Tumor Biology and Clinical Trials: The Richard and Hinda Rosenthal Foundation Award Lecture

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Summary

Laboratory research is often described as basic and clinical research, prognostic or empirical. In this address, the point is made that research may be clinical or laboratory. Good clinical research may give important biological answers. Breast cancer clinical trials are described in terms of their biological interpretation. A list of significant biological questions that need answering are presented.

The theme of my lecture has been expressed aptly by Alexander Pope, the 18th century English poet. He stated in his poem, "Essay on Man," "Know thyself, presume not God to scan. The proper study of mankind is man."

Laboratory investigations in basic cancer research are extremely important and have contributed enormously to our understanding of the cell biology of both normal and cancer cells. In fiscal year 1976 49% of a $762,000,000 NCI budget was devoted to basic cancer research, tumor biology, cause, or prevention. On the other hand, clinical research, particularly clinical trials research, received $68,000,000 (in fiscal year 1976) or 9% of the NCI budget. The term "clinical trials" has the connotation of being empirical, applied, or nonscientific. The comparison standards of productivity between the basic science and clinical research programs cannot be measured in terms of cost or quantity of publications (Table 1). The elements of basic research are chemicals, viruses, bacteria, or mice. Chemicals and viruses are available readily in most laboratories, and experiments can be completed in a matter of hours or days. Escherichia coli and many tissues culture cells have generation times of 12 hr. Numerous experiments can be attempted and repeated within weeks. Tumor studies in mice can be completed in 20 to 60 days. If an experiment does not work, then there is no remorse or public outcry over a few mice or bacterial cultures that were sacrificed for naught.

Dr. Zubrod, ladies and gentlemen of the AACR, and guests. It is my pleasure to present the first Rosenthal lecture at the AACR meetings. As a clinical scientist, I am particularly honored to present this address to my colleagues, especially the large preclinical membership of the AACR. The title of my talk is "Tumor Biology and Clinical Trials." The topic was chosen to present my views on the importance of clinical therapeutic trials as they impact on our developing an understanding of the biology of cancer.

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The resources for laboratory experiments are relatively few in terms of personnel, equipment, and laboratory space. Since the clinical investigator must involve patient resources, often highly characterized and selective, he must resort to collaborative or interinstitutional clinical trials. These trials are expensive, are often slow in achieving their goals, and may not appear to be productive. In dealing with patients, the clinical investigator has to ask questions that must not be life threatening or too dangerous, because if his patients die sooner than usual he faces enormous ethical and even legal problems.

On the surface, the questions asked by the clinician may appear to the basic scientists to be technical rather than substantive ones. For instance a clinical trial in breast cancer treatment may involve one operation compared to another, one combination chemotherapy program against an alternative, or one new drug versus another. Clinical trials to the basic scientist may appear premature and empirical, but the clinician engaged in clinical cancer research faces the reality of attempting to improve the treatment for some of the 390,000 cancer patients who will die in 1977 (62).
The reaction of the laboratory investigator to this is often to explore. The accepted progression of research data has such as breast cancer, which is best treated with excisional biopsy, and excisional biopsy. The race operations came into vogue (42, 67). Not only were the operations dominated the treatment of breast cancer, acclaiming their results as better than others based on selected data. How he selected his patients (12, 16, 25, 67). Surgeons realized their failures and relied more and more on postoperative radiotherapy. The indications for postoperative radiotherapy were varied and were related to the size of the tumor, location of the tumor, the degree of vascular invasion, and the staffs of the operations offices.

