PARADIGMATIC SHIFTS IN THE MANAGEMENT OF BREAST CANCER

It has been almost exactly 100 years since William Halsted published his seminal report on the use of radical mastectomy "for the cure of cancer of the breast,"[1] and it is fitting that this issue of the *Journal* includes the long-term results of two randomized trials evaluating treatment for breast cancer that might be cured with mastectomy alone.[2,3] Halsted's ideas and his operation dominated our thinking about the treatment of breast cancer until approximately 25 years ago, when a major paradigmatic shift began. The premises underlying the Halsted approach were that metastases occurred by centrifugal and contiguous spread from the primary tumor in the breast and that, as a result, improved local control should decrease the frequency of metastases and death from cancer.[4] In his first report, Halsted stated that an operation should be judged on the achievement of local control rather than "ultimate cure." Thus, subsequent generations of physicians have rejected the use of any local treatment associated with a rate of local recurrence higher than that achieved with radical mastectomy.[1]

Six randomized trials have demonstrated that the survival of patients treated with a breast-conserving operation (variously referred to as lumpectomy, tylectomy, wide excision, or quadrantectomy) plus radiotherapy is equivalent to that of patients treated with mastectomy.[2] However, the same degree of local control is not always achieved with these two procedures. In the study by Jacobson et al. reported in this issue of the *Journal*,[2] 18 percent of patients had a recurrence within the irradiated breast; 5 percent of the patients receiving the breast-conserving treatment had a local or regional recurrence — that is, one involving regional lymph nodes, skin, or muscle — or could not undergo surgery for some other reason at the time of recurrence. Of course, none of the patients in the mastectomy group had a recurrence within the breast, but 10 percent had a local or regional recurrence. In general, a local recurrence after mastectomy has about the same prognostic importance as a distant recurrence,[5] and it is often assumed that a recurrence within the breast after irradiation has the same implication as any other type of local or regional recurrence. The fact that the overall survival of patients randomly assigned to receive breast-conserving therapy and radiation therapy in these studies is equivalent to the survival of patients who underwent mastectomy in spite of the higher local-failure rate suggests that recurrences confined to the irradiated breast do not have the same prognostic importance as recurrences in the lymph nodes, skin, and muscle. Another possibility is that the rate of local recurrence is not a good surrogate end point for survival, as assumed by Halsted and his successors.

The use of breast-conserving operations and radiotherapy does not, however, represent a paradigmatic shift. If anything, this form of local treatment is more extensive (or more radical), because the supraclavicular and internal mammary nodes are treated more effectively with radiation than they are with even the most radical forms of surgery. For a true evaluation of Halsted's hypothesis, patients in several studies have been randomly assigned to receive breast-conserving therapy alone or with radiotherapy.[6-8] In these studies too, a higher local-recurrence rate among women who underwent lumpectomy alone did not compromise survival. However, a recent reanalysis of one of these studies suggests that this finding may not hold true with follow-up periods of more than 10 years.[9] Local failure is a particularly difficult consequence of therapy for most patients because it is readily apparent and is thus a constant reminder that the tumor is no longer curable. For both these reasons, the importance of local control cannot be dismissed as entirely irrelevant.[3]

The first reports describing an improvement in disease-free survival with the use of adjuvant chemotherapy also stimulated intense controversy.[10,11] Many argued that an improvement in disease-free survival would not necessarily lead to an improvement in overall survival, that early results would not necessarily be confirmed with longer follow-up, and that this research was "diverting the funds away from more valuable basic research."[12] However, the results with adjuvant chemotherapy have been confirmed in additional studies and in an overview of all adjuvant studies.[13] The report by Bonadonna and his colleagues in this issue of the *Journal* demonstrates that the effects are lasting.[3]

The underlying rationale for the use of systemic therapy as an adjuvant to surgery is that patients die despite the achievement of good local control because blood-borne micrometastases are present in distant organs long before the diagnosis of breast cancer can be made with the most sensitive techniques now available.[14] This clearly represents a shift from the views of Halsted and other surgeons of the 19th and early 20th centuries. The results of these adjuvant-chemotherapy trials provide substantial evidence, if not proof, that this new concept is correct and is much more important than the relatively small survival benefit that is achieved, because it indicates that further improvement in the survival of patients with breast cancer will be achieved by better systemic rather than local therapy.

