



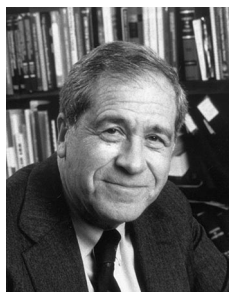
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From Halsted to Prevention and Beyond: Advances in the Management of Breast Cancer During the Twentieth Century

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Dr Fisher's laboratory investigations relative to tumour metastasis during the late 1950s and 1960s led him to formulate hypotheses that he then evaluated by means of large randomised clinical trials. The findings from successive studies that he and the NSABP designed and conducted have contributed to the paradigm shifts in the management of breast cancer.

This commentary evaluates progress made in the treatment of breast cancer during the twentieth century. Most of the period from 1900 to 1970 was governed by the 'non-science' of anecdotalism and classical inductivism and was marked by the absence of a scientific gestalt. In keeping with the Halstedian concept that breast cancer was a local disease that spread throughout the body by contiguous extension and could be cured by more expansive surgery, the disease was treated with radical surgery. In 1950, however, a new era of enlightenment began to emerge. The awareness that there was a scientific process in which hypotheses generated from laboratory and clinical investigation could be tested by means of randomised clinical trials was a seminal advance, as were findings from studies that laid the groundwork for the modern era of steroid hormone action, including identification of oestrogen receptors. Expanding knowledge regarding tumour cell kinetics, tumour heterogeneity, and technological advances related to mammography and radiation therapy were also to play a role in making possible the advances in therapy that were subsequently to occur. In the past 30 years, as a result of laboratory and clinical investigation, the Halstedian thesis of cancer surgery was displaced by an alternative hypothesis that was supported by findings from subsequent clinical trials. A new paradigm governed surgery for breast cancer, and lumpectomy followed by radiation therapy became accepted practice. A second paradigm that governed the use of adjuvant systemic therapy arose as a result of laboratory and clinical investigation. Treating patients who were free of identifiable

metastatic disease with systemic adjuvant therapy because some of them might develop distant disease in the future was a revolutionary departure from prior treatment strategy and became a new exemplar. Not only did the chemotherapy favourably alter the outcome of breast cancer patients, but the anti-oestrogen tamoxifen benefited patients with all stages of the disease. Tamoxifen also reduced the incidence of contralateral breast cancer, as well as tumour in the ipsilateral breast following lumpectomy. The use of preoperative therapy was also found to enhance breast-conserving surgery in women with large tumours, although its value in other circumstances is still being defined. The observation that, as a result of tamoxifen administration, invasive and non-invasive breast cancers can be prevented in women who are at increased risk for such tumours, and the finding that pathological entities such as atypical hyperplasia, lobular carcinoma *in situ* (LCIS) and intraductal carcinoma (DCIS) can identify women who should be considered candidates for tamoxifen serve as a fitting capstone to the accomplishments of the twentieth century. Breast cancer prevention has now become a reality. Unfortunately, a variety of circumstances have arisen as the result of advances in the understanding and treatment of breast cancer over the last 30 years that threaten to nullify the progress that has been achieved. This distressing phenomenon may be reviewed as a 'paradox of accomplishment'. The numerous uncertainties, issues and questions that have arisen following the report of each advance in treatment, the surfeit of new information that has not yet been integrated into treatment strategies, the undesirable consequences of enhanced tumour detection, a reversion to Halstedianism and anecdotalism, and the uncertainty of therapeutic decision making resulting from the demonstration of small but statistically significant benefits, particularly in patients with good prognosis, need to be addressed. Inappropriate interpretation of those circumstances threatens to deny women with breast cancer and those at high risk for the disease the opportunity to benefit from treatments that have been proven to be of worth. Perhaps the most important accomplishment of the twentieth century relates to the change in the process of therapeutic decision making. The continued use of the scientific process to test scientifically based hypotheses in well-designed clinical trials must continue if future progress is to be made in the treatment of breast cancer. © 1999 Elsevier Science Ltd. All rights reserved.

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PROLOGUE

IN VIEW of the multiplicity of new cases and deaths from breast cancer that occur each year worldwide, it is easy to understand why so many women harbour the perception that little progress has been made towards achieving a cure. The impression that women continue to be subjected to the same, largely unsuccessful, treatment their mothers and grandmothers received more than 50 years ago is still widespread. When considered in the context of history, however, the last half of the last century of the second millennium is likely to be remembered as a period in which unprecedented progress was made in the understanding, treatment, and prevention of the disease.

Although numerous seminal contributions were made in the biological, medical and physical sciences before the onset of the twentieth century, none of these were relevant to the understanding and treatment of breast cancer. Halsted [1, 2], Grubbé [3], and Beatson [4] offered the hope, but not the proof, that perhaps surgery, radiation and endocrine manipulation in the form of oophorectomy might play a role in the treatment of the disease. So little was understood about the nature of breast cancer that it was hardly surprising that no therapy of proven worth was available to treat it. Although, during much of the first half of this century, breast cancer therapy continued to reflect its inheritance, events that would eventually influence the future treatment of the disease were beginning to take place.

1900–1970: NON-SCIENCE TO SCIENCE

For most of the twentieth century, breast cancer was treated by the Halsted radical mastectomy [1, 2]. Surgeons often disagreed, however, about how expansive that operation should be [5]. Some believed that the radical mastectomy was insufficient to satisfy the concept upon which it was based, i.e. that breast cancer was a local disease that spread throughout the body by contiguous extension. These 'non-conformists' espoused the worth of extended- or super-radical mastectomy to fulfil Halstedian principles. Other surgeons, disappointed because radical mastectomy failed to cure all patients, reported their experiences with less extensive procedures such as modified radical mastectomy, simple mastectomy, and breast-conserving operations. Despite the fact that no scientific or clinical investigations were being carried out to provide information that could have led to conclusions that would have justified such dissension, disagreement about which operation was the most appropriate continued to intensify. This period was a frenetic one during which a great deal of energy was expended in an effort to promote personal bias [5]. Anecdotalism was the driving force and classical inductivism played the principal role in therapeutic decision making. Although, during the first half of the twentieth century, evidence of a scientific gestalt was lacking in clinical activity, a new 'era of enlightenment' was beginning to emerge. During this time, a number of events

occurred that would subsequently make possible many of the advances of the last quarter of the century.

