Improving the Therapeutic Index in Breast Cancer Treatment: The Richard and Hinda Rosenthal Foundation Award Lecture

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Abstract

Improving the relationship between desired and undesired effects of therapy, the therapeutic index, is a major goal of cancer therapy. Clinical research pertinent to breast cancer treatment attempting to manipulate this therapeutic index is not restricted to studies in patients. Described herein is research in humans, mouse, machine, marrow, and molecule, concerned with either increasing care or decreasing treatment complications.

Molecular studies use $^{125}$I-tamoxifen as a specific cytotoxic agent for cells which contain estrogen receptors able to bind the agent and transport it into the nucleus where the limited range radiations are cytotoxic. Murine bone marrow stem cells are heterogeneous as regards their self-renewal potential. Chemotherapeutic agents used in the adjuvant treatment of breast cancer have different effects on these cells. L-Phenylalanine mustard is toxic to the most primitive stem cells and produces a permanent stem cell self-renewal deficit when given to mice in an "adjuvant" setting. Cyclophosphamide and 5-fluorouracil act primarily on later stem cells and do not produce such proliferative limitations. Eliminating breast cancer while preserving normal structure and function is the goal of combining radiation therapy and tumor excision. Results with this technique are comparable to those following mastectomy without loss of the breast or chest musculature.

I am deeply honored in being awarded the Richard and Hinda Rosenthal Foundation Award for Clinical Research this year. Clinical research, in my opinion, must be considered in the broadest of terms. Obviously, it includes research projects with humans or human material as the subject. However, I believe that it should also include research suggested by clinical observations, even if the experiments themselves are performed in animals, on cells, or in test tubes. Clinical research is a vantage point, an orientation, a way of looking at problems. One brings clinical observations to the laboratory and laboratory implications to the clinic when they appear pertinent.

The purpose of clinical research in cancer is to improve the means of prevention, diagnosis, and treatment of malignant disease. In this discussion, I shall be concerned with improving the treatment of the disease. This may require understanding of the basic biology of normal tissues, understanding their alteration due to disease or due to treatment, developing new therapies, or improving old ones. Goodman and Gilman, in the Pharmacologic Basis of Therapeutics (16), describe the relationship between desired and undesired effects of therapy as the therapeutic index. In most circumstances, the therapeutic index between unacceptable damage to normal tissues and successful cure is small. Nowhere is this more so than in the treatment of malignant disease. The research I would like to describe is concerned with improving this therapeutic index. I should like to use as a model a number of different studies performed by my colleagues and me which can be focused on breast cancer, although the implications are more generally applicable.

Chart 1 shows the standard sigmoid dose-response relationships found when one plots the extent of therapy against any observed clinical effect, be it the likelihood for complications or the likelihood for cure. The purpose of treatment is to separate the curves. If they move together along the abscissa, little is gained. If the curves are separated, then one can either increase the cure for some accepted level of complication or decrease the complications for some accepted level of cure (3).
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Chart 1. Likelihood of tumor control or major complication as a function of dose of effective agent. This usually has a sigmoid shape. Complications are portrayed to occur at higher doses since unless this is the case the therapy is not usually accepted.

I would like to describe examples of clinical research pertinent to breast cancer done by my colleagues and myself in humans, mouse, machine, marrow, and molecule attempting to manipulate this therapeutic index for both types of gain.

