

PRESIDENTIAL ADDRESS

Improved Understanding of Mammary Cancer

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Interest in cancer of the breast has begun to yield a concentrated sequence of specific information as to its basic nature, dietary influences, and its hormonal and genetic determinants. Clearly, the advent of improved early diagnosis has allowed the presentation to the clinician of a more favorable aspect of the tumor than has previously been seen, and has altered the overall clinical character of the disease. These advances open the possibilities of greatly expanded and enhanced treatment options, both for the informed physician and the inquiring patient. The rewards of early diagnosis include the possibilities of functional reconstruction, which may alter the potential patient attitude to such an extent that even earlier diagnosis will be achieved in years ahead. The complex issues of multimodality therapy and the honest and valid stratification of patients are the key issues in the further study of this challenging illness.

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I AM DEEPLY APPRECIATIVE of the honor of serving as President of the Society of Surgical Oncology and appreciate, all the more, the fact that I am but the second person to hold such office who never had the privilege of a formal relationship with the Memorial Hospital and/or its successors. This may have represented some personal disadvantage; however, I think that we should all look upon it as a final step in the transformation of the most meaningful surgical alumni club, the James Ewing Society, to a nationally representative organization for the betterment, ethical growth, and development of surgical oncology as the discipline that continues to cure more patients of neoplastic diseases than all other disciplines combined.

The interested participant may wonder at the selection of a title. Why a survey of a common cancer in times of virtually revolutionary change in medicine? These questions are all the more appropriate in consideration of the fact that the current essayist has never been the first author of a major paper on breast cancer and has been near the epicenter of many of the worrisome changes taking place in medicine. The answer to that question is fairly simple. The skills that have led to American leadership of world

scientific surgery are not political and social. Although we still have much to do in terms of representing ourselves and the best interests of our patients in such times of rapid change, it is, in my opinion, wise from time to time to return to the basics of the scientific study and treatment of human illnesses that are amenable to surgical therapy. The current situation in breast cancer emphasizes the value of true interdisciplinary efforts.

This understanding will not be an overview of the current status of the management of breast cancer, but will focus on some advances that have recently taken place and are currently taking place in our understanding of this illness. The clinical presentation of the disease today is as different from that encountered by William S. Halsted¹ at the turn of the century as the very nature of the women who bear the disease and their role in our society. The illness has the same pattern and propensity for metastasis and death, but we now see it in an earlier form so that it literally warrants, as is so true for malignant melanoma,² an altogether different approach from that taken by our surgical forebears. Accordingly, it is necessary to be very cautious in any criticism of our surgical predecessors when the illness they treated is so very different from the one that we discuss today.

Furthermore, I emphasize to the unique collaborations among my colleagues at the University of Louisville over the last decade, which has represented a remarkable amount of surgical and interdisciplinary leadership in oncology. The coordinated contributions of our colleagues in medical oncology, pathology, and diagnostic radiology

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in these undertakings was supplemented by special skills in biochemistry, radiotherapy, and biostatistics. I believe that the interdisciplinary nature of our unit has contributed much to scientific productivity and to our ability to examine our evolving perceptions of breast cancer.³

Improved Understanding of the Basic Disease Process

Increasingly documented are the large variations in incidence in different ethnic and culturally and geographically diverse groups.⁴⁻⁶ a common thread in many of these are dietary factors, which are assuming an increasingly dominant role.⁷ For example, in nonmalignant forms of breast disease and, particularly, the painful variant of chronic cystic mastopathy, the role of substances such as caffeine, chocolates, and hormonally rich cheeses is significant in pathogenesis. Often, for many patients, when these foods are removed from or reduced in the diet, some relief is provided that is more significant than that resulting from any medicinal or surgical manipulation. Further to the point, impressive data show that fat and dairy products, in particular, are closely related to the prevalence of breast cancer within a population, and may become important cocarcinogens under certain circumstances.^{8,9} Indeed, simple obesity is an important determinant, not only of the development of breast cancer, but also for the likelihood of recurrence.¹⁰

The family history, particularly among first-degree female relatives, has also become a major consideration within the last decade, and is most helpful in decision-making regarding florid nonmalignant disease. It is especially useful in helping a woman to assess honestly the likelihood of cancer developing within the mammary glands and in providing alternatives for her selection of methods for surveillance and/or treatment.¹¹