The scientific process

Foremost among these events was the introduction of the 'scientific process' for clinical problem-solving. The French physiologist Claude Bernard, considered to be the father of experimental medicine, promulgated the thesis that 'A hypothesis is ... the obligatory starting point for all experimental reasoning' [6]. According to Bernard, a hypothesis was only of value if it could be tested. Others had noted that a hypothesis constructed without an adequate programme for estimating its worth 'is a burden to science and to the world' and emphasised that any scientist who put forth hypotheses that could not be tested 'is a purveyor of rubbish' [7].

For most of the twentieth century, few, if any, investigators who attempted to make decisions about the proper therapy for breast cancer considered the impropriety of their inductivist efforts. It was not until less than 50 years ago that there arose an awareness of the need for replacing the inductivist process of reaching conclusions via anecdotal information with the testing of credible hypotheses by appropriate laboratory experiments or within randomised clinical trials. Implicit to the adoption of the Bernardian approach to clinical problem-solving is the need for credible information upon which plausible hypotheses can be formulated and for an appropriate mechanism to evaluate their worth. Fortunately, a variety of mechanisms for fulfilling those needs were beginning to evolve.

Laboratory investigation

Laboratory and clinical research efforts were increasing and an awareness of the value of clinical trials for evaluating hypotheses having therapeutic relevance was emerging. The conduct of laboratory and clinical research by full-time investigators in academic environments began to increase after World War II. In the 1950s and 1960s, funding became more readily available for scientists, and academic freedom made it possible for them to pursue their own scientific ambitions rather than those of others. As a consequence of this expanded effort, an opportunity arose for the synthesis of better hypotheses from laboratory research that deserved testing in a clinical setting, a prelude to what has been more recently referred to as 'translational research'. My own efforts during that period were a result of those circumstances.

The observations of others in the mid-1950s that circulating tumour cells could be found in the venous blood of patients who underwent surgery and speculation that arose with regard to the significance of such cells stimulated our studies in tumour metastases. Between 1958 and 1970, our laboratory investigations into metastatic mechanisms led me to formulate a hypothesis contrary to that which gave rise to the Halstedian paradigm, the exemplar that had dictated the treatment of primary breast cancer for nearly three-quarters of this century. That paradigm was based upon the concept that tumour cell spread was related to anatomic principles and that more expansive operations that could eradicate 'one more tumour cell' would cure more patients. It was considered that 'proper' cancer surgery removed a primary tumour with its regional lymphatics and lymph nodes by an *en bloc* dissection—the hallmark of the operation.

Because cancer was considered to be a local-regional disease, it was thought to be more 'curable' if the surgeon

broadly interpreted what constituted the 'region'. Local-regional recurrences were too often considered to be the result of inadequate application of surgical skills rather than a manifestation of systemic disease. The use of postoperative regional radiation therapy was, similarly, based upon Halstedian principles. The alternative thesis that I formulated in the late 1960s from extensive laboratory investigation using animal models contended that, because operable breast cancer was a systemic disease involving a complex spectrum of host-tumour inter-relations, the ultimate outcome of the patient would unlikely be influenced solely by local-regional treatment.

Randomised clinical trials

Since 1948, when Bradford Hill described findings from the first 'modern' clinical trial conducted to evaluate the worth of streptomycin for the treatment of tuberculosis, the prospective randomised clinical trial has played an increasingly greater role in the scientific process [8]. That mechanism, which has become progressively more sophisticated during the past 25 years, is one of the most important achievements of the twentieth century. Not only are clinical trials of value for hypothesis testing, but they have also been found to be of worth for obtaining natural history information, for determining the worth of therapies, and for conducting clinical research. Most important, new concepts and hypotheses not uncommonly arise from the findings that result from the conduct of such studies. I cannot emphasise too emphatically that clinical trials are an integral part of the discovery process in breast cancer research, not entrepreneurial exercises used solely for drug testing—a perception that has gained too much prominence in recent years.

Although numerous critics have objected to the clinical trials process because, in their view, such trials take too long, are too cumbersome, and should be replaced by other mechanisms that are less costly, such studies continue to provide the most appropriate way of obtaining the kind of information necessary for verifying hypotheses and for evaluating therapies. Unfortunately, many of the critics of the process do not participate in clinical trials, do not understand either their complexities or the diligence required to obtain credible data from them, and would prefer to continue to believe in the worth of retrospective information for therapeutic decision making. As the physician and medical writer, Lewis Thomas, so aptly stated years ago, "From here on, as far as one can see, medicine must be building, as a central part of its scientific base, a solid underpinning of statistical knowledge. Hunches and intuitive impressions are essential for getting the work started, but it is only through the quality of numbers at the end that the truth can be told" [9].

One aspect of clinical trials that is often misunderstood by doctors, the lay public, and even by the physicians who participate in them relates to why seemingly appropriately conducted prospectively randomised clinical trials that test the same or a similar hypothesis appear to yield contradictory findings. Contrary to popular belief, such discordance does not occur because one of the trials is 'better' or 'worse' than another. Clinical trial findings are governed by boundaries that have been defined in a protocol established before the onset of the study. This fact is often overlooked. Because any two studies aimed at obtaining an answer to the same question are rarely identical, it is likely that differences (regardless of how slight) in study design, patient populations enrolled,

tumour characteristics and other dissimilarities would account for any divergent outcomes that might occur.