Molecule

To begin with the molecule, an obvious way to gain a therapeutic advantage is by increasing the specificity by which toxic agents can be delivered to tumor cells as compared to normal cells. In search for such drugs, we look for specific qualities of tumor cells as compared to normal cells which will allow a differential effect. Originally, tumor cells were thought to proliferate more rapidly than normal cells, and so drugs which interfered with the process of cell proliferation were used. Such drugs have had a useful place in cancer chemotherapy. Attempts to look at differences in the metabolism of tumor cells versus normal cells have also been of value. We have chosen a somewhat different tack. It is well known that many breast cancers contain high levels of estrogen receptors. Although such receptors have been identified in a variety of other tissues, they are relatively deficient in the usual dose-limiting normal tissues (the bone marrow or gastrointestinal mucosa). Thus, it seemed possible that a molecule which bound to the estrogen receptor might allow some specificity. The mechanism by which steroid sex hormones appear to affect the cell involve specific binding to receptors of high affinity and low capacity (27). Once formed, the specific receptor-steroid complex is translocated from the cytoplasm to the nucleus of target cells. My colleagues, William Bloomer, Glenn Tonnesen, Ralph Weichselbaum, and James Adelstein and I are attempting to use this system as a way of delivering very-short-range radiation to the DNA of tumor cells. Labeling with nuclear components. This is presumably due to the release of many low-energy electrons and X-rays of very short range; e.g., in the halogenated pyrimidine iododeoxyuridine is quite cytotoxic but only when incorporated into DNA as shown by Bloomer and Adelstein (1). Tamoxifen, a nonsteroidal antiestrogen, competes with estradiol for the estrogen receptor protein and is translocated into the nucleus (23). Carrier-free 125I-tamoxifen, was made and tested against an in vitro line of human breast cancer cells (MCF-7) which contain biologically active estrogen receptors (4). The effect of the drug on this cell line was compared to V-79 Chinese hamster cells which are relatively deficient in receptors. The specific cytoplasmic receptor levels for MCF-7 and V-79 cells were 60 and 4 fmol/mg of protein, respectively. The cellular uptake of 125I-tamoxifen by both the MCF-7 and V-79 cells is a direct function of media concentration. The linear relationship observed between cellular uptake and media concentration suggests that the entry of 125I-tamoxifen into the cells occurs by passive diffusion. It is identical for both cell lines. In contrast, Chart 2 shows the toxicity of 125I-tamoxifen or sodium [125I]iodide. 125I-tamoxifen was differentially cytotoxic to MCF-7 cells. At the highest levels of radioactivity tested, there was a 2-decade difference in survival fraction between the 2 cell lines. In contrast, no radio toxicity was noted with sodium iodide at equal doses. Sodium iodide is effectively excluded from both cell lines and remains in the extracellular space. Finally, nonradioactive 127I-tamoxifen and tamoxifen itself were nontoxic when tested at levels comparable to the 125I-tamoxifen. From these studies, we can conclude that this drug is differentially cytotoxic for cells containing estrogen receptor. We speculate that the marked cytotoxicity in MCF-7 cells results from the close approximation of the 125I with the genetic apparatus as a result of the carrier molecule being translocated as a part of the receptor complex from cytoplasm to the nucleus. The minimum toxicity of 125I-tamoxifen on V-79 cells probably reflects transmitted cytoplasmic radiation effects while the nontoxicity of sodium [125I]iodide gives further evidence of the restricted range of the nuclide. These results, while limited to tissue culture, suggest a potential methodology for using hormones as diagnostic agents and carriers of radionuclides for therapeutic purposes. Such a technique could allow a significant increase in the therapeutic index.

Marrow and the Mouse

Now to the marrow and the mouse. The bone marrow is the dose-limiting normal tissue for many chemotherapeutic agents...
Therapeutic Index in Breast Cancer Treatment

SERIAL TRANSFER

Chart 3. CFUs per hind limb initially and at each passage (P) in control animals and at 15, 40, and 110 weeks after busulfan or L-PAM. D, day.

Chart 3 reveals that a permanent defect in serial transfer persisted throughout the life of the animals treated with 2 alkylating agents, busulfan and L-PAM. On the abscissa is the number of transfers; on the ordinate is the number of CFUs at 15, 40, and 110 weeks after drug. Thus, the defect persists more than 2 years or throughout the life of the animal. L-PAM is commonly utilized in the adjuvant therapy of breast cancer (14). Some other consequences of the drug used are listed in Table 1. A similar mechanism of stem cell failure in other cell renewal tissues may be the cause of the hair graying and possibly of cataract formation. The mechanism of leukemia and Harderian gland tumors is not clear. It is of interest, however, that only L-PAM caused these cancers, and in fact only at the lower dose. This stem cell-proliferative limitation has led us to describe a model of the stem cell shown in Chart 4. The model has 2 important elements: (a) the stem cell compartment is heterogeneous, being composed of cells of varying characteristics; and (b) cells move from left to right (17). The cells on the left are the most primitive with the

as well as for radiation. Short-term bone marrow aplasia is of less importance as we learn about platelet and granulocyte replacement. Ultimately, however, it is the hematopoietic stem cell which is of greatest concern. My colleagues, Leslie Botnick and Eileen Hannon and I did these studies to determine whether there was a limitation stem cell proliferation and, if so, whether this had implications for the long-term toxicity of drugs and X-rays.

