained for an appropriate time are followed by necrosis and absorption of the products of the necrosis with a reduction in the size of the tumor. The patients reported who had received this treatment were, as one would expect, advanced cases with metastases and poor prognosis. Dr. LeVeen was encouraged by the shrinkage of some of the tumors, and by the absence of living cells found in the tumors of patients who came to autopsy or who had nodules removed surgically after being shrunk. So far, however, survivals have, for the most part, been brief and the trials too short for general evaluation.

Turning now to the field of immunotherapy, there have been interesting observations by Hellstrom and Hellstrom at Seattle on blocking antibodies, particularly in patients with melanoma. In one striking case, followed by Dr. Ingegard Hellstrom, the antibodies which blocked tumor cells in culture from being attacked by patients' lymphocytes suddenly disappeared, with the subsequent destruction of the tumor cells in vitro by the lymphocytes. At the same time the subcutaneous nodules of the patient stopped growing and regressed. This seemed to be a clear-cut instance in which, for reasons unknown, the formation of blocking antibodies was interrupted, and the body's cellular immune system rapidly reduced the tumor.

Various efforts have been made to augment the patient's immune response. Most successful has been the use of BCG injected intrasessionally in cutaneous and subcutaneous melanoma metastases. This has led to regression in many instances. C-Parvum has similarly been used to stimulate an immune response.

Immunotherapy has been combined with other modes of therapy and increasingly, tests are being carried out to test the immune response of the individual with cancer. General anergy, or a lack of immune response, seems to be a sign that the tumor is likely not to respond to therapeutic efforts.
Another use of immune reactions has been in diagnosis where much work has gone on with CEA (carcinoembryonic antigen), described at McGill University in Montreal by Gold and Freedman, as a diagnostic marker of colon carcinoma. These authors recognized that this antigen might be positive in certain other malignant tumors, such as carcinoma of the pancreas. An extensive study was organized by the American Cancer Society and the Canadian Cancer Society. The results were largely disappointing. However, the method is of some use in determining prognosis. The main objective to using it in screening is that it is more regularly positive in advanced tumors, and infrequently positive in early tumors.

The fact that this particular marker to which Dr. Cole and I both addressed considerable attention a few years ago proved less valuable than we had hoped does not mean that some other immunologic marker may not be discovered which will be of far greater use in the early diagnosis of cancer. The immunologic methods are so sensitive that extremely small amounts of characteristic substances can often be identified, particularly by radioimmunoassay.

As I have already said, there has been comparatively little recent cancer research support in surgery, even though most primary tumors are treated surgically, and most five year survivors of cancer have been operated upon as their primary treatment. In spite of this, our perception of the role of surgical excision in cancer treatment has undergone far-reaching and fundamental change, and much of this has occurred in the past five years. The classical rationale for surgical treatment of tumors was to operate when they were small so as to remove them entirely before they had spread. To this end, a large area of surrounding tissue which appeared normal was removed for insurance and in recognition of the fact that tumors often extended microscopically considerably beyond changes visible to the naked eye.

It followed that if a tumor had metastasized, it was not worthwhile to operate on it beyond doing a biopsy to confirm the diagnosis and to permit the pathologist to render a prognosis or make the observation on the basis of which others might present a prognosis.

While many minds have run in the same channel, my own thinking on this subject was accelerated by the request to deliver the Ewing Lecture at the Maui Meeting of the James Ewing Society in 1974. I was impressed in that year with a number of cases of cancer which acted peculiarly. There was the young woman with breast cancer who developed bone metastases in her second post operative year, yet was surviving and at work ten years after her operation with the help of oophorectomy, radiation to areas of pain, and chemotherapy. She is still alive, though she now has a left supravacuicular mass and another in the right parietal region. Another patient with a breast carcinoma went fourteen years without a sign of difficulty only to develop a skin recurrence above the medial end of her mastectomy scar.

Such experiences seem best explained by a capacity for resistance which enables the body to hold microscopic and other metastases in check for long periods of time. Accordingly, I asked our tumor registry to look up the cases in which I had personally done mastectomy for breast carcinoma and obtained the following data:

—The five year results were about the same as had been achieved in many other series.
—The incidence of axillary node involvement was 55%.
—The average age of the patient was 54 years.

Those patients who had been followed ten years, however, showed that about as large a proportion of the five year survivors had died in the second five years as had succumbed in the first five years. We have not, I regret to say, tracked these down to
establish how many died of other causes. The fact that the series was five years older, however, would be insufficient to explain a large part of the fall-off. Such information strongly suggests that much of the so-called "early breast cancer" is really not early, that the removal of the primary tumor adjusts the tumor-host relationship in favor of the host, that the five year survival is a relatively poor index of cure in breast carcinoma, as it has long been known to be in thyroid carcinoma, and that surgery is to be thought of more as a means of assisting the body's natural resistance to malignant cells than as a method of completely extirpating a tumor before any of the cells have spread elsewhere.