Another aspect of clinical trials that is often misunderstood is the fact that many suffer from deficiencies such as a lack of sufficient participants or number of events so that there is inadequate power to determine the significance of findings that result from their conduct. Richard Peto and his associates have made a significant contribution to the analytical aspects of clinical trials by combining the results obtained from a multiplicity of such randomised trials [10, 11], a statistical method known as a meta-analysis. That mechanism makes it possible to summarise the overall effects achieved. It does not, however, preclude continued conduct of large randomised studies with subjects who are rapidly accrued. Such trials are, in themselves, meta-analyses in that their findings represent a summation of the results obtained from the contributions of numerous institutions and investigators.

Oestrogen receptors and anti-oestrogens

One of the most significant aspects of the era of enlightenment that emerged during the 1950s and 1960s were studies that laid the groundwork for the modern era of steroid hormone action. Seminal contributions made by Elwood Jensen and his colleagues aimed at determining what happens to the oestradiol molecule as it initiates growth; identification of a true oestrogen receptor (ER), which differentiates between two types of breast cancer, i.e. that with and without ER; and evidence to indicate that the ER content of human breast cancer could be useful in identifying patients who were most likely to benefit from endocrine therapy were to have a profound effect on breast cancer management [12]. Of equal importance was information that evolved in the late 1950s relative to the development of drugs that displayed anti-oestrogenic properties. In conjunction with knowledge regarding oestrogen and ERs, the discovery of tamoxifen in 1962 by Arthur Walpole [13] was to have a dramatic effect on research into the therapy for, and eventually the prevention of, breast cancer.

Technological advances

Aside from expanding knowledge regarding tumour cell kinetics and tumour heterogeneity, another circumstance that contributed to the evolution of breast cancer therapy in the last quarter of this century related to the advances in the diagnosis of tumours by mammography and other modalities that were made during the 1960s and 1970s [14, 15]. Despite several decades of uncertainty regarding who should receive mammography and how often the procedure should be carried out, and despite political, emotional and economic pressures, the ability to identify non-clinically detectable, phenotypically expressed occult invasive and non-invasive breast cancers represents a seminal advance in the management of breast cancer. The shift from the detection of advanced disease to the detection of early-stage breast cancer will continue to have profound therapeutic implications. Advances in the technology of radiation therapy and its application have made its use for the prevention of local-regional recurrent disease more acceptable, particularly when this therapeutic modality is used in conjunction with others.

The advances made by the National Surgical Adjuvant Breast and Bowel Project (NSABP) during the past four decades of this century were largely achieved by traversing the pathways of science that I have already mentioned.

Hypotheses were formulated from laboratory and clinical investigations, and clinical trials provided the mechanism for me to get information that could not have been obtained in any other way. Without them, the anecdotalism that had governed therapy for the first half of this century would have continued unabated, and the paradigm shifts that occurred based upon 'the numbers' would have been unlikely.

1970–2000: PARADIGM SHIFTS

Thomas Kuhn, a theoretical physicist, philosopher, and historian of science described the developmental pathways of science as transitions from paradigm to paradigm that occur as a result of scientific revolutions [16]. Kuhn used the term paradigm to encompass 'all of the beliefs, values, and techniques shared by members of a (scientific or medical) community'. Most importantly, he emphasised that a new paradigm is better than the one it replaces. It was Kuhn's portrayal of the scientific process that has provided me with a framework upon which my research can be related to the investigations of others [17]. Much of the breast cancer research conducted by the NSABP has been responsible for the paradigm shifts in the treatment of the disease that have occurred during the past 30 years. Some of our contributions are likely to result in the emergence of new paradigms that will dictate the future management of the disease [18–23].

Creation of a surgical paradigm

I was fortunate to have had the opportunity of conducting two clinical trials, not only to obtain data to support my alternative hypothesis, but also to determine the worth of surgical procedures that were based on principles antithetical to the Halstedian paradigm. The first trial, NSABP B-04, which was implemented in 1971, compared the outcome of clinically node-negative patients who were treated by a Halsted radical mastectomy with patients who underwent either a total (simple) mastectomy with local-regional irradiation but no axillary dissection, or total mastectomy with no irradiation and removal of axillary nodes only if these became clinically positive. Despite the therapeutic non-conformity and the finding that approximately 40% of patients in the latter two treatment groups had pathologically positive nodes left unrecovered, no significant difference in overall treatment failure, distant metastases, or survival was noted among the three groups after 10 or 20 years of follow-up [24, 25]. The B-04 findings supported our alternative hypothesis and corroborated our previous contention that variations in the treatment of local-regional disease were unlikely to affect survival. Moreover, they supported our thesis that tumour-bearing nodes served as indicators that tumours had biological properties for establishing metastatic disease. Contrary to what might be inferred from these statements, I do not dismiss the idea that all efforts should be made to prevent local-regional tumour. The B-04 trial was most important in that it promoted the realisation that more patients would be cured only by the use of systemic treatment in conjunction with surgery and eliminated most of the biological considerations that might have contradicted evaluating breast-conserving operations by means of a randomised trial. Until the findings from B-04 became available, justification for breast preservation had been based on arguments derived solely from anecdotal experience.

In October 1973, the NSABP began planning a study to re-evaluate the alternative hypothesis and, at the same time, to appraise the worth of lumpectomy and axillary dissection.

The B-06 trial, which began in 1976, enrolled nearly 2000 women who were randomly distributed among three treatment groups: total mastectomy, lumpectomy alone or lumpectomy followed by breast irradiation. Women in all groups underwent an axillary dissection. Findings after 12 and 15 years of follow-up indicated no significant difference in distant disease-free survival or survival among the three groups [26, 27]. This was despite the fact that there was a 35% cumulative incidence of ipsilateral breast tumour recurrence in women treated with lumpectomy and no breast irradiation, a 10% incidence in women who underwent lumpectomy followed by breast irradiation, and zero incidence in women treated with total mastectomy. These findings provided further support for our alternative hypothesis and demonstrated that there was neither a biological nor a clinical rationale for opposing our conclusion that almost all patients with stages I and II primary breast cancer should be treated with lumpectomy followed by breast irradiation.