Let us first look at the problem of breast cancer. In 1976, 90,000 new cases were diagnosed and 35,000 deaths were recorded. The mortality has not changed in the past 40 years (63). Until recently, the treatment of primary breast cancer was quite straightforward. All the surgeon appeared to have to do was perform a radical mastectomy. The radical mastectomy was devised in the last century by Halstead (56), primarily as a method for decreasing local recurrences. He advocated the importance of wide excision of the tumor including the breast, the underlying pectoral muscles, and the draining axillary lymph nodes. The basis for this operation was that the cancer was a localized process that spread consecutively to the nearest lymph nodes, and then to the more distant nodes in the local drainage area before invading the blood stream to cause widespread dissemination. As a logical extension of this hypothesis, the superradical or extended radical cancer operations came into vogue (42, 67). Not only were the pectoral muscles and axillary nodes removed but also a retrosternal dissection of the internal mammary nodes and a resection of anterior chest wall were performed. The race was on to do more and bigger operations. The more frequent operations used in the treatment of breast cancer are the extended radical, superradical, radical mastectomy, modified radical, total mastectomy, segmental mastectomy, and excisional biopsy.

Breast cancer treatment was therefore regarded as a technical problem, whereby good results were equated with local control and lowest morbidity. Since the surgical techniques required skill and precision, breast surgeons dominated the treatment of breast cancer, acclaiming their results as better than others based on selected data. However, 6 to 24% of patients developed local recurrences depending not only on the skill of the surgeon but also on how he selected his patients (12, 16, 25, 67). Surgeons realized their failures and relied more and more on postoperative radiotherapy. The indications for postoperative radiotherapy were varied and were related to the size of the tumor, location of the tumor, the degree of vascular invasion, and the staffs of the operations offices.

Our experimental colleagues often are excited by their findings in the laboratory, and yet when these hypotheses are put to the clinical test the results may not be confirmed. The reaction of the laboratory investigator to this is often one of frustration because the clinical trials may not have duplicated exactly the treatment situation in the laboratory. For instance Bacillus Calmette-Guérin i.t. has been shown to be highly effective in certain transplantable hepatomas in guinea pigs (70, 71), but hepatomas in humans do not present as single s.c. nodules with axillary regional lymph node metastases. The clinical trial of Bacillus Calmette-Guérin i.t. may not be ethically justified in small tumors such as breast cancer, which is best treated with excisional surgery. The cure rate of small breast cancers with standard treatment may be 80% (14, 31).

Clinical trials, like good laboratory experiments, should ask important biological questions. The answers to these clinical questions will have enormous impact on our understanding of cancer biology as well as of how to treat the patient. To illustrate how some of the clinical trials have helped answer important biological questions, I would like to use examples of clinical trials primarily in breast cancer in which I have been fortunate to be involved as a member of NCI, as a participant in the Breast Cancer Task Force, as chairman of the ECOG, and, more recently, as a member of the University of Wisconsin Clinical Cancer Center. I am most grateful to my colleagues, particularly Dr. Bernard Fisher, Dr. Gianni Bonadonna, Dr. Douglass Tormey, Dr. Nathaniel Berlin, and Dr. Marvin Zelen. In addition I appreciate the effort and results from our ECOG investigators and the staffs of the operations offices.

In my discussion, I would like to explore the theme that good clinical trials are in fact asking important fundamental biological questions. The answers to these questions not only will benefit the patient with cancer but also should provide new clues to the basic researcher. Accurate assessment of clinical trial results should introduce important new leads for the patient as well as for the basic researcher to explore. The accepted progression of research data has always been depicted as laboratory → clinic. What I would like to suggest is that the arrows, like many chemical reactions, are really going in both directions. Laboratory = clinic. This cartoon illustrates the appropriate attitudes of basic and clinical research (Chart 1). In addition during this discussion, I would like to suggest a shopping list of important research problems that would be extremely helpful to the clinical investigator in attempting to treat cancer patients.

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and the number of lymph nodes involved (27). Rarely were these factors tested adequately in a clinical trial, but the rate to report the least number of local recurrences has been extremely frenetic. What emerged from these reports was the appreciation that, although no 2 series were exactly the same, the results were quite comparable. There was no impact on survival, and local recurrences were decreased to 6% (25). Breast cancer treatment results reached a plateau for more than 40 years.

