The Evolution of Paradigms for the Management of Breast Cancer: A Personal Perspective

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Introduction

Although female breast cancer remains a major public health problem, notable improvements have occurred in its treatment. For most of this century, women with primary breast cancer have been treated by radical mastectomy or some variation of that procedure. In recent years lumpectomy has become the recommended operation for most patients. Before the mid-1970s, postoperative adjuvant systemic therapy was not used; now it is a major component of treatment strategies. How have these drastic changes come about? Are they the result of anecdotal recitations of personal experiences or the outcome of more abstruse circumstances? How are future changes apt to occur? Are we to believe that science has little or nothing to do with the process?

Science will continue to determine how breast cancer is perceived and managed in the future. Clinical practice must be based on a rational foundation that underlies our comprehension of the disease; this understanding relates to the “science” of the time in which we practice. The science of breast cancer in 1992 is different from that of 1892, and the science of breast cancer in the next decade will differ from that of today. As the burgeoning science of molecular biology unfolds, it is unrealistic to expect that operative procedures and systemic therapy modalities now used to treat breast cancer will remain static, any more than it could have been assumed that surgery would remain unchanged during the past century, given the changes in our understanding of the disease during that time.

The increased use of mammography and recent advances in basic tumor biology (particularly as they relate to cancer etiology) have resulted in an expanded perception of the breast cancer problem. This essay will describe how breast cancer therapy has evolved and will continue to advance as a consequence of transitions from paradigm to paradigm. It will also present several scientific developments that have the potential for creating new paradigms for breast cancer management in the not too distant future. How adequately past, present, and future paradigms relate to the currently expanding view of the disease is also considered.

An Expanded Perception of the Breast Cancer Problem. In 1969, 66,000 new cases of breast cancer were diagnosed and 29,000 women died from the disease. By 1975 there were 88,000 new cases and 33,000 deaths, with 1 in 14 women at risk for developing the disease. During the 1990s, more than 1.7 million women (about 175,000 per year) in the United States will develop the disease in her lifetime (1). Surveillance, Epidemiology, and End Results program (SEER) data indicate that, as age increases, so does the incidence of breast cancer (2). Whereas, for women 50–54 years of age the incidence is 212 per 100,000, it increases progressively over the next 25 years to 435 per 100,000 for women 80 to 84 years old. As ominous as they may seem, these statistics do not begin to portray the magnitude of the problem. The 75,000 or more women with invasive breast cancer clinically and/or mammographically diagnosed each year represent only the tip of an iceberg. Those women comprise only one cohort of the female population whose breasts contain a spectrum of aberrations, among which are the detected cancers (Fig. 1).

At the top of the spectrum (Fig. 1A) are women whose breasts contain invasive and noninvasive cancers of sufficient size to be detected clinically. In that same category are women with palpable benign lesions considered to carry no added risk, as well as those whose breasts contain lesions that put them at increased risk for invasive cancer, e.g., atypical ductal or lobular hyperplasia, and florid or solid papillary hyperplasia. Near this end of the spectrum (Fig. 1B) are women with abnormal breasts harboring lesions similar to those above that can be detected only by mammography. Among those with “normal” breasts in the middle of the spectrum (Fig. 1C) are women with the previously described lesions that are nondetectable but, if malignant, are likely to eventually become clinically or mammographically identifiable. Near the bottom of the schema (Fig. 1D) are women, considered normal, who may have breast tissue that has undergone biological alteration, a term used to encompass molecular-biologic, genetic, and biochemical factors that may play a seminal role in the etiology of invasive breast cancer. If modern concepts of carcinogenesis as they relate to the process of initiation and promotion are applicable to breast cancer, there is reason to believe that there are women within the so-called normal population who have “biological breast cancers.” These lesions have not yet become what we recognize under the microscope as cancers (phenotypic), but they have undergone molecular-biologic changes that will result in tumors that may, at some future time, be diagnosed by current clinical and mammographic methods. It is here that a single normal cell is “emancipated” from host controls and that—as a result of its altered growth regulation—the resulting neoplastic stem cell gives rise to a clone of tumor cells. These phenomena and those that follow depend upon a series of complex events involving alterations in cellular oncogenes, tumor suppressor genes, gene products, and growth factors that can augment or inhibit cell proliferation, and related activities (3–5). As neoplastic growth progresses, new mutations occur and new clones, which have a growth advantage over their predecessors, appear. At some point, genetic alterations may occur which give rise to cells that have acquired competence for establishing metastases. Early the better the chance there is of getting it.
breast cancer, I became familiar with the work of Thomas Kuhn, a theoretical physicist, philosopher, and historian of science, who described the developmental pathways of physical sciences as transitions from paradigm to paradigm which occur as a result of scientific revolutions (7, 8). Kuhn and others who have discussed the evolutionary process of science have not given meaningful consideration to how radical changes take place in biology and medicine (9, 10). Some theorists, in fact, contend that Kuhnian revolutions do not occur at all in these sciences (11). Others dispute that perspective (12). It is my contention that Kuhn’s interpretation of the nature of scientific revolution is directly relevant to medicine and that his description of the pathway of paradigmatic change can be used to illustrate how the treatment of breast cancer has evolved to its present stage. (I hasten to point out that, although retrospectively relating progress in medical science to a particular schema is legitimate, following the steps comprising that pathway does not necessarily guarantee success in obtaining new knowledge.)

Developmental Pathways of Science

The Transition from Paradigm to Paradigm According to Kuhn. At some time in history, according to Kuhn, a scientific community acknowledges the existence of scientific achievements so unprecedented that they attract an increasing number of adherents away from the model that governs the community’s activity (Fig. 2). For a time, the new science serves as a foundation for the practice of these “converts.” The model governing their activity is called a paradigm, a term used to encompass “all of the beliefs, values, and techniques shared by members of a [scientific] community” (7). Although a paradigm is accepted because it seems better than its competitors, it seldom explains all of the enigmas that confront it. Consequently, it provides a variety of problems that must be resolved by its adherents. To do so, they resort to a circumstance known as normal science, which flourishes as long as the paradigm is the exemplar that governs the activity of the community. Most of the research conducted by a scientific community is normal science, its aim being to define more precisely the attributes of a paradigm and to make it more acceptable. Such “mopping-up” activities are mainly fact-gathering endeavors carried out by experimentation and observation to resolve ambiguities and solve the problems generated by the paradigm.