To continue to argue in favour of Halstedian principles of cancer treatment is to either ignore, deny, or be unaware of the valid information obtained during the past two decades from laboratory investigations and clinical trials that support our thesis. The Halstedian paradigm must now be permitted to assume its proper place in the annals of surgical history. Halstedian principles of cancer surgery are historical 'milestones' against which progress in breast cancer treatment can be measured and nothing more. The total (modified radical or simple) mastectomy, which is considered the 'radical' surgery of today, is a vestige of the Halstedian era. Surgeons who perform such operations should realise that the rationale for the procedure is no longer the same as it was at the time of its origin, when it was performed because it was believed that a curability rate similar to that achieved with the Halstedian radical mastectomy would result. Today, the operation is performed to accomplish local-regional tumour control only when it is believed that lumpectomy cannot be as effectively used for that purpose. As has occurred with radical mastectomy, total mastectomy will ultimately be relegated to a position of historical significance. Similarly, axillary node dissection, which is no longer performed to enhance curability but rather to aid in determining the type of systemic therapy that should be used, is destined to become outmoded. Quadrantectomy, at least as it was described at the time of its origin, might also be viewed as a procedure that was aimed at fine-tuning the Halstedian paradigm [28] in that it employed *en bloc* dissection and removal of the pectoralis minor muscle and fascia, whereas lumpectomy abandoned every principle of the Halstedian paradigm.

In the 14 years between the initiation of the B-04 study and the report of findings from B-06 (from 1971 to 1985), a radical shift occurred in the treatment of primary breast cancer. Most significantly, the events described, which began in the laboratory and continued in the clinical setting via clinical trials, led to emancipation from conventional thinking about breast cancer and its treatment and set the stage for a multiplicity of new scenarios that were to occur in rapid succession. In a sequence that represented an orderly scientific process, one paradigm governing breast cancer management was displaced by another.

The systemic adjuvant therapy paradigm

Whilst progress was occurring on the surgical front, the era of systemic adjuvant therapy was beginning to evolve. As

awareness increased that breast cancer could be cured only through the use of systemic therapy, interest in that therapeutic approach achieved prominence. Observations in the mid-1950s, which demonstrated that cancer cells were found in the circulating blood during surgical removal of tumours [29] and that chemotherapeutic agents had a cytotoxic effect on disseminated tumour cells in experimental animals [30], led to the hypothesis that adjuvant chemotherapy would prevent tumour recurrence and improve the survival of breast cancer patients. The NSABP first tested that hypothesis in a clinical trial in 1958. Although the results from that study demonstrated both a decrease in tumour recurrence and an improvement in survival in premenopausal, node-positive patients after 10 years of follow-up, findings showed that all patients had not been cured. Because they were disappointed with these results, practitioners were slow to adopt the systemic adjuvant therapy concept [31]. Consequently, no paradigm arose to govern its use. Nevertheless, those observations proved to be harbingers of future findings in that they provided the first evidence that the natural history of breast cancer could be altered by adjuvant chemotherapy and demonstrated that differences in the response of patient cohorts could occur.

After a hiatus of almost a decade, the NSABP launched another trial to evaluate adjuvant therapy. A new set of concepts, which were based mainly on kinetic principles of tumour growth that had been elucidated from animal experiments conducted in the 1960s and early 1970s, provided a rational basis for formulating another hypothesis that could be tested in clinical trials [32]. In 1971, the NSABP began the first trial to evaluate adjuvant chemotherapy and to test the hypothesis that supported the use of such therapy. In that study (B-05), a single chemotherapeutic agent (L-phenylalanine mustard) was administered to patients with positive axillary nodes. The results, first reported in 1975, demonstrated that such therapy could alter the natural history of patients with primary breast cancer [33]. A study conducted by Gianni Bonadonna and associates using cyclophosphamide, methotrexate, and 5-fluorouracil produced findings to confirm that conclusion [34]. As a consequence of our findings and of those by Bonadonna and, subsequently, as a result of findings from trials conducted by a multiplicity of other investigators, a new paradigm for breast cancer management arose. The new exemplar, which involved treating patients who were free of identifiable metastatic disease with systemic adjuvant therapy because some of them might develop distant disease in the future was a revolutionary departure from prior treatment strategy.

Further support for the validity of the systemic therapy paradigm was provided by a demonstration of the efficacy of the anti-oestrogen tamoxifen. Extensive study of that drug in experimental systems [35–39] and proof of its benefit in patients with metastatic breast cancer [40–43] provided the justification for the conduct of randomised clinical trials to evaluate its worth for the treatment of stage II breast cancer [44–46]. In 1981 we demonstrated that there was a benefit from the addition of tamoxifen to chemotherapy in node-positive patients, particularly in those ≥ 50 years of age [47]. A subsequent study demonstrated that tamoxifen and chemotherapy in the form of doxorubicin and cyclophosphamide resulted in a better outcome than did tamoxifen alone in node-positive breast cancer patients aged ≥ 50 years [48]. These trials provided evidence to justify the use of tamoxifen

for the treatment of axillary node-negative (stage I) patients with ER-positive tumours [49, 50]. Aside from demonstrating a benefit in disease-free survival and survival, which has endured for more than 10 years of follow-up, the use of tamoxifen significantly reduced both the incidence of contralateral breast cancer and of tumour in the ipsilateral breast following lumpectomy. It was also demonstrated that the administration of tamoxifen for more than 5 years provided no greater therapeutic advantage than was observed from its use through 5 years. We also found that the addition of chemotherapy to tamoxifen was more effective than was tamoxifen alone in node-negative patients with ER-positive tumours [51].