In the past 10 years individual investigators such as Peters (53), Crile et al. (13), McWhirter (46), Atkins et al. (1), and Fisher1 began to report results with less than radical surgery that were very similar to the more radical operations. A large cooperative trial done by the National Surgical Adjuvant Breast Project clearly showed that radical mastectomy with radiotherapy produced no better results than did radical mastectomy alone (25). Atkins et al. (1) from England showed that a segmental mastectomy plus radiotherapy was equivalent to radical plus radiotherapy for early lesions.

Superficially, the problem may appear to be an argument over techniques, one operation versus another, but in fact these clinical studies raise important biological questions as to the natural history of cancer progression. The fact that the extended radical operations (49) and addition of wide-field radiotherapy (25) to the next lymph node chain do not significantly increase survival of patients would imply that cancer does not spread in a logical sequence through the lymph nodes and that the local lymph nodes are not mechanical barriers to spread but appear to be more like sieves. Tumor cells have been shown in the laboratory to filter right through lymph nodes, attach to 2nd- or 3rd-level lymph nodes, or spread by blood stream invasion without node involvement (11, 21, 22). In fact we know that the tumor cells are constantly being shed into the circulation (59, 61). Breast cancer is cured by simple local treatment as well as by the more radical procedures. The key question, therefore, is, “How can we determine the biological potential of the cancer that appears to be localized in the breast?”

Thus, my 1st request for our preclinical colleagues would be to develop methods to determine the metastatic potential of a specific cancer (Table 2). Is a specific tumor more likely to have widespread metastatic potential or is the tumor destined to be localized? This would involve a detailed study of the tumor itself as well as methods to evaluate effective host resistance. Measurements of tumor factors or host factors alone may not be enough. A strong host protective potential may overcome the propensity of a tumor to metastasize.

Another aspect of these clinical studies has been the appreciation that cancer of the breast may be multifocal in about 40% of the breasts with 1 cancer having other cancers or precancerous lesions in the same breast (26, 58). Biopsies of the opposite breast are often positive as is the high rate of occurrences of 2nd cancers in the opposite breast (19, 38, 69). Thus breast cancer may be a tissue disease and the inciting carcinogenic factor(s) may persist in the host or give use to anomalies that will result in other distinct cancers. The clinical cancer lump may be a biological accident, and neoplastic lesions may have disappeared or new ones may have appeared subsequently. This hypothesis may be tested clinically in trials that are under way in which only the single cancer lump in the breast is removed and the remaining part of the breast is not treated or is treated by high-dose radiotherapy. The schema of the current National Surgical Adjuvant Breast Project trial is shown in Chart 2. The rate of development of cancers in the same breast or opposite breast will be most interesting to observe. Early ipsilateral failures would be interpretable as inadequate treatment (Table 3). Late recurrences are highly likely to be new cancers because of persistence of carcinogenic factors or cancer as a multifocal disease. If the radiated breast does not develop cancer whereas the opposite untreated breast continues to develop 2nd cancers, this would be an indication that the initiating carcinogenic phenomenon occurred early in the patient’s life and may not be persisting. Another important lesson from this study will be the ability of radiotherapy to control preclinical cancer in the same breast. These trials would also examine the differences in rates of cancer development in the segmental mastectomy group without X-ray treatment as compared to the group that received radiation and a segmental mastectomy. This trial is extremely important biologically and illustrates how the back flow of information from clinic to laboratory can be important.

My 2nd request would then be to have information on the apparent “normal” tissue in the same breast that has a

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cancer (Table 2). We need to know the biological behavior of the precancerous lesions in the breast, particularly whether those lesions that we recognize as cancer in situ will develop into overt clinical cancers.

The trials of radical mastectomy versus total mastectomy with or without radiotherapy have other interesting biological information to be gained (Table 4). In the patients randomized to radical mastectomy, 39% had histologically proven cancer in the axillary lymph nodes. Since the patients were also randomized to the other 2 arms from the same overall mix of patients, the same percentage of axillary node involvement must be present in the total mastectomy alone or the total mastectomy plus radiotherapy. After 4 years of follow-up, the survivals of the 3 groups are comparable. If the figures persist, then one could deduce that the impact of local lymph nodes as immunologically beneficial does not exist. Removal of the lymph nodes or sterilization with high-dose irradiation does not have an adverse effect on survival. Thus attempts in the laboratory to define the effect of local lymph nodes on the containing of tumor growth would seem relevant and important.