Are some patients cured by adjuvant treatment whereas others derive no benefit at all? Or is the survival of most patients prolonged only transiently, with no patients or very few cured?[15] Adjuvant-chemotherapy trials do not provide much insight into these questions. The curves shown in Figure 1 of the article by Bonadonna et al.[3] could be used to support either one of these interpretations. However, the latter explanation seems more probable. At the time of the analysis, 138 of the 179 patients randomly assigned to the control group had died, but only 10 of these women (7 percent) died without evidence of disease recurrence.[3] Of the 207 women randomly assigned to receive adjuvant chemotherapy, 137 had died, but only 14 (10 percent) died without evidence of disease recurrence (P not sig-

nificant). These findings suggest that the percentage of women who died of breast cancer in the two groups was nearly the same but that the time at which they died was different. To some women, especially those with a good prognosis, it is important to know whether adjuvant therapy will prolong their lives rather than eradicate the disease and, if so, how much their lives will be prolonged.[15] Unfortunately, even after 25 years of study, we can only roughly estimate the additional months or years of life that any one patient might gain as a result of this treatment.

The benefits of adjuvant chemotherapy may result from a direct cytotoxic effect of the therapy on the cancer cells, as is most often presumed, or from an indirect effect mediated by an endocrine organ such as the ovary. These effects are not mutually exclusive. It is striking that in almost all individual studies and in an overview of all adjuvant-chemotherapy trials, the beneficial effects of adjuvant chemotherapy are smaller among postmenopausal women than premenopausal women.[13] Bonadonna and his colleagues argue that this difference arises from the use of reduced doses of chemotherapy in older women.[3] In addition, they reason that if the effects of adjuvant chemotherapy are the result of a chemical ovarian ablation, the reduction in mortality produced by chemotherapy should be greater among premenopausal women with drug-induced amenorrhea than among treated premenopausal women who did not become amenorrheic. This was not observed. Theirs is not the last word on this subject, however. A better experiment would be a randomized comparison of ovarian ablation with chemotherapy in premenopausal women. One such study has recently been reported, and it failed to show a significant difference in outcome related to the treatment used.[16]

The importance of this question lies in the research paths we pursue in the next decade. If, in fact, the survival benefits of chemotherapy are primarily a result of ovarian ablation, then therapy involving manipulation of the dozens of newly identified growth factors is particularly promising. On the other hand, if the survival benefits result primarily from the direct cytotoxic effects of the drugs, then very-high-dose chemotherapy and other strategies that circumvent the rapid resistance that develops to chemotherapy hold greater promise.

In both these papers possibly the most important point, which should not be overlooked, is the survival of patients in all treatment groups after 10 to 20 years of follow-up. In the study from Milan,[3] which included only patients with histologically positive lymph nodes, 25 percent of the patients treated with mastectomy alone and 34 percent of the patients who received adjuvant chemotherapy were still alive at 20 years. The study from the National Cancer Institute[2] included a number of patients with a better prognosis; the 10-year survival of all patients exceeded 70 percent. These data should be reassuring to the many patients with cancer who believe that a diagnosis of breast cancer is a death sentence. Taken together, these numbers also demonstrate that many patients survive for long periods with local therapy only and presumably, at least in part, as a result of that therapy. Adjuvant chemotherapy prolongs the survival of other patients.