Numerous investigators conducted additional clinical trials to compare a variety of treatment regimens, to define optimal duration of therapies and/or drug doses, and to evaluate timing and different routes of drug administration. Still other trials related a variety of host and tumour characteristics, such as patient age and tumour size, hormone receptor content, growth kinetics, markers of gene expression and histological types to therapeutic response. Many of these efforts provided additional support for the use of systemic therapy, as did reports from a number of meta-analyses [52]. At the conclusion of two United States National Institutes of Health consensus conferences, one conducted in 1985 [53] and the other in 1990 [54], it was determined that adjuvant chemotherapy and hormonal therapy were effective treatments for breast cancer. Perhaps the most disappointing of all therapeutic investigations conducted over the last decade have been those that evaluated the merit of 'high-dose' chemotherapy for the treatment of women with advanced breast cancer or with tumours associated with large numbers of positive axillary nodes. Our studies that have evaluated dose intensification and increased total dose of a single chemotherapeutic agent (cyclophosphamide) as adjuvant therapy for node-positive patients demonstrated no advantage over standard therapy [55, 56]. Moreover, as yet, high-dose therapy with stem-cell or bone marrow transplant support has not been proven to be superior to standard dose therapy. It would seem that a lack of sufficient information about the mechanism of action of the various drugs employed, the cause of drug resistance, or the heterogeneity of the tumour cell population being targeted may all account for the weakness of the hypothesis that gave rise to the testing of high-dose therapy. Consequently, it is likely that the formulation of a more credible hypothesis is necessary before additional trials to test that therapeutic approach can be conducted.

Although systemic adjuvant therapy failed to benefit all patients, or even all within a particular cohort, and was accompanied by toxicity, its worth has justified its use in appropriate patient populations. As a result of the findings from our studies, I concluded around 1980 that the treatment of breast cancer was governed by two independent paradigms, one concerned with eradicating local manifestations of the disease without compromising prospects for cure, while maintaining the best possible cosmesis, and the other with eradicating systemic disease.

Origin of a unified paradigm

The two-paradigm concept changed when it was observed that the rate of ipsilateral breast tumour recurrence following lumpectomy decreased significantly when systemic adjuvant therapy was administered in the form of chemotherapy or

tamoxifen. Use of such therapy enhanced the acceptance of lumpectomy for the treatment of primary breast cancer, even for women with large tumours and positive axillary nodes. Thus, there was reason to conclude that the two independent paradigms for breast cancer management had converged into a single, unified paradigm. Consequently, it was no longer possible to consider the surgical management of breast cancer without considering how other therapeutic modalities would influence that treatment, and vice versa. Within the short space of less than two decades, patients with primary breast cancer received both the opportunity of preserving their breasts and the potential of experiencing an improvement in disease-free survival and survival.

Preoperative chemotherapy for breast cancer management

Hypotheses formulated from biological and clinical information obtained during the 1980s led us to initiate the first randomised clinical trial (B-18) to evaluate the role of preoperative chemotherapy for the treatment of primary operable breast cancer [57, 58]. Although its use failed to improve the overall benefit from systemic therapy beyond that of patients who were randomised to receive the same therapy postoperatively, the findings demonstrated that preoperative chemotherapy could be used without fear of decreasing the disease-free survival or survival of patients who received it. The most compelling findings were those which demonstrated that the response of a primary breast tumour to such therapy related to subsequent patient outcome. Women whose tumours displayed a clinical and pathological complete response had a more favourable outcome than did women whose tumours displayed either a clinical complete response or a clinical partial response. Thus, we concluded that the response of a breast tumour to preoperative chemotherapy could serve as a surrogate or intermediate end-point for determining the response of micrometastases to systemic therapy. Because breast tumour response could be determined within weeks after preoperative chemotherapy was administered, it became possible to predict a patient's outcome and then to provide her with information so that she and her physician could consider other treatment strategies without having to postpone therapy until a treatment failure occurred.

As a result of these findings, it is now justifiable to evaluate, in the preoperative setting, new chemotherapeutic regimens alone, in combination, or in sequence with those that have already been proven to be effective. Conclusions regarding the worth of these therapies can be drawn on the basis of their effect on the intermediate end-point, i.e. breast tumour response. In addition, it now seems appropriate to evaluate the worth of promising new therapies such as growth inhibitors, antihormonal agents, and anti-angiogenesis factors in the preoperative setting rather than in patients with advanced disease [59]. Another finding of particular importance demonstrated that the downstaging of large tumours after the use of preoperative chemotherapy permitted more patients to be treated with lumpectomies. As a consequence, I have proposed that women with tumours judged by surgeons to be too large for lumpectomies, or women whose surgeons are ambivalent about performing that procedure, should initially have the option of receiving preoperative chemotherapy to determine whether the primary tumour sufficiently decreases in size so that lumpectomy and breast irradiation, rather than mastectomy, can be carried out in an

attempt to enhance quality of life without increasing the risk for distant disease. Finally, the finding that preoperative chemotherapy downstages axillary lymph node status, i.e. converts nodal status from positive to negative, must be taken into account before a decision with regard to the management of axillary nodes can be made.

Whether or not preoperative chemotherapy is sufficiently important to replace postoperative systemic therapy remains to be seen. At least at this time, there is ample justification to suggest its use in certain circumstances.