Nowhere is long-term marrow toxicity more significant than in the consideration of the treatment of breast cancer. Not only is chemotherapy important in the palliative treatment of metastatic disease but more recently there is promise that adjuvant chemotherapy given to patients whose prognosis suggests a high risk of eventually developing metastasis may delay or perhaps prevent the appearance of these metastases (5, 14). Many of the agents used are known to affect the bone marrow.

Understanding the stem cells and how they respond to radiation and chemotherapeutic agents has been of long-standing interest of our laboratory. We attempted to simulate adjuvant chemotherapy using a murine model (6, 7). It has been well known that hematopoietic cells will not proliferate indefinitely when serially transplanted into irradiated syngeneic recipients (12, 34) even when a prolonged period is allowed between transfers (22, 32, 33). This suggests a limited proliferative capacity for hematopoietic stem cells, although other explanations may obtain (28). Even if the proliferative capacity of the stem cells is limited, the failure of this cell renewal system is rarely the cause of death in humans or mice; therefore, the system must have a proliferative capacity which far exceeds the life span of either species. We wondered, however, whether this would be the case when agents which killed stem cells were used in adjuvant fashion in patients for whom there was the likelihood of extended survival. A variety of chemotherapeutic agents was given to groups of mice in an “adjuvant fashion” to provide a temporary depression of some formed blood elements, but the animals recovered and their marrows morphologically returned to normal. As function of time after this, serial bone marrow transplantation was done, and the maximum marrow transfer time was determined as well as the number of stem cells produced as measured by the CFUs assay (35). Chart 3 reveals that a permanent defect in serial transfer persisted throughout the life of the animals treated with 2 alkylating agents, busulfan and L-PAM. On the abscissa is the number of transfers; on the ordinate is the number of CFUs at 15, 40, and 110 weeks after drug. Thus, the defect persists more than 2 years or throughout the life of the animal.

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The abbreviations used are: CFUs, spleen colony-forming units; L-PAM, L-phenylalanine mustard; ADC, agar-diffusion-chamber colonies.
cycle activity, and self-renewal capacity.

The stem cell compartment contains a heterogeneous population of cells varying in their commitment to differentiation, resting cell cycle activity, and self-renewal capacity.

<table>
<thead>
<tr>
<th></th>
<th>Premature graying (0-5 scale) (%)</th>
<th>Harderian gland tumors (%)</th>
<th>Leukemia (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Busulfan</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Low dose</td>
<td>8.9</td>
<td>0.29</td>
<td>0</td>
</tr>
<tr>
<td>High dose</td>
<td>94</td>
<td>3.5</td>
<td>0</td>
</tr>
<tr>
<td><strong>L-PAM</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Low dose</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>High dose</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td><strong>Cyclophosphamide</strong></td>
<td>0</td>
<td>0.26</td>
<td>0</td>
</tr>
<tr>
<td>5-Fluorouracil</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Control</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
</tbody>
</table>

Chart 4. Model of the stem cell compartment containing a heterogeneous population of cells varying in their commitment to differentiation, resting cell cycle activity, and self-renewal capacity.

The greatest self-renewal potential, the least commitment to differentiation and the least resting proliferative activity. As cells divide, on the average, they move to the right. They cannot move back even after time for recovery. This is a description then of the proliferative limitation on stem cells. A large series of experiments have been done to test this model and reconcile it with both the early and late consequences of drug treatment as well as bone marrow transplantation. Detailed descriptions of this are published elsewhere (6-8, 25). Suffice it to say that animals, as long as 2 years following busulfan, have stem cells which have a resting mitotic activity far greater than normal (25). Concomitant with this is a significant reduction in the number of CFUs produced in the marrow by a given number of CFUs administered. This is a measure of self-renewal potential. A limitation similar to that following busulfan and L-PAM was not seen following 5-fluorouracil or cyclophosphamide, 2 other drugs used frequently in the adjuvant treatment of breast cancer. In order to predict which drugs are potentially toxic to the more primitive stem cells, and thus may give rise to late stem cell failure, we have studied patterns of stem cell recovery measuring the CFUs and relative sensitivity of the CFUs as compared to ADC.3 The latter measure cells more committed to granulocytic and macrophage differentiation than do the CFUs, although both probably assay cells with a spectrum of proliferative capacities. Chart 5 shows the acute survival of CFUs and ADC after exposure to some of the drugs used in chemotherapy. Vinblastine is more toxic to the ADC while sparing to some extent the CFUs. Cyclophosphamide is equally toxic while busulfan and 1,3-bis(2-chloroethyl)-1-nitrosourea are more toxic to CFUs. A similar difference may be seen if one studies recovery of the CFUs following a single drug dose. Those drugs damaging the more primitive cells show a delayed nadir and slower recovery. We suggest that cells causing late damage are those which preferentially damage the primitive stem cells. It is of interest that both 1,3-bis(2-chloroethyl)-1-nitrosourea and busulfan have been shown to result in eventual marrow failure in some patients4 and may be predicted by using the assays and recovery kinetics.