If this is indeed the case, one questions the value of the ultraradical procedures, but one questions even more the rationale of doing nothing once a distant metastasis has been revealed. During the past five years adjuvant therapy with chemotherapeutic agents has been tested by the Eastern Cooperative Oncology Group (Dr. Bernard Fisher, Chairman) and by Dr. Bonnadonna in Milan, Italy. Dr. Fisher utilized a single agent at a relatively low dosage which made it more acceptable to patients and physicians. Patients received L-PAM every six weeks for more than a year. Bonnadonna used three drugs: Cytoxan, Methotrexate and 5-Fluourouracil. He pushed the dose often to the limit of tolerance. Both series, Fisher's at two years and Bonnadonna's at 18 months, show a far lower incidence of early recurrence than controls. It is still premature to predict how these series will turn out; it seems reasonable to hope that there will be an overall extension of survival as counted in the average number of months per hundred patients.

Questions which are not answered are how great the survival will be, how long it will last, how the patients will react to other forms of therapy if recurrence supervenes, and finally, whether the known carcinogenic actions of some of the drugs involved will become manifest with the appearance of other tumors in the late survivors. Currently, both series have been quite limited to patients with proven axillary metastasis. The results of these studies are that surgeons are less convinced that much is gained by a full radical mastectomy as compared with a modified radical mastectomy, which leaves a large part or all of the pectoral muscles intact. Some physicians question whether the lymph nodes should be removed. This is certainly necessary for staging, and common sense would hardly lead one to leave them behind since most of them are so easily accessible and since they comprise so small a fraction of the total lymphatic apparatus of the body.

There is now a deep interest in the interrelationship of nutrition and cancer. This has several aspects. There is a possibility that some types of food may contain carcinogens that initiate and/or promote the growth of cancers. That foods can do this seems almost certain from animal experiments. Thus, aflatoxins occurring in decaying nuts are potent carcinogens. Likewise some of the Nitroso compounds will produce nearly a 100% incidence of carcinoma in appropriate strains of rodents following a single administration of the chemical.

The overall relation of general nutrition to tumor formation is more difficult to evaluate. It is believed that there is more breast carcinoma among individuals who are obese; it is known from animal experiments that a tumor-bearing animal will live longer than its controls if starved. This experiment has recently been repeated with refinements by Dr. Jeffrey Oram-Smith [5], using controlled intravenous nutrition in the rat. The tumor-bearing rat does better if it is given amino acids and abundant calories in the form of glucose even though the rate of growth of the tumor is slightly increased. If it is given the amino acids without glucose, the host dies of starvation while the tumor grows rapidly. On the other hand, Dr. Edward M. Copeland and
associates [6] in approaching the problem of the patient undergoing intensive anti-cancer treatment, has found intravenous nutritive support helpful. He has related this to the cellular immune response of the individual, referring back to the paper of Law, Dudrick and Abdou [7], in which cellular immune response was augmented by intravenous hyperalimentation in a series of patients not necessarily harboring cancer. In Copeland's series of patients, six had positive response to at least one test for cellular immunity before the onset of treatment. Of the other eleven who were anergic, all but four converted so that at least one of their tests became positive following intravenous hyperalimentation. All of the positive responses to chemotherapy in this series occurred among the patients who had a positive test for cellular immunity before the onset of the treatment or afterwards.

In summary, the cancer program has had important and far reaching effects on clinical practice. These are most obvious in the field of chemotherapy where some eleven tumors, formerly almost uniformly fatal, have been shown to respond either to chemotherapy alone or to combined therapy. In the field of radiation therapy there have been gains on the equipment front, and there have been exploratory experiments with the use of heat induced differentially within tumors, and there have been very important advances in radiologic diagnosis, particularly in the field of computerized axial tomography. In immunotherapy there has been much questing and a fair demonstration of the usefulness of BCG in cutaneous metastases of melanoma.

In surgery there have been no more than modest gains in surgical technique. There continue to be strong gains in supportive therapy which have permitted some further extension of the scope of surgery. Most importantly, however, there has been a profound change in our thinking concerning the role of surgery in the treatment of cancer and its interrelation with other forms of treatment. There has been an increasing recognition of the role of large tumor masses on the one hand, and of their removal, on the other hand. Thus, surgeons are less and less concerned about the tumor being operable, meaning that it has not spread, and increasingly of the view that it is often worthwhile to debulk a tumor in the hope of enhancing the effectiveness of other treatments such as chemotherapy.

Thank you.

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