Sooner or later during these investigations, anomalies occur...
or results from unrelated scientific efforts are reported. These give rise to doubt regarding the merit of the paradigm. The awareness by paradigm adherents that “something has gone wrong” results in a crisis, which precedes a scientific revolution. Kuhn uses the term revolution because of the similarities between the conditions that exist before scientific upheavals and the circumstances that precede political revolutions. In the latter, one segment of society defends the status quo, another attempts to introduce a new order, and society is not governed at all. A similar circumstance occurs in scientific revolutions. When one paradigm competes with another, individuals express their uncertainty, discontent, and disillusionment by displaying a willingness to improvise, by trying strategies that may have previously been considered inappropriate, and by engaging in endless debate.

The process of paradigmatic change is repetitive. While it is unlikely that one paradigm will ever be completely accepted before another takes its place, a scientific community can be governed by only a single paradigm. To reject one is a decision to accept another. To reject one without substituting another is to reject science itself, since a paradigm is based on science and to acknowledge a change in science without accepting the paradigm that arose from that change is illogical. These truisms account for much of the perceived confusion that exists in breast cancer management.

Despite his emphasis on the importance of scientific achievement in the development of a paradigm, Kuhn fails to consider how historic scenarios depicting the scientific method relate to the science that inspires the paradigm. Although it might be inappropriate to consider such a connection in the physical sciences, there is justification for noting such an association in the biological sciences, particularly in medicine. Because a paradigm governs the activity of the members of a given scientific community, it is important to examine its origins in order to estimate the credibility of the science that went into its construction (Fig. 3). Was that science a product of inductive reasoning, as described by Francis Bacon in the early seventeenth century and John Stuart Mill in the nineteenth, or was it the result of hypothesis-testing by rigorous experimentation, i.e., deduction, as advocated by Claude Bernard over a hundred years ago? The late Sir Peter Medawar aptly stated, “Induction is the arguing from the particular to the general” (13). It is a scheme of reasoning in which ideas, observations, results of experiments, and anecdotal experiences give rise to general statements that do more than summarize the information imparted by the data; according to Medawar, “it expands our pretensions to knowledge” (13). In the view of the inductivist, this enlargement of experience leads to an enlargement of understanding. Such a misconception continues to plague physicians who attach more significance to anecdotal experience than is justified.

Bernard, the French physiologist who focused attention on deductive scientific research, wrote: “A hypothesis is . . . the obligatory starting point of all experimental reasoning,” and he insisted that a hypothesis is of value only if it can be tested (14). Such testing must be carried out by appropriate experiments conducted in the laboratory or, more recently, within randomized clinical trials. These mechanisms provide information that can lead to rejection, modification, or support of the hypothesis. The greater the number of investigations that support a hypothesis, the more credible it becomes and the more likely that a new paradigm will result. More attention must be given to the results obtained from testing a hypothesis than to the plethora of anecdotal reports of inductivist-generated findings, which result only in clinical confusion.

It is important to point out that one of the major deficiencies in our knowledge of breast cancer relates to the fact that so much of the disease is perceived comes from information on demographics, natural history, biology, and treatment obtained from patients with tumors large enough to be detected by clinical examination and by mammography, i.e., those with end-stage or near end-stage disease (Fig. 1, A and B). Because studies designed to test the hypotheses upon which current paradigms are based were conducted almost exclusively in women with disease at that stage, these paradigms govern the treatment of women with clinically detectable cancers.

With the above information as background, it is appropriate to examine how the Kuhnian pathway relates to the evolution of paradigms that currently govern the management of breast cancer.

Paradigms Governing Breast Cancer Management

The First Surgical Paradigm. This paradigm originated when William S. Halsted combined the features of various operations devised in the late eighteenth century (15) into one operation that became known in 1890–1891 as the Halsted radical mastectomy (16–19). Evidence indicating the success of that operation was derived over the next half-century from anecdotal reports of observational information, i.e., Baconian inductivism. Halsted's writings indicate, however, that there may have been some biological justification for his efforts. He was influenced by W. Sampson Handley, who contended that cancer of the breast spread by extension along lymphatic pathways, preserving continuity with the original growth (20). Handley believed that tumor permeated, not metastasized to, distant sites such as bone, that the bloodstream was of little significance as a pathway for metastases, and that regional lymph nodes were an effective barrier to the passage of tumor cells (21).

The anatomical and mechanistic basis for Halstedian cancer surgery gave rise to the “proper” cancer operation, which consisted of removing a primary tumor, regional lymphatics, and lymph nodes by en bloc dissection—the hallmark of the operation. Because cancer was believed to be a local-regional disease, it was considered more curable if the surgeon was more expansive in his interpretation of what constituted the “region.” Moreover, this concept was time-oriented, and the management
of breast cancer was an "emergency." The concept gave rise to the Halstedian paradigm, which, for almost a century, governed the management not only of breast cancer but of most solid tumors as well (15).

It is appropriate to designate Halsted's efforts as a paradigm as defined by Kuhn because it arose from beliefs, techniques, and achievements that attracted an ever-widening group of adherents. It became universally accepted because of lack of competition and because proponents indoctrinated succeeding generations, who adopted it without qualification. It is not surprising that it remained intact for a protracted period despite what, in retrospect, might be viewed as weakness in its scientific origins.

The Halstedian paradigm provided an abundance of problems to be resolved. Normal science flourished. Almost all efforts were directed toward formulating a more precise definition of the operative procedure (15). Arguments, still considered respectable today in some circles, related to how thin skin flaps should be, how extensive an axillary dissection should be carried out, and whether supraclavicular and/or internal mammary nodes should be removed. Expansion of the operation was in keeping with the hypothesis. Super-radical surgery, more adequately than the radical mastectomy, embodied the principles on which the hypothesis was based. Aside from the fact that more expansive operations neither provided a basis for challenging Halsted's principles nor aided in the understanding of the disease, the technical aspects of the operation were beyond the average surgeon, since he was without the support systems necessary to perform them. For these reasons, super-radical surgery did not attract enough converts and, thus, failed to replace radical mastectomy.

The Halstedian paradigm also dictated radiation therapy. It was believed that, because residual tumor cells could be destroyed by radiation therapy, regional irradiation following mastectomy had a greater likelihood of effecting a cure than did mastectomy alone. Less extensive operations, such as modified-radical and simple mastectomy, followed by irradiation, were done because some believed that they better fulfilled Halstedian principles or because of frustration with the inability of radical mastectomy to cure more patients. The same dissatisfaction provided a rationale for performing breast-conserving operations followed by irradiation. Sporadic reports demonstrated that patients could, indeed, survive disease-free for many years after breast-preserving surgery. However, because the practice of local tumor excision was not based upon any new biological principles, because no studies had been conducted to compare the merits of this operation with more radical procedures, and because proponents of the Halstedian paradigm could see no reason to replace the mastectomy with it, breast conservation failed to receive adequate support.