Because the model predicted something about the basic physiology of the marrow, we attempted to see whether we could show that those cells measured by the CFUs assay were, in fact, heterogeneous with regard to their self-renewal capacity and, if so, whether they could be separated. We were interested in seeing if we could determine whether cells with a decreased self-renewal capacity were descendents of those with a greater self-renewal capacity. My colleagues, Peter Mauch, Joel Greenberger, Eileen Hannon, and Leslie Botnick and I studied our modification of the long-term bone marrow culture system (31) originally described by Dexter et al. (13). Marrow plugs are placed in culture flasks, cells adhere, and media are changed each week removing all supernatant cells. In this system, one can have long-term growth of bone marrow giving rise both to stem cells as well as to more mature forms. Table 2 shows initial attachment and describes a measure of self-renewal, Rs. This is an expression of self-renewal as the ratio of CFUs produced in an irradiated recipient 14 days after a known number seed the limb (25). The higher the Rs, the

Table 1
Late effects of 6 weekly i.p. injections of cytotoxic agents given in an 'adjuvant' setting


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Chart 5. Survival fraction of CFUs and ADC 24 hr after vinblastine (A), cyclophosphamide (B), 1,3-bis(2-chloroethyl)-1-nitrosourea (BCNU) (C) and busulfan (D).
greater is the self-renewal capacity. Those cells which adhere to the flask have a much greater self-renewal than do those in the supernatant. Normal marrow has an $R_s$ of 20 to 40 (31), while adherent cells have an $R_s$ of about 100. As the culture is established and the stem cell pool is expanded, self-renewal decreases. Following culture establishment there is no further loss in self-renewal, but in each instance the culture allows separation of CFUs with very different self-renewal capacities, those adherent having a much greater capacity for self-replication than do those in the supernatant. Since we remove all cells from the supernatant each week when refeeding, supernatant cells must be derived from adherent cells. Thus, the process demonstrates heterogeneity of stem cells as measured by their self-renewal capacities as well as some evidence of progression from high to low self-renewal capacity.

From these and other considerations, I believe that it is possible to speculate on a more general explanation for the long-term toxicity of cytotoxic agents (24). Oncologists are quite familiar with both acute and late effects of radiation. The acute effects are usually seen in cell renewal tissues, e.g., mucositis when the oral cavity is in the treated volume, epidermitis following skin irradiation, and diarrhea when the small bowel is irradiated. These effects can be modified by allowing sufficient time between radiation fractions and reducing the size of each individual fraction such that sufficient proliferation and cellular repair can occur. For example, John Chaffey and I (10) varied the fraction size on endogenous hematopoietic CFUs. A 250-rad/day dose causes progressive cell depletion. When the fraction size is reduced by 200 rads/day, cell birth equaled cell death and a steady state was reached. Thus, it is not acute tolerance that limits the total dose, but rather it is the knowledge that following excessive doses late complications will occur. These late effects will include necrosis, fibrosis, fistula formation, and persistent nonhealing ulceration. The mechanisms involved in the production of such late effects are not known. Similar acute effects of cytotoxic chemotherapeutic agents are also seen; mucositis, diarrhea, epilation, and hematopoietic depression may all accompany chemotherapeutic treatment. Similarly, these can be modified by changes in dose scheduling. The late effects of chemotherapy are less well known presumably because extensive and intensive use of such agents has only recently been used in patients expected to have prolonged survival. Even so, persistent bone marrow aplasia, bladder ulceration, cardiac failure, and pulmonary fibrosis have all been seen in patients after extensive chemotherapy. As adjuvant therapy becomes more common, these late effects may become a problem. Leslie Botnick and I proposed that both the acute and late effects of X-ray and chemotherapy are due to cell depletion of the major target cell renewal tissues, such as the skin, gastrointestinal mucosa, bladder epithelium, and bone marrow (24). While acute effects depend on the balance between cell killing and compensatory cellular replication, the developments of late effects may be due to the limited proliferative capacity of the stem cell. Compensation for extensive or repeated cell killing may exhaust this capacity, resulting in eventual tissue failure. This tissue failure can be observed clinically as mucosal or skin ulceration, cataract formation, premature graying, and, of course, bone marrow aplasia, all seen in the laboratory and in the clinic.