My 3rd request would therefore be to develop a better understanding of the role of local lymph nodes in controlling cancer cell growth (Table 2). Why do some cancers that have spread to the local lymph nodes appear to remain static or disappear, whereas others develop a lethal potential?

If we examine the role of chemotherapy in breast cancer we see that, unlike the results of clinical treatment in patients with Stage IV Hodgkin’s disease (17) or acute lymphocytic leukemia of childhood (63), patients with advanced breast cancer rarely experience dramatic responses and prolongation of survival (7, 8, 65) (Table 5). In patients with Hodgkin’s disease after 6 months of combination chemotherapy with nitrogen mustard-vincristine-procarbazine-prednisone, we are able to achieve an 80% complete remission rate; 50% of these patients have been in remission for 10 years or longer with only 6 months of treatment. With combination chemotherapy in patients with advanced breast cancer, while we can achieve 60 to 70% remissions or tumor shrinkage we rarely see complete responses, and the effect on survival is measured in months (8). One difference between breast cancer and acute leukemia is the obvious difference in growth kinetics; yet Hodgkin’s disease and advanced breast cancer untreated have about the same survival times (50, 52, 54).

How can we explain the relative refractoriness of breast cancer to chemotherapy? One hypothesis would be that our agents are not effective. I called this drug resistance, namely, that the drugs we use either alone or in combination are ineffective to induce permanent long-term remissions. The solution, therefore, would be to develop new and better drugs. I regard this as a pessimistic approach. Thousands of compounds are screened and tested annually for antitumor activity. A few reach clinical testing. How much longer will the screening need to take place? Are the screens the right ones? Those questions themselves will take years to answer.

However, an alternative hypothesis can be inferred to explain refractoriness to drugs. I will designate this as kinetic or high-volume resistance. To elaborate on this, one must appreciate that chemotherapy has been reserved for treatment of a large volume of end-stage patients, namely, those that have failed surgery, radiotherapy, and hormonal therapies. In the animal systems tested by Fuggman et al. (29), Martin et al. (43), Schabel (60), Bogden et al. (4), and others, resistance to chemotherapy occurs in large bulky tumors. Sensitivity can be restored by combining chemotherapy with effective local treatments or by using chemotherapy to treat micrometastases. Resistance is a function of large tumor cell numbers and low growth rates; adjuvant studies are a possible solution.

Thus one is faced with at least these 2 diverse hypotheses, drug resistance or kinetic resistance (Table 6). Which is correct? Answers to this have been approached by a series of clinical trials. The ECOG studies in advanced breast cancer with L-PAM and CMF (8) coupled with those in which the same agents are used after surgery by Fisher et al. (23) and Bonadonna et al. (5) are essentially clinical tests of the mechanism of resistance of human tumors to drugs. In patients with advanced breast cancer L-PAM produced responses in 19% of patients, whereas CMF resulted in 53% complete and partial remissions. The duration for survival gain was 12 months for partial remission and 18 months for complete remission as contrasted to nonresponders of 6 months. These results are not as dramatic...
or persisting as with nitrogen mustard-vincristine-procarbazine-prednisone treatment of patients with Hodgkin's disease. In patients with minimal residual breast cancer following surgery, the same agents resulted in significantly prolonged disease-free intervals as compared to surgery alone. As yet survival information is not available to evaluate the long-term gains, but we did make an impact on disease-free survival.

With L-PAM treatment a major impact on improving disease-free survival occurred only in the premenopausal patients. Recurrences were not prevented in the postmenopausal patients (23, 24). More recently, Bonadonna has likewise reported that the effect of CMF was most prominent in the premenopausal patients. In postmenopausal patients there was a significant delay in recurrence, but by 2 years the 2 disease-free survival curves for the surgery alone and surgery plus CMF patients were similar (6). In patients with advanced disease, an analysis of ECOG data revealed no differences in response rates between women under 50 as compared to those over 50 when the women were treated with chemotherapy (D. C. Tormey and M. Bauer, personal communication, ECOG Studies, 1977).