Tamoxifen for the prevention of invasive breast cancer

The concept that tamoxifen could be used to prevent breast cancer had its origins in the late 1970s and 1980s, when the drug was shown to be of value in a variety of laboratory and clinical settings. Particularly germane to the concept of breast cancer prevention was tamoxifen's demonstrated ability to reduce the incidence of contralateral breast cancer [60]. To test that thesis, the NSABP implemented in 1992 the P-1 prevention trial [61, 62]. In that study, women at increased risk for invasive breast cancer were randomly assigned to receive either placebo or tamoxifen for 5 years. The study findings indicated that tamoxifen decreased the overall risk of invasive and non-invasive breast cancer by 50%, a reduction that occurred in all age groups and in all categories of risk. In addition, the incidence of ER-positive tumours, but not those that were ER-negative, was reduced. The findings obtained in women who had a history of lobular carcinoma *in situ* (LCIS) or atypical hyperplasia—pathological entities considered to increase the risk of invasive breast cancer—were of particular importance, as they not only provided the only quantitative information available from a clinical trial to indicate the magnitude of their risk, but also demonstrated that the risk could be substantially reduced by tamoxifen administration. These findings have particular relevance to those that were recently obtained from our studies in the evaluation of strategies for the treatment of ductal carcinoma *in situ* (DCIS).

In 1985, because of uncertainty regarding the management of DCIS, we initiated the first randomised clinical trial (B-17) to test the hypothesis that the treatment of localised DCIS by lumpectomy with tumour-free specimen margins followed by breast irradiation was more effective than lumpectomy alone in preventing the subsequent occurrence of invasive tumour in the ipsilateral breast [63]. The 1993 report of our findings supported that hypothesis and demonstrated that postoperative breast irradiation markedly reduced the subsequent occurrence of invasive ipsilateral breast tumours. When the outcome of patients was examined relative to a wide array of pathological and mammographical characteristics, we failed to identify a discriminant that identified any group of DCIS patients who did not benefit from postoperative radiation therapy.

Because our previous studies, and those of other investigators, had demonstrated a benefit from tamoxifen administration in a variety of settings, it was considered that the drug might interfere with either the development of a primary invasive cancer from its start, or with the progression of residual DCIS to invasive cancer in women with a history of DCIS. Consequently, we initiated a second randomised clinical trial (B-24) in 1991 to test the hypothesis that, in patients who had DCIS removed either with or without tumour-free specimen margins, treatment with postoperative radiation

therapy and tamoxifen would be more effective than radiation therapy alone in preventing invasive and non-invasive cancers in the ipsilateral and contralateral breasts [64]. The results of that study demonstrated that the risk of ipsilateral breast cancer was lower in the tamoxifen group, even when specimen margins were not tumour-free and when DCIS was associated with or without comedonecrosis. Because the benefit from tamoxifen was due to a decrease in the rate of ipsilateral, contralateral and metastatic invasive breast cancers, it seemed reasonable to conclude that focusing only on the frequency with which ipsilateral breast tumours occur was too limited and that an assessment of the effect of treatment on all of the sites combined seemed more appropriate. Finally, because women in the P-1 trial who had a history of LCIS or atypical hyperplasia were thought to be at sufficiently high risk of developing an invasive cancer to warrant being considered candidates for tamoxifen administration, it seemed reasonable to recommend that women with DCIS should also be considered candidates for taking tamoxifen, as this group is at an even greater risk for developing invasive disease, even after they have been treated with radiation therapy.

There has often been more of an emphasis on the adverse effects of tamoxifen than on the benefits resulting from its use. Findings from the NSABP P-1 and B-24 trials, as well as the results of other NSABP studies that have evaluated tamoxifen, have failed to justify concerns about quality-of-life issues, liver damage, hepatoma, retinal toxicity and cancers at other sites. The excess risk of endometrial cancer and of vascular-related events such as stroke, deep-vein thrombosis and pulmonary embolism that were observed in the tamoxifen group, as compared with those in the placebo group in these studies, has caused the most concern. In the P-1 study, less than 1 woman per 100 (0.7%) in the tamoxifen group developed endometrial cancer over a 5-year period. All were International Federation of Gynecology and Obstetrics (FIGO) stage 1, and no deaths from endometrial cancer have been reported. The undesirable vascular events in the tamoxifen group in excess of those in the placebo group, over a 5-year period were few; 0.2–0.3% of women experienced a stroke, approximately 0.2% had a pulmonary embolism and between 0.2 and 0.3% exhibited deep-vein thrombosis. Those events occurred less frequently in women ≤ 49 years of age and were slightly more frequent in women ≥ 50 years of age, being approximately 1% for endometrial cancer and less than 1% for each of the vascular-related events over 5 years. In view of the relatively few side-effects that have resulted from tamoxifen administration, we have concluded that its use as a breast cancer preventive agent is appropriate in many women at increased risk for the disease.

Commentary

In this portion of my commentary, I have provided a brief overview of some of the more notable improvements that have been made in the management of breast cancer during the last 30 years. Radical mastectomy has become of only historical importance. Lumpectomy followed by breast irradiation is now recommended for most patients with stage I and stage II tumours, largely because of the detection of earlier-stage breast cancers and because of information obtained from clinical trials that has failed to demonstrate that breast-conserving procedures have an adverse effect on distant disease-free survival and survival. Because adjuvant

systemic chemotherapy and hormonal therapy have, both alone and in combination, non-uniformly altered the natural history of breast cancer in different cohorts of patients, they have become major components of treatment paradigms. Of particular significance are recent findings indicating that, in women at increased risk for breast cancer, there has occurred a significant reduction in the risk of invasive and non-invasive breast cancers as the result of tamoxifen administration. These findings demonstrate that breast cancer prevention is now a reality. Moreover, pathological entities, such as atypical hyperplasia, LCIS and DCIS, which were heretofore considered to be markers for increased risk for invasive breast cancer, can now be considered indicators of those women who should be candidates for tamoxifen.

It must be emphasised that these NSABP accomplishments, which have altered our understanding of breast cancer, were the consequence of our investigative efforts that led to the replacement of Halstedian anatomical and mechanistic principles that governed cancer therapy with those related to a new understanding of the biological nature of the disease. Most importantly, our findings were obtained by means of randomised clinical trials conducted to test the efficacy of hypotheses created from information obtained by scientific and clinical investigation. As such, they represent a shift from the use of non-science to science for making progress in the treatment of breast cancer and must be viewed as significant landmarks in the advancements made in the management of breast cancer in the last quarter of this century.