Wittliff, in our Department of Biochemistry, has been among the leaders in the study of the impact of hormone receptors on breast cancer,¹² confirming the important work of Block and Jensen.¹³ Their work in estrogen and progesterone receptors has met high biochemical standards and, most importantly, has served to indicate that such receptors represent independent variables that determine outcome in breast cancer almost as strongly as they do the likelihood of its response to hormone manipulation.¹² Furthermore, the overall prognostic significance of estrogen receptor status is now as clinically meaningful as the time-honored role of axillary lymph nodal status.¹⁴ What is most important of all in this highly significant area is that a patient who has very low or absent levels of estrogen receptors is very unlikely to respond to hormone manipulation after disease recurrence. Under these conditions, many patients can be spared unproductive hormonal ablation procedures, and not only avoid that disabling undertaking, but also move along more promptly to forms of therapy that are more likely to produce results.

One of the most interesting issues relates to the wide

use of conjugated estrogens for treating variably significant menopausal symptoms in middle-aged women.¹⁵ Here again, our group, led by Laman A Gray, Sr., has taken the lead in providing long-term follow-up, which is now widely appreciated. The woman who is a long-term user of these compounds, particularly in cyclic fashion, is free of any increased risk of breast cancer and may well have a slightly decreased frequency.¹⁶ There is a price to pay for this; the woman who retains an intact uterus may have an increase in the likelihood of the development of endometrial cancer, but its safety with respect to breast cancer is, at this point, incontrovertible.

Improved Early Diagnosis

Xeromammography has clearly provided a method by which nonpalpable breast cancers can often be diagnosed, even though there are appreciable false-negative and, to a lesser degree, false-positive rates.¹⁷ The important role of mammography, in this form, is its ability to define minute primary lesions and to do so with an impressive reduction in total irradiation required. This undertaking has had many overt benefits. First is the detection of tumors of such small size as to bear sharply diminished axillary lymph nodal metastases as compared with any prior patients whose disease was detected by more traditional methods. Yes, there is a recognizable false-negative rate, which is but a challenge to our successors.¹⁸ Another benefit is an improved understanding of the development and growth of very small breast cancers.^{19,20} Clearly, we have been able to define relatively fast- and relatively slow-growing breast cancers and to translate those characteristics, not surprisingly, to enhanced 5-year survival rates of individual patients.²¹⁻²³ Furthermore, these data have allowed the evolution of a reasonable strategy for repeated examinations, recognizing in every circumstance that there is always a chance that a rapidly growing tumor that develops between examinations may reach an unfavorable stage before the next scheduled examination.²⁴ Such risks are inevitable when a physician is committed, as we all are, to minimizing radiation-related complications. The continued reduction in radiation to a dose of less than 1 rad per breast per examination will certainly allow an enhanced role for repeated studies. However, we still must define the wisest strategy for cost-effective lifetime use of this modality, recognizing a sound consensus as to its overt value.²⁵

There are some breasts, particularly in older women, which retain such a florid pattern of youthful, active changes that it may be reasonably surmised that ultimate development of neoplastic disease is likely.²⁶ We, among others, have undertaken a careful study, under the leadership of Buchanan, of the significance of parenchymal patterns in the ultimate development of breast cancer.^{16,17} Unfortunately, we were unable to define any specific relationship of these patterns to ultimate outcome and to

the development of breast cancer, a finding now being increasingly widely recognized.

For reasons to be discussed below, much of the strategy of the initial Breast Cancer Demonstration and Detection Projects was altered by the political response to and a pseudoscientific inquiry about the dangers of irradiation. Viewed most sympathetically, this query may have accentuated the search for lower exposures,^{27,28} with sustained high resolution and definition of architectural abnormalities. Again, for emotional and poorly defined reasons, a consensus evolved that younger women, by virtue of requisite frequent examination over a longer residual lifetime, should be spared early screening. This practice still holds in some quarters, despite the seemingly sound evidence of Bland and his associates²⁹ that the woman younger than 50 benefits at least as much as the woman older than 50 from repeated examination as part of a carefully developed screening strategy.