We know that chemotherapy can affect the hormonal output of the ovaries. On the other hand, prophylactic oophorectomy per se does not prolong recurrence in patients with early breast cancer (47). Are there other effects? Is the effect of chemotherapy a medical oophorectomy, or is it mediated through a pituitary suppression of prolactin? Is it prolactin or are there other hormonal effects? Moreover, in patients with recurrent disease, several studies have revealed that chemotherapy combined with oophorectomy results in improved survival and disease-free survival (Ref. 68; G. Falkson and L. Leone, personal communication, CALGB, 1977). The effect in premenopausal patients may be a combined chemotherapy-hormone effect. This should suggest that one might combine chemotherapy with hormonal therapy in postmenopausal patients.

Before leaving adjuvant therapy, I would like to stress that the validity of adjuvant therapy is not any less likely if the results with L-PAM or CMF turn out to be only temporary. A negative study would indicate that the specific type of systemic therapy tested might be relatively ineffective. One must use systemic therapy along with effective local treatment to improve survival. What is disappointing is that, if a relatively potent and toxic treatment like CMF is not effective, then chances of finding a more tolerable and effective nontoxic treatment appear less promising. Possible other approaches include use of Adriamycin-containing combinations or combining chemotherapy with immunotherapy or hormonal treatments (9, 32, 64).

My 4th request for basic scientists would be to study the differences between premenopausal and postmenopausal human breast cancer (Table 2). We know that the epidemiological factors relative to age incidence indicate that there is a different slope of incidence (age related) for breast cancer in women less than 50 years old as compared to women over 50 (18, 40).

Hormonal treatments for breast cancer have been a mainstay since Beatson (2) first reported the beneficial effects of oophorectomy in the 19th century. Adrenalectomy, hypophysectomy, and additive hormones have been more recent additions to the hormonal management of breast cancer. Since these treatment regimens produced responses lasting for 12 months or more in 20 to 30% of patients, until the development of combination chemotherapy all patients underwent attempts at hormonal control prior to chemotherapy. In the past decade exciting findings in the laboratory by Gorski et al. (30) stimulated the work of Jensen et al. (35), McGuire (44), and others to apply the ER assay to human material. ER assay was found in 70% of biopsies of primary tumors and a lower percentage in biopsy material from recurrent lesions. Two years ago, after a breast cancer conference, McGuire, Vollmer, and I published a compilation of the data (45). Hormonal responses occurred in 57% of patients with ER+ and in only 7% of the ER- group. This was one of the 1st biochemical tests that could be used to direct systemic therapies. Subsequent research has revolved on better predictive methods including measurements of progesterone receptors (34), nuclear receptors (41), and RNA stimulation by a receptor-hormone complex (36). Block et al. (3) has suggested that the quantitative level of ER material may be more sensitive. However, as a clinician I must remind the biochemists that a response measured as a 50% decrease in tumor size has to be a result of a 90% or more cell kill. Conceptually, therefore, one would want to take advantage of any cell kill if one were going to combine chemotherapy with hormone therapies. Breast cancer masses may all contain some degree of ER positivity, as suggested by Heuson et al. (33). This may be extremely important in

### Table 5

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<tr>
<th>Stage IV Hodgkin's Acute lymphocytic leukemia</th>
<th>Survival rates</th>
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<tr>
<td>80% complete remission; 50% long-term</td>
<td>40% 5-yr</td>
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<tr>
<td>20% complete remission; 40% partial remission</td>
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<tr>
<td>Duration, 9 mos.</td>
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<tr>
<td>Survival, 12 mos.</td>
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### Table 6