CONTEMPLATING THE TWENTY-FIRST CENTURY

I have recently expressed my thoughts with regard to the difficulty of attempting to predict the future of breast cancer research [65]. Science is too complex and unpredictable for me to anticipate future directions for such investigation. Because events that are yet to occur in the immediate future are apt to shape the more distant future, long-range speculation is of limited value. In fact, it is not in the best interest of either physicians or their patients to focus exclusively on the future and disregard recent advances. Because, however, the immediate future of breast cancer research is likely to be related to present circumstances, it is appropriate to consider some aspects of the twentieth-century legacy that will influence the course of breast cancer therapy in the early part of the next century.

Despite the fact that the last 30 years were marked by unprecedented advancement in the understanding and treatment of breast cancer, a variety of circumstances have arisen that threaten to nullify the achievements of that period. The following is a description of some of the situations that are bound to affect research into the treatment of the disease during the first part of the next century.

Unanswered questions

It has become evident that we have entered a new era of medicine in which success is creating more cause for concern than is failure. Each report of a therapeutic advance engenders, not exhilaration, but rather uncertainty and pessimism. The reason for this disturbing phenomenon, which might be termed a 'paradox of accomplishment', relates to the fact that every clinical trial participant does not achieve a benefit and that, despite intense effort, only minor success has been achieved in determining with certainty which patients will do

so. In addition, questions arise such as those related to how long a therapy should be given, how much of a benefit is worthwhile, and whether any toxicity that results, when compared with the degree of benefit achieved, justifies administration of the therapy. No matter how credible its findings, a single study is unlikely to provide sufficient information to resolve all of the doubts associated with it. The inability to immediately resolve all of these issues and other putative uncertainties does not, however, detract from either the credibility or the importance of the findings that gave rise to them. While researchers are engaged in the process of obtaining information that will settle unresolved issues, thousands of women stand to benefit in the interim. This contention is best exemplified in the case of systemic adjuvant therapy. Despite the fact that many women have benefited from it during the 25 years after its benefit has been proven, innumerable questions regarding its use remain unanswered. A similar situation has occurred with lumpectomy, a procedure that has enabled countless women to preserve their breasts despite the unresolved issues related to its use.

Unfortunately, it seems that we are about to replay a modern version of the old scenario that was enacted during much of the first half of this century. As I previously noted, that era was marked by passionate debate, based solely on personal bias and anecdotal experience, about which type of operation was the most effective for treating breast cancer. Unlike what occurred during that period, the current debate is characterised by disagreement based on individual opinion regarding whether or not a particular patient should receive a particular therapy that has already been proven in appropriately conducted scientific endeavours to have benefited a particular group that may not be identical to the patient in question. The existence of unresolved issues and unanswered questions only adds fuel to these disputes. The P-1 study is a case in point. Despite the fact that the findings from that trial were obtained in a credible scientific fashion and have justified the administration of tamoxifen to women at increased risk for breast cancer, critics of the study would prefer to wait for another 10 years or so to determine whether a survival benefit will be demonstrated, thus penalising, in the interim, women who stand to benefit from the drug.

Plethora of new information

Another paradox of accomplishment relates to the plethora of new information emanating from an ever-increasing number of laboratory and clinical investigations. Whereas previously there was a relative paucity of new findings and even fewer testable hypotheses, there is now such a surfeit of new data that it has become increasingly more difficult to prioritise and evaluate their worth in the clinical setting. How this will be accomplished will, in no small part, determine the future direction of breast cancer research. Almost daily, a multitude of agents are being touted in both the medical and lay press as being candidates for the future eradication of breast cancer. These include anti-angiogenesis factor, metalloproteinase inhibitors, HER-2 antibody, growth factor suppressors, raloxifene, gene therapy, tumour vaccines and markers, to name only a few. However, until there is evidence from appropriately designed studies to demonstrate the proven efficacy of these agents, these anecdotal reports can be considered merely interesting and nothing more. The plethora of such reports that exist, but that have not yet been

integrated into treatment strategies, has resulted in 'intellectual chaos' among breast cancer clinicians, investigators and the public. How to cope with this trend is a subject for considerable thought as we enter the new century.

Halstedianism and anecdotalism revisited

In 1985, when we reported the worth of lumpectomy and radiation therapy for the treatment of invasive cancer, we were faced with the paradox that the operation for non-invasive cancer (mastectomy) was more radical than that for invasive disease. That circumstance led to our studies relative to DCIS, the findings from which demonstrated that lumpectomy followed by breast irradiation, and, more recently, by the addition of tamoxifen, eliminated the need for mastectomy for the treatment of DCIS and made the surgical treatment for invasive and non-invasive disease concordant. Currently, however, a new paradox has arisen. With recent improvements in mammography, ultrasound, magnetic resonance imaging and other technologies, aberrations in the breast that were previously undetected are now able to be identified. Similarly, as a result of zealous pathological examination of resected breast tissue, additional microscopic pathological irregularities are being discovered at sites in the breast that are unassociated with the index lesion. As a consequence of these advances, there has been an increase in the number of mastectomies being performed, a circumstance that has occurred because of the notion that breast conservation for either an invasive or non-invasive lesion cannot possibly be justifiable as long as there is the possibility that an abnormal cell remains unremoved, a concept that is in accord with the Halstedian paradigm for the treatment of breast cancer. Paradoxically, despite the fact that Halstedian principles of cancer surgery are no longer valid and that lumpectomy followed by breast irradiation and systemic therapy, where appropriate, has replaced mastectomy, there appears to be reversion to Halstedian thinking and, consequently, to the use of mastectomy. The idea that, with removal of one more tumour cell, more expansive operations will result in a cure continues to provide justification for axillary-node dissection in patients with clinically negative nodes. In that regard, sentinel node biopsy is based upon a Halstedian precept that tumour spread occurs in an orderly fashion, i.e. first to the sentinel node. Finally, unilateral or bilateral prophylactic mastectomies are procedures that are Halstedian in concept and are difficult to rationalise at this time in history.