The fullness of time now unequivocally shows the extreme destructive impact of political pseudoscience on this remarkable project. As you all know, the follow-up has been abandoned within this calendar year, and the likelihood of further meaningful observations from this unique undertaking is largely lost. It must also be realized that it was lost amidst a sequence of media-related charges of exposure to radiation that was extrapolated from prior experiences with primitive modalities that were neither physiologically nor scientifically related to the current undertaking. Although a number of individuals, no doubt, found this an ego-gratifying undertaking, its effect upon a relatively soundly evolved scientific inquiry and a valuable demonstration method has been extraordinarily deleterious. At this point, we can only try to pick up the pieces of what is left of this inquiry and go forward with disappointingly incomplete knowledge. The continuing appearance of scientifically creditable studies that unequivocally support the value of such screening speaks for itself, and loudly. We can only anticipate that the screening process will, in some way, be reborn like the Phoenix and, in an increasingly cost-conscious society, find a role that will offer minimization of cost, a full exposé of the bugaboo of excess radiation, and a continuation of the diagnosis of breast cancer in a size and stage previously unrecognized in civilized society.^{30,31}

As is so often the case, the Breast Cancer Detection and Demonstration Projects evolved an entirely different technical issue—that of localization of the nonpalpable primary—but this was mastered in a very constructive way, and has been adapted to the outpatient setting that is increasingly required by cost-containment processes.³²⁻³⁴ A further contribution, needle aspiration cytology, has proved often definitive and is obviously very cost-effective in reducing the need for biopsy of fluid-filled lesions, which do not recur after aspiration.³⁵

The bulk of the data available in the last decade has focused on the remarkable modality of mammography;

however, breast self-examination, as described by Foster and Greenwald and their associates,^{36,37} and now widely promulgated and practiced, has the ultimate cost-benefit ratio. The data that suggest that women who practice the process regularly, with appropriate supervision and instruction, can detect breast cancer in a more favorable form than they can when they depend upon even routine physician examinations are now no longer subject to challenge.³⁸ The physician's obligation to implement appropriate patient-education activities, with a major emphasis upon breast self-examination, is greater than ever. These current trends and practices in health and medicine offer an opportunity for this Society and its members to take local leadership roles of great importance.

Rewards for Early Diagnosis

The rewards for early diagnosis, which have evolved from the foregoing points, have most dramatically changed the nature of options available to the woman who is given the previously dreaded diagnosis of cancer of the breast. Ignoring the semantic differences between favorable, small, and early breast cancers, the woman whose primary tumor is discovered while it is very small has an impressive list of options for treatment. When considering these options, however, four basic factors regarding the fundamental behavior of breast cancer must be remembered: (1) estrogen receptor status^{3,39}; (2) the presence or absence of axillary lymph node metastases¹⁴; (3) the size of the primary tumor; and (4) an evolving array of histopathologic correlates of outcome that reflect the variant biologic behavior of breast cancer. With these constantly recalled caveats, individualized treatment options, which include multimodality therapy, are under wide study and are generally broadly available in the practice community. In undertaking such a study or evaluating the same, it is crucial that the groups be defined physiologically and biologically, that the cooperative trials be undertaken among groups capable of enlisting appropriately similar patients and dealing with such succession honestly and, finally, that the treatment sequences be agreed upon and practiced rigidly.⁴⁰

In my opinion, the swing to broad therapeutic conservatism began with the failure of extended radical mastectomy to show major improvement in survival rates compared with the Halsted operation. Local disease control was increased, but ultimate 5- and 10-year survival rates, even as reported by Urban⁴¹ and Sugarbaker,⁴² were not statistically significantly better than patients treated by more conservative surgical procedures. Inescapably, the belief arose that perhaps even more conservative procedures, in a time in which more and more favorable cancers were being discovered and brought to treatment, might be applicable.

The current options are so numerous as to challenge both the sympathetic surgeon and the intelligent patient.