I believe that these experiments, although done in the mouse and in tissue culture, have direct relevance to the clinic. They combine a clinical question (What are the late consequences of cytotoxic agents?) with general study of bone marrow physiology. They have resulted from clinical concerns which may influence the choice of adjuvant agents and offer a method of separating those drugs more likely to cause such stem cell difficulties from others less likely to do so. In addition, the drug studies were useful in developing a further understanding of the organization of the marrow stem cell compartment and, finally, in providing a hypothesis for late effects.

**Machines and Humans**

The final portion of this presentation brings us to machines and humans. Radiation may gain some of its therapeutic advantage by carefully locating the tumor and directing the radiation toward the tumor, limiting the dose as much as possible to the normal tissues. Now with computer-assisted tomographic scanning, this becomes even more exacting as tumor and dose-limiting normal tissue location are more accurately defined. However, we need improvement of the radiation delivery system. An example of this is the use of computer-controlled radiation therapy (30). In this technique, my colleagues, Martin Levene, Bengt Bjarngard, Lee Chin, and Peter Kijewski, control all the parameters of radiation therapy in an attempt to direct the radiation to the tumor (e.g., a pelvic cancer with the draining pelvic and paraaortic lymph nodes), while limiting the dose as much as possible to the normal tissues (11). During such treatment, all the parameters of the machine may change including dose rate, field size, and patient position, while all are monitored to assure that the radiation is maximally directed to the tumor. This is a good example of an attempt to physically separate the curve for complications from that for local control by taking advantage of these and other mechanical aspects of radiation therapy (Chart 6). The curve in the middle is that of complications using conventional treatment. This is displaced to the right with this computer-controlled treatment since, for

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**Table 2**

<table>
<thead>
<tr>
<th>Time in culture</th>
<th>Adherent</th>
<th>Nonadherent</th>
</tr>
</thead>
<tbody>
<tr>
<td>Normal marrow</td>
<td>20-40</td>
<td>122</td>
</tr>
<tr>
<td>40 hr</td>
<td>93 ± 23*</td>
<td>25 ± 4.6</td>
</tr>
<tr>
<td>6 days</td>
<td></td>
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</tr>
</tbody>
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* Mean ± S.E.
a given tumor dose, the transited normal tissues receive less irradiation. This should result in an increase in curability for a given level of complication.

We also take advantage of limiting normal tissue dose in our studies of the treatment of breast cancer. In the use of radiation in the treatment of this disease, while we are primarily concerned with increasing curability, we are also concerned with decreasing morbidity, i.e., separating the complication curve from the cure curve. One complication or undesired constant accompaniment of mastectomy is the cosmetic deformity produced by loss of the breast. All my clinical colleagues at the Joint Center for Radiation Therapy have joined Dr. Harris, Dr. Levene, Dr. Botnick, and myself in a series of studies which take advantage of radiation therapy combined with limited surgery. Thus far, these techniques have cure rates similar to those of surgery with preservation of structure and function (19–21, 26, 29, 36). Careful beam definition is used to treat the tumor-bearing volume. With careful understanding of the anatomical spread to regional nodes, one can fashion a radiation plan which treats these areas and the breast, yet irradiates as small a volume as possible of normal tissue. Following this, the temporary local implantation of radioactive material such as $^{192}$Ir is performed because of its characteristic of permitting high local dose with much lower surrounding doses. This allows a much more effective tumor dose while sparing the normal tissues. Close cooperation between surgeon and radiation therapist is required to remove the gross tumor without distorting the breast. This allows a more moderate dose of radiation to be effective. Radiobiology and clinical radiotherapy have indicated that microscopic tumor may be controlled with a lower dose of radiation than that for gross tumor because of numerical as well as physiological differences between the cells in the 2 circumstances (15).