As in the first half of the twentieth century, normal science between 1945 and 1970 was concerned primarily with "fine-tuning" the Halstedian paradigm (15). New principles of host and tumor biology were noticeably absent (the concept of breast cancer as a systemic disease remained obscure), and, as a result, no new exemplar surfaced to attract a sufficient number of surgeons away from the Halstedian paradigm. Disagreements that occurred among disciples of the same paradigm were related not to the paradigm itself but to variations in nuances of treatment proposed to strengthen it. When the era is viewed in retrospect, it appears that the Halstedian paradigm persisted so long because the normal science associated with it failed to answer all of the questions it posed and because no anomalies arose to challenge its tenets.

Origin and Development of the Current Surgical Paradigm. If the first surgical paradigm was related to tumor growth and spread, new knowledge questioning that facet of tumor biology might have been expected to challenge the reigning paradigm. Such was, indeed, the case. During the 1950s and 1960s, new perceptions of metastatic mechanisms arose. Our contributions, as well as those of others, led us to formulate a new hypothesis regarding tumor metastases and to test our theory in several clinical trials.

When we began our studies in the late 1950s, the prevailing theory was that lymph-borne tumor cells had one destination—the lymph nodes—that tumor cells in the blood vascular system lodged in the first capillary bed they encountered, and that tumor cells disseminated in an orderly pattern based upon temporal and mechanical considerations. Our findings 26 years ago indicated that the blood and lymphatic systems are so interrelated that it is impractical to consider them as independent routes of neoplastic dissemination, a major departure from the theory of tumor cell dissemination at the time (22, 23). We proposed that metastases are not dictated only by anatomical considerations but are, instead, influenced by intrinsic factors in tumor cells and by the organs to which they gain access, a thesis supported and broadened by recent expansion of knowledge in molecular biology. Consequently, we proposed that tumor cells are not spread in an orderly pattern, a theory contrary to that which provided the basis for the Halstedian paradigm.

Our experiments reported in 1966 revealed for the first time (24) that RLNs3 are not an effective barrier to tumor cell dissemination, as Virchow proposed in 1863 (21). In the 1960s we adopted the thesis that the RLN is an indicator of host-tumor relations and that negative nodes reflect conditions that inhibit the occurrence of metastases elsewhere, whereas positive lymph nodes indicate an interrelationship between host and tumor that permits the development of distant metastases. Thus, RLNs are not the instigators of distant disease. To consider RLNs merely as mechanical receptacles for tumor cells and way stations for further dissemination is an anachronism (25, 26).

Our findings failed to coincide with the prevailing theory of metastatic mechanisms that provided justification for the Halstedian paradigm. Consequently, based on our concept of tumor dissemination, which differed from that of Halsted, we formulated a hypothesis proposing a biological basis for breast cancer treatment that was antithetical to the mechanistic principles upon which surgery and radiation therapy were based (27). Our hypothesis contends that operable breast cancer is a systemic disease involving a complex spectrum of host-tumor interrelations and that variations in local-regional therapy are unlikely to affect survival. Unlike Halsted's, our theory is not time oriented. (Although many of these concepts may be self-evident today, such was not the case in the 1950s and 1960s.)

As noted, hypothesis-testing is an integral facet of the scientific method and is necessary in order to support or reject a theory. While the Halstedian hypothesis was accepted without such testing, we have had the opportunity to conduct two clinical trials not only to obtain data regarding the credibility of our hypothesis but also to provide information regarding the

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3 The abbreviations used are: RLN, regional lymph node; NSABP, National Surgical Adjuvant Breast and Bowel Project; IBTR, ipsilateral breast tumor recurrence; ER, estrogen receptor; DCIS, duct carcinoma in situ.
justification for continuing to use Halstedian principles of cancer surgery. The first trial (NSABP B-04), implemented in 1971, evaluated the outcome of patients having invasive breast cancer and no clinical evidence of axillary node involvement. In that trial, almost 1700 women were randomized among three different treatment regimens: conventional Halstedian radical mastectomy, total (simple) mastectomy with local-regional irradiation but no axillary dissection, or total mastectomy with no irradiation and removal of axillary nodes only if they became clinically positive. The significant aspect of that study was that 40% of the patients treated by radical mastectomy had histologically positive nodes. Thus, about 40% of those in the other two groups had positive axillary nodes that were not removed. Despite the therapeutic nonconformity and the fact that positive nodes were unremoved, no significant difference in overall treatment failure, distant metastasis, or survival was noted among the three groups after more than 14 years of follow-up (28–30). These findings supported our alternative hypothesis and corroborated our long-held contention that tumor-bearing nodes are “indicators,” not “instigators,” of metastatic disease.

Because the findings from B-04 negated the radical mastectomy and its principles, they provoked uncertainty about the merits of the Halstedian paradigm as an exemplar for breast cancer therapy and, thus, provided the impetus for a Kuhnian crisis, which resulted in aberrant responses among disciples of the Halstedian paradigm. Of primary importance, the findings eliminated most of the biological considerations that might have contraindicated evaluating breast-conserving operations. Until that time, any justification for breast preservation had been based upon arguments derived from anecdotal experiences.

To reevaluate our hypothesis and, at the same time, appraise the worth of lumpectomy and axillary dissection, we initiated a second trial (NSABP B-06) in 1976. In that study, nearly 2000 women were randomly assigned to total mastectomy, lumpectomy alone, or lumpectomy followed by breast irradiation. All had axillary dissection. After more than 9 years of follow-up, despite the fact that 43% of the women treated by lumpectomy without breast irradiation and 12% of those who underwent lumpectomy and breast irradiation experienced an IBTR, there was no significant difference in distant disease-free survival or survival among the three groups (31, 32). (Obviously, none of the women treated by total mastectomy had an IBTR.) This led to the conclusion that no causal relation exists between an IBTR and distant disease or survival, a finding similar to that described for axillary node involvement in B-04. Most important, the B-06 findings further supported the biological principles that had resulted in the formulation of the alternative hypothesis and provided justification for lumpectomy. Because of these changes, even more physicians began to doubt the merit of the Halstedian paradigm. Thus, the crisis that arose after publication of the B-04 findings expanded and became a Kuhnian revolution. A reevaluation of prior fact had necessitated a restructuring of prior theory.