They would include the following:

- (1) wide local excision of the primary tumor, sufficient axillary sampling, and radiotherapy to the field⁴³;
- (2) primary radiotherapy to the tumor and to the breast with axillary sampling⁴⁴; and
- (3) some form of traditional mastectomy and reconstruction, done either as a primary or secondary undertaking, and using either local tissue plus prostheses or myocutaneous flaps, which may apparently be safely combined with other esthetic procedures at the same setting. Currently, some form of mastectomy, combined with early reconstruction, may be performed without increasing either the local or the systemic failure rate.⁴⁵

These observations have been based on the contributions and leadership of many within this society and do get right to the heart of the issue of cooperative trials, the honesty thereof, and the dangers, not of participation, but of wrongly interpreted data. A good example of this has been the recent wide publicity regarding the value of local excision alone for breast cancer, and the de-emphasis in many public comments of the significance of local recurrence.⁴⁶ Recent data suggest that for the vast majority of women, failure to control the disease on the chest wall is tantamount to death of metastatic breast cancer and is generally accepted as a premonitory symptom of systemic disease.⁴⁷ The suggestions that wide local excision is an acceptable alternative when the "only problem" was a significant increase in locally recurrent breast cancer can only be viewed with extreme concern. As a further caution, the ultimate carcinogenic effect of therapeutic irradiation of the breast may not be known, as is true for other radiation-induced cancers, for another 20 years or more.

The new basics of treatment for the favorable primary tumor are very simple, and can include any one of several methods designed to achieve the following goals: (1) wide local excision of the primary tumor; (2) some kind of appropriate treatment, at this time surgical or radiotherapeutic, of the field; (3) appropriate axillary lymph node sampling; and (4) always the consideration of reconstruction for patients whose tumors prove to be favorable.

Because so much of this discussion has been oriented to the favorable breast tumor, we must not neglect the remarkable contributions of our domestic and European colleagues in demonstrating, through carefully stratified and controlled trials, the value of systemic chemotherapy to the premenopausal woman whose breast cancer may have metastasized to a few axillary lymph nodes. Here again it is valuable to identify a group that is extremely likely to fail with local and regional treatment and for whom increased survival has been associated with the presumed systemic treatment of micrometastases.^{43,48,49} This is an exceptional circumstance, but it is the exception that proves the rule, and has represented another major advance, not only in current treatment, but also in our understanding of the illness. Furthermore, the assessment

of the real value of and indications for bone scans and chest roentgenograms in both preoperative evaluation and postoperative care have been defined. Once again, the current rage with cost-effectiveness has defined the considerable limits of both in clinical Stage I disease.⁵⁰

Random Issues

Many other questions regarding breast disease continue to plague the physician and the patient alike. Not the least of these is the alleged frequency of cancer arising in chronic cystic mastopathy. A current article in *CANCER*⁵¹ shows that a whole variety of impressive but noncancerous changes in breast tissue may exist over long periods and actually carry little, if any, increase in the likelihood of the ultimate development of invasive breast cancer. In response to other data,⁵² Hutter has further refined the definition of the overtly safe variance of fibrocystic disease.⁵³

The complexity of care of the breast cancer patient leads more and more physicians to turn to honestly stratified flow diagrams for the management of their patients; this means that more and more of us must turn to those kinds of standard references, which have stood the test of time and continue to be updated with a broad perception of these changes.⁵ Most importantly, insightful analysis of solid data and evolving trends will allow us, as Gardner⁵⁴ did so well, to examine the continuing evolution of this vital clinical problem.

As I have indicated previously, there has been a change, not only in the illness of breast cancer, but also in the life and times in which we live and practice. The commitment of the Society of Surgical Oncology and its members to participation in cooperative trials has been addressed before and, indeed, has made possible discussions such as those that are taking place today. On the other hand, there is vast room for improvement and elaboration of our efforts in the broad field of patient education. In my opinion, every sophisticated patient contact center must make a substantial effort toward patient education. There is no field in which that is more significant than that of both benign and malignant diseases arising in the female breast.

The potential wise application of cost controls by both public and private insurers of medical care promises much for our society. The specific protection of the full range of direct and indirect costs of medical education, in the broadest sense, has already received special attention; similar respect for honest and ethical clinical trials is no less mandatory.

Improvement in patient care, manifested by decreased treatment morbidity and mortality and enhanced long-term survival, represents a number of hard-won victories. Each and every one of them will, to some degree, be followed by 5 to 10 years of increased understanding of the basic processes involved in the disease or in its multiple treatments. This is precisely where we stand in our understanding of human breast cancer and exactly why we

have an opportunity and an obligation to implement our improved knowledge into a new level of well-being not hitherto appreciated by the American public.

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