Table 3 shows our current treatment outline. A moderate dose of external radiation therapy is given to the tumor bed and draining nodes following gross tumor removal and sampling of the axillary lymph nodes. The latter is done not so much for radiation treatment but to indicate which patients might be candidates for adjuvant chemotherapy. Following the external beam radiation, a temporary interstitial implant is placed into the tumor bed. As this treatment technique is an evolving one, we have had the opportunity to study the effects of variations in the radiation dose, use of the implant, and whether the tumor has been excised on both local control and cosmetic results. Implantation has markedly improved local control in Stages I and II (Chart 7). There has been only one local failure in the 73 patients treated in this fashion. These results as well as the survival data shown in Chart 8 are quite comparable to those with conventional surgery. Chart 9 shows the local control data for Stage II and III breast cancer with and without gross tumor removal. These data confirm the value of this type of limited surgery as a method of displacing the control curve to the left. It also has allowed a higher likelihood of control at the higher doses since without tumor removal even at these doses some larger tumors are not controlled.

We have been impressed not only that adjuvant therapy has improved relapse-free survival but also that it has benefited local control in patients with advanced disease. This was demonstrated in a matched-pair analysis of our Stage III patients receiving chemotherapy as compared to patients not so treated (9). Since there is little overlapping toxicity, this combination of

<table>
<thead>
<tr>
<th>Surgery</th>
<th>Tumor excision: determination of estrogen receptor status; axillary sampling.</th>
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<tbody>
<tr>
<td>External radiation</td>
<td>4600 rads over 4.5–5 wk to breast, axilla, and internal mammary lymph nodes; 4-MeV linear accelerator; no bolus; compensating filters; no field overlap; fraction size, 200 rads or less.</td>
</tr>
<tr>
<td>Interstitial radiation</td>
<td>Afterloading $^{192}$Ir implant; 2200 rads to target volume at 35–40 rads/hr.</td>
</tr>
</tbody>
</table>
radiation and chemotherapy allows improvement in survival without significant increase in toxicity. The cosmetic result in early patients is also dependent on dose (21). As dose is increased, the fibrosis and retraction also increase. The implant will raise the dose to the tumor bed but not much to the normal structures, providing increased local control without increasing cosmetic compromise. Fig. 1 provides examples of patients who had received primary radiation therapy. While these results may offer little if any advantage in survival over conventional surgery, they offer a great advantage in cosmetic and functional results. Survival in breast cancer, while it may somewhat depend on local control, is largely influenced by whether or not the patient has an occult micrometastasis when first seen. No local therapy can affect this, but there is hope from new studies using adjuvant chemotherapy and/or hormonal therapy that survival may also be significantly improved. Hopefully, the use of limited surgery, radiation therapy with both external beam and interstitial radiation and, finally, adjuvant chemotherapy when indicated will achieve the dual goals of increased patient survival with preservation of function and structure.

Thus, I have taken you on a tour of our clinical research pertinent to breast cancer from $^{125}$I-tamoxifen to bone marrow physiology to laboratory models of adjuvant chemotherapy, and finally to the clinical improvement in the results of breast cancer treatment. All these studies are concerned with improving the therapeutic index and in so doing hopefully increasing the likelihood of cure with as little sacrifice as possible of normal structure of function both acutely or in the long term. While these studies are separate in terms of both the questions asked and the techniques used, they are all clinical research.

References

31. Mauch, P., Greenberger, J. S., Botnick, L. E., and Hellman, S. Evidence for...
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Fig. 1. A. patient who had a T1No tumor of the left breast 6 years earlier. B, patient who had a T1No tumor of the right breast 7 years earlier. Notice slight evidence of field overlap between breast and axillary fields. C, patient who had a T1No tumor of the left breast 6 years before the slide was made. D, patient who had a T1No tumor of the left breast and received external irradiation, implantation of both the primary lesion and axillary lymph node, and adjuvant combination chemotherapy, all completed 3 years earlier.
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