With the erosion of the Halstedian paradigm, many of its disciples (as well as those yet uncommitted to any paradigm) accepted the validity of the B-04 and B-06 findings, and a new paradigm for the management of breast cancer evolved. Evidence to indicate that it has become established is inherent in the statement issued after a NIH consensus conference in June 1990, when it was concluded that breast preservation is the preferable treatment for women with stages I and II breast cancer (1). To use Kuhn’s analogy, it would seem that those currently governed in their treatment of breast cancer by the Halstedian paradigm are being ruled by the science of a previous era. In that regard, it is important to emphasize that the lumpectomy is an operation that has abandoned every principle of the Halstedian paradigm. In the lumpectomy, the surgeon removes only an amount of normal breast tissue necessary to provide tumor-free specimen margins as demonstrated by the pathologist. The aim is to ensure that gross tumor is not left unremoved. A lumpectomy is completely different from a quadrantectomy. The latter is a procedure that continues to embody the principles of the Halstedian paradigm, i.e., it employs en bloc dissection and removal of the pectoralis minor muscle and fascia (33). It is either an effort to compromise by using principles of both paradigms simultaneously, which is antithetical to Kuhn’s principle that a scientific community can be governed by only a single paradigm, or it is a procedure aimed at fine-tuning the Halstedian paradigm.

The new breast cancer paradigm has introduced a new set of problems requiring resolution to strengthen its tenets. Normal science has become active. Technical questions about how much normal breast should be removed in a lumpectomy, whether breast irradiation is necessary for all patients, whether certain tumor characteristics or host factors preclude the conduct of a lumpectomy, and whether systemic chemotherapy will reduce the incidence of postlumpectomy breast recurrence have become the object of study. Differences that have occurred in studies conducted to resolve these issues are not to be construed as uncertainties regarding the credibility of the paradigm.

A recently conducted investigation, which is part of the normal science associated with the new paradigm, has produced important findings regarding the significance of an IBTR following lumpectomy (32). This study was carried out to address the reluctance of many physicians to accept the lumpectomy. Despite the similarity in distant disease-free survival and survival between lumpectomy and mastectomy patients, many physicians feared that patients treated by lumpectomy who subsequently developed an IBTR would be at increased risk for distant metastases because any tumor that might not be removed during the primary operation would grow and disseminate cancer cells during the time between the operation and recognition of the IBTR. (These physicians are still disciples of the Halstedian paradigm.) Our findings, recently reported, indicate that, with the diagnosis of an IBTR after lumpectomy, a patient is, indeed, at increased risk for distant disease (3.41 times greater) than she was before the IBTR was recognized, but this increased risk is not because of disseminated tumor cells that could have been avoided had a mastectomy been performed. An IBTR is a marker of a risk for distant disease present at the time of primary tumor removal, and that risk would have been the same even if radical surgery had been carried out initially. Mastectomy or breast irradiation after lumpectomy eliminates or reduces the opportunity for identification of a marker of risk (an IBTR) for distant disease but does not reduce the development of distant disease. The relationship of an IBTR to distant metastatic disease is analogous to that of a woman without breast cancer who learns on one particular day that her sister has been diagnosed with the disease. On that day, the “normal” sister becomes at greater risk for developing breast cancer than she was the day before, even though her increased risk existed before her sister’s diagnosis. Thus, although mastectomy and breast irradiation following lumpectomy prevent expression of the marker, they do not lower the risk of distant disease any more than treating the sister who has breast cancer with an effective preventive agent.
before she develops the disease would eliminate the risk of breast cancer in her normal, untreated sibling. The results of this study strengthen the paradigm by providing information that confirms the biological nature of breast cancer—particularly as local recurrence relates to metastatic disease—and support our theory proposed more than two decades ago. Moreover, they continue to justify lumpectomy.

In this section, I have demonstrated how a paradigmatic shift has occurred in breast cancer management. I have indicated how laboratory research in the biology of metastasis gave rise to a hypothesis that was tested by clinical trials and how the findings from these endeavors refuted the principles that resulted in a paradigm that governed breast cancer management for more than three-quarters of a century. With a shift in the surgical paradigm and an increasing awareness over the past two decades that the curability of breast cancer relates to more effective systemic therapy, greater emphasis has been given to the use of that modality. The current systemic therapy paradigm has evolved in a manner similar to that described for the surgical paradigms.

Origin and Development of the Current Systemic Therapy Paradigm. Observations in the mid-1950s indicated that cancer cells could be found in the circulating blood during surgical removal of tumors (34) and that chemotherapeutic agents had a cytotoxic effect on disseminated tumor cells in experimental animals (35). These findings led to the hypothesis that adjuvant chemotherapy would lower tumor recurrence and improve the survival of breast cancer patients. That hypothesis was first tested in a clinical trial begun by the NSABP in 1958. The premise of this trial was that chemotherapy administered during and for a short period after operation would destroy tumor cells disseminated as a result of the surgery. Although study results demonstrated both a decrease in tumor recurrence and an improvement in survival of premenopausal, node-positive patients after 10 years of follow-up, disappointment with the overall findings led to the conclusion that the hypothesis had not been supported (36). Consequently, aside from a few exceptions, practitioners were not attracted to systemic adjuvant therapy, and, therefore, no paradigm arose to govern its use. Nevertheless, the observations obtained from this trial are important. They provided the first evidence that the natural history of breast cancer could be perturbed by adjuvant chemotherapy and that there were differences in the response of patient cohorts to a therapy—a prediction of future findings. Subsequent events revealed that the original hypothesis was valid but that the premise upon which the trial was based was inappropriate. The eradication of surgically disseminated tumor cells was probably less important than the response of existing micrometastases to cytotoxic agents.

Mendelsohn in 1960 (37) and Skipper and associates in the early 1970s (38-40) defined the concept of a growth fraction in a tumor cell population and provided an array of tumor growth kinetic principles that were instrumental in formulating a hypothesis that postulated the value of adjuvant chemotherapy. The first trial to evaluate adjuvant therapy and to test this hypothesis was begun by the NSABP in 1971. In that study, L-phenylalanine mustard was administered after radical mastectomy to patients with positive axillary nodes. The results, reported in 1975, indicated that such therapy could alter the natural history of patients with primary breast cancer (41). That conclusion was confirmed by findings from the Milan study, carried out by Bonadonna and associates using cyclophosphamide, methotrexate, and 5-fluorouracil (42). Both trials lent support to the hypothesis regarding the use of adjuvant therapy. As a consequence, a new paradigm governing the management of breast cancer arose. 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.