To provide justification for the increase in mastectomies, proponents of that operation have suggested that, when presented with the option of breast preservation or mastectomy, more women choose the latter. The reason often proposed for this decision is that, because women are being confused and frightened by the controversial information they have been exposed to, they select mastectomy in order to obtain a quick resolution to their problem. If, indeed, that is the reason for their actions, then the scientific process that has been carried out during the last quarter of this century in an effort to obtain credible information for therapeutic decision making is in danger of being repudiated.

Unfortunately, much of the current reversion to revisionism is based upon anecdotal information that was never collected with the aim of being used to address current issues. Most important, the data for justifying the revival of Halstedian concepts is of little value, as most of it was gathered before chemotherapy and hormonal therapy began to be used

in conjunction with surgery. The continued publication by prestigious medical journals of manuscripts using anecdotal information to support biases rather than hypotheses further constitutes rejection of the scientific process and creates confusion in medical practice.

'Small' benefits and a 'good' prognosis

Another paradox that has arisen from the accomplishments achieved through breast cancer research during the last quarter of this century relates to the circumstance that arises when it must be decided whether or not a therapy that has been shown to result in a 'small' but statistically significant benefit should be administered. Such a decision is even more difficult when a patient is considered to have a 'good' prognosis without the therapy. Because the number of patients in this category is great, and is increasing with more frequent use of better mammographic techniques, the need for making such a decision has become a major source of uncertainty with regard to therapeutic decision making relative to breast cancer.

It must be emphasised that, although the prognosis of a patient in the short term, e.g. 5 years of follow-up, may be considered so good as to preclude additional therapy, after 10 or more years, such may not be the case. It must also be appreciated that there are thousands of women who, each year, are adjudged to have a 'good prognosis' but who eventually demonstrate a treatment failure or die of breast cancer, and that, at present, it is not possible to identify them, a priori, with precision. Moreover, the opinion that the benefit from a particular therapy is too small to be worthwhile is precarious. A decade ago I stated that there were no absolute criteria for deciding how great a benefit must be for a therapy to be considered appropriate for use, nor were there rules for evaluating that benefit relative to its toxicity, the cost of treatment, and other variables [66]. It was my view at that time that, until better markers were available for more precisely identifying patients who would benefit from a therapy, a physician's bias should not deny a patient the option to either accept or reject the opportunity to receive the therapy. My current viewpoint is even more emphatic than the one I expressed a decade ago. Although some progress has been made in identifying markers for selecting patients who should receive a particular therapy, considerable uncertainty remains in that regard. Consequently, because advances in the treatment of breast cancer continue to be achieved in small increments, it is my view that every patient should be given the opportunity to take advantage of any benefit that is currently available to her. Even if the benefit is moderate, it could have important public health consequences by affecting the course of a considerable number of patients with primary breast cancer.

CONCLUSION

The twentieth century must, indeed, be viewed as a period of unprecedented progress relative to the understanding, treatment and prevention of breast cancer. The transition from treatment based on Halstedian principles to prevention of the disease, which occurred in a little more than 25 years, could not have been remotely anticipated at the turn of the century. Neither could anyone have predicted the expansive clinical, biological and molecular-genetics discoveries that were made during that time. The bequest by contemporary investigators to those of the twenty-first century is more

substantive than that which we inherited from Halsted, Grubbé and Beatson at the beginning of the twentieth century.

Should the scope of the research carried out during the past 25 years continue during the first part of the twenty-first century, it is likely that surgery for the disease will continue to diminish in importance as improved methods of detection and tumour cell eradication become more commonly used. Unfortunately, however, surgery will continue to be employed as a treatment for breast cancer in those environments in which improvements in the management of the disease have not been implemented.

It also seems likely that the use of radiation therapy for the treatment of the disease will be redefined. Its effect on biologically altered breast cells before the phenotypical expression of a tumour may be looked upon as another means of preventing breast cancer. Refining the ability of radiation to eradicate tumour cells may also necessitate alterations in its current use.

It is my view that primary, i.e. preoperative, systemic therapy will play a substantive role in further advancing our understanding of how primary breast cancer responds to therapy. Such therapy will also be used to evaluate the worth of new therapeutic agents that will further minimise the need for surgery. More effective systemic therapies and biological agents, either alone or in combination, will be used, however, only if the toxicities associated with their administration can be minimised.

Although it is possible that a change in our perception of the biology of breast cancer could cause us to alter current paradigms for its management, the probability of that occurring within the next decade or so seems highly unlikely. It also seems unlikely that the use of such modalities as gene therapy, immunotherapy, or biological modifiers of tumour growth will lead to the creation of new paradigms for breast cancer management during that time. It seems more likely that the prevention of breast cancer will play an increasingly greater role in the management of the disease. This approach will not only involve the use of chemopreventive agents but will also prompt efforts aimed at identifying and eliminating aetiological agents, i.e. primary prevention, and at detecting and eliminating phenotypically expressed breast tumour cells and their precursor cells as early as possible, i.e. secondary prevention. Success in those endeavours would radically alter the way in which the disease is managed.

Perhaps the most important accomplishment of the twentieth century relates to the change in the process of therapeutic decision making. The transition from non-science to science, i.e. from anecdotalism and inductivism to the testing of scientifically based hypotheses using well-designed clinical trials for determining the worth of a therapy before it is used on a population as a whole, is accountable for most of the advances that have been made in the management of breast cancer. The continued use of this scientific process is imperative if future progress is to be made in breast cancer research and treatment.

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