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<th>Agent</th>
<th>Late disease response (%)</th>
<th>Premenopausal early disease recurrence rates (% decrease)</th>
</tr>
</thead>
<tbody>
<tr>
<td>L-PAM</td>
<td>19</td>
<td>50</td>
</tr>
<tr>
<td>CMF</td>
<td>53</td>
<td>80</td>
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developing more effective therapies. These facts lead me to ask for answers to 2 more important biological questions, Problems 5 and 6 in Table 2. We need to understand how hormonal treatments and chemotherapeutic drugs kill breast cancer cells. Are there 2 different populations of cells, hormonally sensitive clones and drug-sensitive clones, or do hormonally positive tumors become hormonally resistant? The pharmacology and mechanism of action of many of the drugs used in breast cancer are known. Can we develop better methods to determine sensitivity of cancer cells to drugs, just as we use antibiotic sensitivities to test for microbial sensitivities?

Research in the treatment of cancer would be immeasurably improved if we could define some biochemical or immunochemical product of tumor cells that correlates with tumor cell numbers. The oncelfetal antigens carcinoembryonic antigen and α-fetoprotein are helpful but are not specific or universal enough to be the immediate solution. In patients with choriocarcinoma the human chorionic gonadotropin is a very useful parameter to follow. In patients with multiple myeloma, immunoglobulins (20) are practical indicators of tumor cell numbers, but as yet we are not able to quantitate tumor cell numbers in breast cancer. Studies by Tormey et al. (66) with patients with breast cancer have examined a variety of tumor markers that appear promising.

Thus on my shopping list as No. 7 for our basic research problems would be the development of better tumor cell markers of cell numbers (Table 2). We must be able to follow more quantitatively the changes in tumor growth rates during treatment and after therapy maneuvers. A sensitive indicator of tumor cell number would be extremely important in deciding how intensive the adjunctive therapy should be as well as how long it should be used.

To our nonclinical colleagues, the effects of chemotherapy are visualized as percentages of responses, merely numbers. However, even though we cannot talk about cures, women with advanced breast cancer do benefit by drug treatment. Bones can be made to heal. Large masses on the chest wall disappear. Pleural effusions resolve and large livers can be seen to return to normal. The patients who do respond can be shown to have improved survivals. However, I feel that the future of cancer treatment will undoubtedly become more biological. This brings me to my last request for the biologists (Table 2). Cancer cells are not completely autonomous. Hormonally sensitive tumors such as prostate, breast, and thyroid cancers can be shown to respond to trophic and tropic hormones. Chemicals can also modify the differentiation state of cancers such as with dimethyl sulfoxide for Friend virus leukemia (28) and acute leukemia (51) and with cyclic 3':5'-AMP for fibroblasts (37) and rat breast cancers (10); chemotherapy itself may cause differentiation of cancers. This occurs experimentally with the mouse neuroblastoma (55) and human teratocarcinomas (R. Golbey, personal communication, 1977), in which malignant cells apparently can become benign tumors. I feel that biological control of cancer growth is an accomplishable feat. As we develop more sensitive indicators of tumor cell numbers and more specific methods of diagnosis, we may be able to appreciate minimal volumes of tumors. Cancers may be diagnostable in a state where only a few thousand cells may be present. These few cells scattered in a 50- or 70-kg adult will not be visible on the X-ray or palpable by the surgeon. We are already able to diagnose lung cancer with cytology, and despite intensive searches with the fiberoptic endoscope no primary can be found. Cytotoxic chemotherapy may be applied in these clinical situations. However, it would be more exciting if we could cause these small cancers to differentiate and disappear by reverting back to normal end-stage nondividing cells. Vitamin A analogs are being contemplated for this use, since they can reverse metaphastic epidermoid and adenocarcinoma cells (49).

The challenge to both clinicians and basic scientists is to do good research; hopefully, there will be an interchange to the benefit of both. The basic scientist and the clinician working together become a powerful team. The basic scientist can learn from the clinician investigator as well as the clinician can learn from the laboratory. This kind of research is highly relevant and practical. My shopping list thus ends with that request, namely, that interdisciplinary research effort be continued, enlarged, and refined. Basic research need not be restricted to the laboratory. Good clinical research is good tumor biology.

References


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