Further support for the validity of the systemic therapy paradigm was provided by investigations demonstrating the efficacy of the nonsteroidal antiestrogen tamoxifen (43-52). Subsequent to extensive study of that drug in experimental systems, and following its demonstrated benefit in patients with metastatic breast cancer, clinical trials were undertaken in Europe and the United States to evaluate tamoxifen alone or in combination with chemotherapy for the treatment of stages I and II breast cancer. Two British randomized trials compared the outcome of patients receiving no systemic therapy with that of those receiving tamoxifen (43, 44). By indicating that tamoxifen has an overall advantage that is independent of nodal, menopausal, or ER status, findings from both trials aided in strengthening the paradigm.

Normal science flourished. Laboratory and clinical investigations were undertaken to answer questions about the use of systemic therapy. Clinical trials have been conducted to compare treatment regimens; to define optimal duration of therapy and/or drug dose; to evaluate timing and routes of drug administration; to determine the relation of host and tumor factors (e.g., age, tumor size, hormone-receptor content, tumor growth kinetic characteristics, markers of gene expression, and histological type) to therapeutic response; and to assess the effect of chemotherapy in conjunction with other modalities (radiation therapy, hormonal agents, and biological response modifiers). As a result, information has accumulated which, on occasion, has resulted in disagreement and even confusion among physicians who treat breast cancer patients. It is often not appreciated that these responses are not the result of anomalies that weaken the credibility of the paradigm but, rather, the consequence of investigations conducted to strengthen it. Evidence to indicate that the systemic therapy paradigm is firmly entrenched is best exemplified by the results obtained from systematic overviews of findings from multiple trials (meta-analyses) (51) and by conclusions from several consensus conferences conducted by the NIH.

NIH consensus conferences held in 1985 (53) and 1990 (1) lent support to the paradigm when they concluded that adjuvant chemotherapy and hormonal therapy are effective treatments for breast cancer patients. Considerable evidence was provided to justify the use of chemotherapy in premenopausal and postmenopausal patients who were node-negative and had ER-negative tumors. Premenopausal and postmenopausal women with node-negative, ER-positive tumors also benefited from tamoxifen. It was recommended that established combination chemotherapy be used for the treatment of premenopausal women with positive nodes, regardless of their tumor hormone receptor status. For postmenopausal women with positive nodes and positive tumor hormone receptor levels, tamoxifen has become the treatment of choice. Recently, however, the addition of chemotherapy to tamoxifen has been found to be more effective than tamoxifen alone in postmenopausal patients with positive nodes and ER-positive tumors (54). Chemotherapy has been recommended for the treatment of postmenopausal patients with positive nodes and ER-negative tumors. An overview of 61 randomized trials among 28,896 women conducted by
the Early Breast Cancer Trialists’ Collaborative Group demonstrated reductions in mortality due to treatment when tamoxifen was compared with no tamoxifen or when any chemotherapy was compared with no chemotherapy (51).

Although adjuvant therapy has not cured all patients—or even all patients within a defined cohort—and is often accompanied by toxicity, there have been sufficient benefits to justify its use. Until new modalities demonstrate greater efficacy, it is appropriate to treat patients according to the current systemic therapy paradigm. As previously noted, to abandon the paradigm without a replacement is to abandon science. Current dissatisfaction with the use of systemic therapy is similar to that expressed in the era of the radical mastectomy and to that now being voiced by some regarding lumpectomy.

In summary, the treatment of breast cancer is currently being governed by two independent paradigms. One is concerned with eradicating local manifestations of the disease without compromising prospects for cure while maintaining the best possible cosmesis. The other serves as the exemplar for the eradication of systemic disease.

It is highly unlikely that either paradigm will endure for a protracted period of time. Laboratory and clinical research is expanding knowledge so rapidly that the half-life of permanency is becoming shorter and shorter! The following section is a commentary on current investigative efforts that have the potential for either altering currently entrenched paradigms or for creating new paradigms for breast cancer management.

Preludes to New Paradigms

One pathway of current breast cancer investigation relates to the development of progressively more effective regimens for the treatment of clinically detectable disease. New therapeutic modalities such as taxol (a complex natural product derived from the bark of the Pacific yew tree), antigrowth factors, immunomodulators, or tumor-infiltrating lymphocytes may one day require evaluation by means of large clinical trials (55). Tumor-infiltrating lymphocytes, for example, may be used to introduce cytotoxic agents like tumor necrosis factor directly to tumor cells or to genetically alter tumor cells in order to suppress their growth. Such approaches may be tested alone or in conjunction with current and new chemotherapeutic agents and hormonal therapies of proven value. Studies evaluating methodologies for overcoming drug resistance and for modulating the action of chemotherapeutic agents based upon pharmacological principles are in progress, as is the testing of currently available modalities in novel ways. Examples of the latter are two interrelated NSABP trials now under way; one evaluates the worth of preoperative (neoadjuvant) chemotherapy, and the other tests the worth of dose intensification and/or increased total dose of chemotherapy. Findings from these studies could result in another paradigmatic shift—the creation of a unified paradigm—which could profoundly alter current breast cancer management.

The Creation of a Unified Paradigm. In 1975, after demonstrating that adjuvant chemotherapy was effective in eradicating occult distant metastases, we conjectured that the use of such therapy would permit less extensive surgical procedures (56). It seemed reasonable to predict that, as systemic therapy improved, the surgical and adjuvant chemotherapy paradigms would eventually unite and become a single “unified” exemplar and that surgery, as a result, would partially or even completely disappear from use.

By 1987, clinical information and several hypotheses derived from biological studies provided justification for the conduct of a trial (NSABP B-18) to evaluate the worth of preoperative chemotherapy for the treatment of stages I and II breast cancer. Almost all of the clinical findings have come from the use of such therapy in the treatment of head and neck tumors (57), esophageal tumors (58), osteosarcoma (59), and locally advanced (stage III) breast cancers (60). Of particular importance was the National Cancer Institute study in stage III breast cancer patients treated with a complex preoperative chemotherapy regimen (61). A complete response occurred in 50% and a partial response in 40% of breast tumors. (The study was conducted not to evaluate preoperative chemotherapy but to ascertain the value of cell synchronization in conjunction with chemotherapy.) Several groups of investigators have evaluated or are investigating preoperative therapy in patients with operable (stages I and II) breast cancer (62–64). In the Milan study (64), which was not a randomized trial, preoperative chemotherapy was administered to women with breast cancer who were candidates for mastectomy because the largest diameter of their tumors was ≥3 cm. The aim was to reduce the size of the tumors so that these women might be treated by breast conservation instead of mastectomy. Sufficient “tumor shrinkage” was reported to have occurred in 127 of 157 women, allowing for breast preservation. It is of interest that 79% of the patients had tumors ≤5 cm, a size that, according to NSABP criteria, would have made them initially eligible for lumpectomy. This study, and all others using preoperative chemotherapy, failed to determine whether such therapy more effectively controls disseminated disease than does the same therapy administered postoperatively.

One of the hypotheses that justified our study relates to concepts promulgated by Skipper in the 1970s (38–40); among these were propositions suggesting that responses of primary and metastatic tumors to chemotherapy may differ. None of the numerous trials conducted since that time were designed to confirm or reject the tenets of the Skipper hypothesis. If the principles of this hypothesis are supported by our study, failure to observe a complete or partial primary tumor response to chemotherapy may not necessarily portend a lack of control of distant disease.

Another theory that provides a biological rationale for evaluating preoperative therapy was formulated from findings obtained in experimental systems which indicate that primary tumor removal affects the growth kinetics of metastases. Our investigations and those of others have demonstrated that, after removal of a primary tumor, an increase in the labeling index of a distant tumor focus occurs, resulting in an increase in tumor size (65). We have determined that the stimulation of cell growth after removal of the tumor is due to the presence of a serum growth factor (66) and that chemotherapy, tamoxifen, or radiation therapy given before the operation prevents the kinetic perturbation (67). Consequently, these agents more effectively suppress tumor growth and prolong survival than when they are administered after removal of the tumor.

A third hypothesis providing justification for testing preoperative chemotherapy proposes that, as a tumor cell population increases, an ever-expanding number of drug-resistant phenotypic variants that are more difficult to eradicate arise due to spontaneous mutation. This thesis maintains that the increase in resistant cells can be minimized by administering combinations of non-cross-resistant drugs as soon as possible, i.e., when a tumor population contains the fewest number of cells (68).
As a result of these hypotheses and the available clinical information, in October 1988, the NSABP implemented a study (B-18) to determine whether (a) preoperative chemotherapy will more effectively prevent tumor recurrence and prolong survival than does the same therapy administered postoperatively, (b) the primary tumor response to preoperative chemotherapy correlates with the prevention of recurrence and prolongation of survival, (c) preoperative chemotherapy will permit more conservative surgery and decrease the incidence of IBTR following lumpectomy, and (d) downstaging of axillary nodal status will occur. More than 1100 patients with operable breast cancer, all diagnosed by fine-needle aspiration or core biopsy, have been randomized to receive either operation followed by systemic therapy or the same systemic therapy followed by operation. It is our view that, until information from this or another large trial indicates that local-regional disease benefits from the use of preoperative therapy are not accompanied by an unfavorable distant disease-free survival and/or survival outcome, this therapeutic approach should be limited to the clinical trial setting.

The second study conducted by the NSABP that has implications for creating a unified paradigm was designed to determine whether intensifying and/or increasing the total dose of a demonstrated effective postoperative chemotherapy regimen will more effectively eradicate distant disease. In that trial, in order to use higher doses of drug, colony-stimulating factor is used in conjunction with the chemotherapy. If a greater benefit is obtained using high-dose therapy than has been observed following current “standard” doses of the same therapy, the high-dose regimen will be administered preoperatively. If, as a consequence, a substantial number of patients show a reduction in primary tumor size and an improvement in distant disease-free survival and survival, a new paradigm, which unifies the treatment of local, regional, and systemic disease, is likely to become established. Even if a decrease in primary tumor size is unaccompanied by an improvement or a deficit in distant disease-free survival or survival, preoperative therapy would be justified if its administration permits the use of less extensive surgical procedures. In those cases where clinical and mammographic examinations indicate that preoperative chemotherapy has completely eradicated a primary tumor, breast irradiation without surgery after completion of the chemotherapy may be adequate to prevent breast tumor recurrence.

Despite its demonstrated benefit, how durable is a single paradigm for breast cancer management that advocates preoperative therapy? As more women are examined periodically with better mammographic equipment, more tumors will be identified when they are even more occult than those currently being detected. Consequently, fewer women will have cancers for which the paradigm dictating the use of preoperative therapy applies. Because the natural history of patients with occult tumors is uncertain, it is also unclear (although probably unlikely) whether systemic therapy, as it is currently used, should be used in their treatment. On the other hand, occult tumors may be the ones that can be cured in all instances by such therapy. Despite this uncertainty, the surgeon's role in the management of such patients will diminish and may even become obsolete. It is likely that the paradigm that will govern the management of such lesions will be dominated by the radiologist, who detects the lesion, localizes it, removes cells for cytological examination, and who, subsequent to pathological examination, destroys it by a procedure such as laser therapy applied directly to the site of the lesion.

The Creation of a Paradigm for the Treatment of Noninvasive Cancer. Because, as has already been indicated, almost all knowledge about invasive and noninvasive breast cancer has, until recently, been obtained from patients with clinically detectable tumors, physicians are at a disadvantage when called upon to make decisions about the management of occult cancers, particularly those that are noninvasive. The present confusion about how best to treat DCIS is due to the fact that there is insufficient biological and natural history information to formulate a paradigm that governs the treatment of the type of DCIS currently being detected with increasing frequency by mammography. The Halstedian paradigm is inappropriate, and the new surgical paradigm advocating lumpectomy has not been fully accepted. As Kuhn indicates, when such a situation occurs, anarchy is apt to exist. It is not uncommon for a patient with DCIS to receive diverse recommendations for her treatment that range from unilateral or bilateral mastectomy with or without axillary dissection to lumpectomy with or without breast irradiation. An incongruous situation has resulted. Whereas mastectomy is becoming less justifiable for treatment of invasive breast cancer, it is more often advocated for DCIS, the rationale being that the operation performed to prevent invasive breast cancer should be more radical than surgery performed to “cure” the disease. The turmoil regarding therapy is related to the absence of definitive information about the frequency of synchronous or metachronous multicentricity or multifocality (in situ or invasive) in the ipsilateral or contralateral breast associated with DCIS. In addition, it remains uncertain how frequently multicentric or multifocal lesions become clinically significant, whether DCIS is an obligatory preliminary step in the development of invasive cancer, and whether all DCIS becomes invasive. Should the progression from DCIS to invasive cancer relate to somatic genetic events, as is currently speculated, it becomes important to determine whether the changes can be monitored by any method other than histopathology, e.g., oncogene expression.

In 1985 we instituted a clinical trial to obtain natural history information that might address some of these issues. A secondary objective of the study was to test the hypothesis that, in patients with localized DCIS which can be completely removed by lumpectomy, the addition of postoperative breast irradiation would effectively prevent recurrence of the disease. While there is currently no definitive information to indicate that breast irradiation either does or does not effectively eradicate DCIS, there is indirect evidence from a variety of sources (69-74) to indicate its possible value.

After that study completed patient accrual, a second trial was instituted using women with more extensive DCIS than that in women who were entered into the first study. That trial was conducted to test a hypothesis that relates to the prevention of ipsilateral invasive breast cancers subsequent to treatment of DCIS by lumpectomy. The purpose for treating local or diffuse DCIS is to prevent such a lesion from progressing to invasive cancer and to eliminate a focus of invasive cancer that might exist in conjunction with the DCIS. Although mastectomy effectively accomplishes that goal, other strategies used with breast conservation may be equally effective. Because breast irradiation following lumpectomy for invasive cancer effectively prevents its recurrence, and because tamoxifen likewise interferes with the development of invasive cancer in both the ipsilateral and contralateral breast, these modalities, used with breast conservation, may have a place in the management of DCIS, particularly in patients with extensive disease.
Because experimental evidence supports the thesis that tamoxifen possesses both antiinhibitor (75) and antipromoter capabilities (76, 77), that drug may inhibit the progression of DCIS to invasive cancer. Recent evidence that tamoxifen may possess antiangiogenesis properties may be important, since it is postulated that angiogenesis is required for the progression from noninvasive to invasive breast cancer (78). Thus, the hypothesis that governs our second study relates to the thesis that, with the use of tamoxifen and radiation therapy for eliminating associated invasive cancer, the clinical significance of DCIS may become similar to that of atypical hyperplasia or to that of a woman with a family history of breast cancer.

The findings from both of these studies are likely to provide the basis for formulating a paradigm to govern the treatment of DCIS. Until then, it seems appropriate that the surgical treatment of invasive breast cancer should govern the management of this disease.

Comments Regarding the Mammographic Detection of Occult, Invasive Breast Cancer. As has already been pointed out, one principal research strategy directed at making breast cancer a less significant public health problem is aimed at devising progressively better regimens for the systemic treatment of clinically detectable disease. Another strategy is directed toward the identification of a greater number of nonclinically detectable, phenotypically expressed, occult, invasive breast cancers by more widespread mammographic screening with the best methodology currently available. This approach should result not only in an increased incidence of breast cancer but also in a change in the distribution of the size of tumors that are discovered; i.e., the percentage of small cancers will increase. If current thinking is correct, patients with tumors detected by mammography before their clinical appearance should be more curable after their tumors are removed. Theoretically, as this strategy comes closer to achieving its goal, the first strategy becomes less important, and—that taken to the extreme—obsolete, since clinically detected tumors would no longer exist. Current biological concepts indicate, however, that as a result of genetic alteration some occult tumors detected by mammography have populations of cells that have already attained competence for successfully establishing metastases, have not yet achieved that capability but will do so as their cells continue to replicate, or will never demonstrate that capacity, even after they are detected by clinical examination. (A substantial proportion of patients with clinically detected cancers do not develop metastatic disease during their lifetime.) Thus, if current concepts are correct, it would seem that the value or limitations of mammography relate not so much to the number of clinically occult tumors detected as to the biological nature of the cells in the tumors that are discovered. Perhaps, with more diligent use of better methodology than is now available, it will be possible to detect and remove more tumors whose cells have not yet undergone the biological changes required for them to attain the metastatic capability that would occur if the tumors were not recognized and not removed.

Pragmatic concerns exist about the extent to which mammography as an independent intervention is likely in the next decade or so to become the paradigm for eliminating breast cancer as a major health problem. Despite extensive encouragement of women to have mammograms, it is estimated that, in the United States, of the new patients diagnosed with invasive breast cancer in 1990, only 50% had stage I disease, whereas 20–25% demonstrated stage II and 20–25% stage III cancers—hardly a testament to the current impact of mammography (1). Another concern is that, after the removal of mammographically diagnosed tumors too small to be detected clinically, women will be at increased risk for the development of second breast cancers and, thus, require continued surveillance. Most frustrating is the realization that organized mammographic programs with sophisticated equipment used on a regular basis by well-trained personnel are unlikely to be available to a substantial number of women in this country. The hundreds of thousands of women worldwide who live with and die of breast cancer treated either in the most rudimentary way or not at all because they lack access to health care are unlikely to be beneficiaries of mammography. These comments are not to be interpreted as criticisms of mammography; indeed, much greater effort must be directed toward promoting it. Such effort is justified, however, only if systems are available to properly treat women who have abnormalities detected as a consequence.

As is shown in Fig. 1, there is a time when a phenotypically expressed breast cancer exists prior to its detection and, even before that, a time when cancer as we recognize it has not occurred, even though the molecular-genetic components for such an event may exist. Neither the two research strategies discussed herein nor current paradigms governing breast cancer are apt to be relevant for patients with either biological or occult, nondiagnosable cancers.

A third investigative approach that might be contemplated is one directed toward devising strategies capable of interfering with the initiation and/or the growth (promotion) of breast cancers so that they never become clinically or mammographically evident. Is now the time to consider implementing such a strategy? If so, has enough experimental and clinical information been obtained to justify formulating a hypothesis that can be appropriately tested and that, if supported, could give rise to a new paradigm—one that relates to prevention of the disease? The following section of this essay considers these questions.

The Origins of a Breast Cancer Prevention Paradigm. There is a consensus that enough information from laboratory and clinical investigations is available to permit the formulation of a hypothesis which contends that an appropriate intervention (such as a low-fat diet, retinoids, or tamoxifen) can prevent the occurrence of biological or phenotypically expressed breast cancers. When deciding whether or not a particular agent should be evaluated in a cancer prevention study, there should be evidence of its worth for preventing the initiation and/or promotion of undiagnosable breast cancer. While several candidates merit evaluation, one agent particularly worthy of appraisal is the nonsteroidal antiestrogen tamoxifen, currently the most widely prescribed antineoplastic agent used to treat breast cancer in the United States. An extensive body of literature exists on the pharmacokinetics, metabolism, and antitumor effects of tamoxifen in experimental animals and in humans—results that provide support for evaluating the worth of that drug as a breast cancer preventive agent (79–82). Although tamoxifen acts as an estrogen antagonist, it may also act as a partial-to-full agonist. The precise mechanism(s) by which it achieves its antitumor effect are unknown. The drug appears to act primarily by competing with estradiol for receptor sites in the cell nucleus, causing estrogen blockade that leads to growth inhibition of malignant cells (83). Several alternative mechanisms of action have been described. Tamoxifen may inhibit cell proliferation by modulating the production of transforming growth factors (α and β) that help regulate breast cancer cell...
proliferation (84); binding to cytoplasmic antiestrogenic binding sites, increasing intracellular drug levels (85); increasing sex hormone-binding globulin, which may decrease the availability of free estrogen for diffusion into tumor cells (86); increasing levels of natural killer cells (87); and decreasing circulating insulin-like growth factor 1 which may, in turn, modify the endocrinological regulation of breast cancer cell kinetics (88). It has recently been reported that tamoxifen may act as an inhibitor of tumor angiogenesis (78).

Tamoxifen impairs tumor initiation. When laboratory animals were treated with it, carcinogen-induced mammary tumors did not appear (75). Investigations using a variety of models have evaluated the effect of tamoxifen on tumor promotion and have shown that, when tamoxifen is given after a carcinogen but before the appearance of a tumor, it prevents the occurrence of a palpable tumor as long as administration of the drug is maintained (76, 77).

Studies have demonstrated a benefit from tamoxifen administration in the treatment of advanced breast cancer (89–92) and in stages I and II disease when the drug has been used as postoperative adjuvant therapy (43–51). The significant reduction in the incidence of cancers of the contralateral breast with tamoxifen is particularly relevant when it is considered as a preventive agent (43, 47, 93–95).

The ideal tumor preventive agent should produce minimal toxicity during prolonged therapy. Adverse reactions to tamoxifen are relatively rare and only infrequently severe enough to require discontinuing treatment. Although doses of tamoxifen many times greater than those given to humans have been found to increase the incidence of liver tumors in animals (96–98), no such increase has been reported in humans treated with conventional doses (20 mg/day). It is likely that the risk of thromboembolic events and endometrial cancer will be no greater after prolonged tamoxifen administration than it is after the use of estrogen-replacement therapy in normal women. When considering the use of tamoxifen as a breast cancer preventive agent, its effect on coronary artery disease and osteoporosis cannot be ignored. Estrogen administration has been associated with an alteration in serum lipoproteins, i.e., a decrease in cholesterol and low-density lipoproteins with an increase in high-density lipoproteins and with decreased mortality from coronary artery disease. Tamoxifen results in similar lipid changes (99–103). Thus, it may also favorably affect mortality from that disease. Similarly, since estrogen lowers the incidence of fractures by decreasing the bone resorption that accompanies surgical or natural menopause (104, 105), the estrogen agonist effect of tamoxifen may prevent bone loss (106). It has been estimated that osteoporosis affects 24 million women in the United States and that 1.3 million fractures occur each year as a result. Consequently, a clinical trial conducted to evaluate the worth of tamoxifen as a breast cancer preventive agent should concomitantly assess its effect in reducing mortality from coronary artery disease and in decreasing the risk of fractures due to osteoporosis.

Tamoxifen has been selected by the NSABP as the agent to evaluate in a prevention trial in which 16,000 women will be randomized so that 8,000 will receive placebo and 8,000 tamoxifen, both groups at 20 mg daily. The study population will consist of women 60 years of age or older and those aged 35 to 59 who have additional breast cancer risk factors, such that their minimum predicted risk of developing breast cancer within the next 5 years is at least as great as that of women aged 60 years or older. The choice of women 60 years of age or older is related to the fact that age is one of the strongest risk factors; rates increase steeply from age 30 to 60 and then plateau. Moreover, postmenopausal women have a substantial and increasing risk of coronary artery disease.

When the trial was in the planning stage, it became increasingly evident that younger women should be included. Not only does a sizable proportion of the morbidity and mortality of breast cancer occur in younger women, but there are also well-established risk factors for breast cancer in women under 60 that identify those with projected lifetime risks sufficiently great to merit their inclusion in the trial. Moreover, because years may elapse between a tumor’s inception and its detection, a preventive intervention may be more effective in women at an early age, even though tumors may appear later in life. In that regard, women with a first-degree relative who had breast cancer when premenopausal are apt to develop the disease at an earlier age. In premenopausal patients, tamoxifen appears to be more effective in reducing the incidence of contralateral breast cancer, life-threatening toxicity from the drug is rare, and non-life-threatening toxicity is much the same as in postmenopausal patients. These observations support its use in younger women. In addition, because younger women at increased risk for breast cancer are often subjected to alternative therapies, such as bilateral mastectomies, which are worse than the side effects observed from tamoxifen, they should not be denied the opportunity to participate in the trial. Finally, the generalizability of the findings would be seriously limited if premenopausal women were excluded from participation in the study. If a benefit was observed in a trial using only postmenopausal women, would those findings justify use of the drug in a premenopausal population, or would another study involving many years of uncertainty be required before it could be used? Thus, there is ample evidence for allowing women aged 35–59 years who have a substantially increased risk of breast cancer the option of participating in the study.

A logistic regression model (107) will be used to estimate, by combining individual risk factors, each potential participant’s composite risk of developing breast cancer. Her percentage probability of developing breast cancer over her lifetime, adjusted for competing mortality risks by initial age and years of follow-up, will also be determined. The variables selected for inclusion in the model are number of first-degree relatives with breast cancer, nulliparity or age at first live birth, number of benign breast biopsies, age at menarche, atypical hyperplasia, and lobular carcinoma in situ.

If a benefit from tamoxifen is demonstrated, a drastic paradigmatic change in the treatment of breast cancer could result— a change from current therapy, which is directed toward the disease at or near end stage, to treatment of the disease when it is non-detectable by any available means, and, perhaps, even before phenotypic expression has occurred. Most significantly, the impact of the findings from this trial on the health of women in the United States and elsewhere could be substantial. It cannot be too emphatically emphasized, however, that the implementation of a trial to evaluate the worth of a hypothesis—and an agent—does not provide physicians with an impetus to administer, outside of the clinical trial setting, the therapy being tested in the trial. Before that can occur, the pathways of science must be carefully traversed and a new paradigm established.
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References

41. Ludwig Breast Cancer Study Group. Randomised trial of chemo-endocrine therapy, endocrine therapy, and mastectomy alone in postmenopausal pa-


97. Gau, T. Open Letter to All U.S. Medical Oncologists Describing the Toxicological Findings in Rats with High-Dose Tamoxifen Treatment. Wilmington, DE: Stuart Pharmaceuticals, A Division of ICI Americas, 1986.


The Evolution of Paradigms for the Management of Breast Cancer: A Personal Perspective

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