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AN ORALLY ACTIVE IRON CHELATOR

IRON is essential for all organisms from bacteria to humans; but like excessive amounts of alcohol, which is so pleasant in moderation, a surfeit of iron is fatal. The lethal effects of iron overload can be immediate, as in an accidental or deliberate overdose of medicinal iron, or slow, as in congenital hemochromatosis and transfusional hemosiderosis. In the slowly developing conditions — the former due to hyperabsorption of iron in food and the latter to iatrogenic, as well as, in the case of thalassemia, hyperabsorptive factors — iron stores in the reticuloendothelial system are filled to the brim with nontoxic ferruginous granules. Spillage of iron into parenchyma and plasma is inevitable, and toxic effects due to oxidation of membranes follow. The excess iron saturates the binding sites of transferrin, the "delivery boy" of iron metabolism, allowing free iron to circulate and oxidize heart-muscle membranes[1] until the patient succumbs to heart failure and arrhythmia.

Thalassemia is one of the most common diseases in regions of the world where malaria has long been rampant. This inherited disorder of hemoglobin synthesis is fatal in infancy without transfusions but is fatal in adolescence even with them. The advent of treatment with subcutaneous deferoxamine has changed this gloomy prognosis. Recent studies demonstrate that over 90 percent of patients who comply with the difficult and expensive regimen of deferoxamine treatment survive without heart disease[2] and with minimal toxic effects if the dose is tailored to the iron burden.[3]

Deferoxamine has a very high and selective affinity for iron that is independent of the iron concentration.[4] The required dose is relatively low (about 40 to 50 mg per kilogram of body weight administered in an overnight subcutaneous infusion). Serious side effects are rare. But the drug is not active orally, and nightly subcutaneous self-administration is onerous, leading to a high frequency of noncompliance, a uniformly fatal "complication" of therapy.

There are only two alternatives to subcutaneous deferoxamine: allogeneic bone marrow transplantation for the 25 percent of patients with histocompatible donors, and an orally active iron chelator. The former has received attention recently because of a report from a center in Italy, where patients with good chelation had more than a 90 percent likelihood of indefinite thalassemia-free survival after bone marrow transplantation.[5] However, the investigators' method of stratifying patients is not readily reproducible, and experience with bone marrow transplantation in young patients with good chelation in the United Kingdom and the United States shows that the rate of disease-free survival is no higher than 75 percent and may be lower.[6,7] Nevertheless, bone marrow transplantation can solve the therapeutic problem once and for all and, until now, has been the only useful option if a patient cannot or will not use deferoxamine or if the blood supply is of uncertain safety and reliability.

In this issue of the *Journal*, Olivieri and her colleagues

feriprone has a checkered history. It was originally synthesized by Robert Hider and his colleagues at Essex University, and the early biologic assessments were performed at University College Hospital in London.[9] The drug was used in the clinic of another London hospital without sufficient studies of toxic effects in animals and without Hider's approval.

Deferiprone has a much lower therapeutic ratio than deferoxamine, for two reasons. First, deferiprone is considerably more toxic and regularly depresses the granulocyte count in both normal and iron-overloaded animals[10]; deferoxamine, in contrast, does not depress the marrow. In clinical studies, deferiprone has caused both agranulocytosis and arthralgia or arthritis; the frequency of these complications is not yet known. Second, though Olivieri and her colleagues clearly demonstrate that deferiprone can reduce iron stores to lower, if still elevated, levels in patients with severe overload, the drug has a concentration-dependent affinity for iron.[4] Three molecules of deferiprone are required to bind one molecule of iron, whereas deferoxamine binds iron tightly in a 1:1 ratio. For this reason, deferiprone must be present at very high concentrations (close to toxic levels) to be effective. It dissociates from iron when the concentration of iron in body fluids falls to the level achieved just a few hours after oral administration.[4] Hence, as demonstrated by Olivieri and her colleagues, deferiprone does not readily reduce excessive body iron stores below a certain level. It is therefore not clear that the drug will provide long-term protection from heart disease.

Not enough is known about the pharmacologic properties of deferiprone. Will the low levels of drug that remain in the plasma continue to chelate free iron and thereby protect heart-muscle membranes, or will the small but highly toxic pool of free iron remain or return to high levels between doses to do its damage? Over time, will the drug's ability to be absorbed prove to be a two-edged sword because it can also permeate the cell membranes of vital organs such as the kidney, with toxic effects? That has been the sad fate of an extremely active oral iron chelator called desferithiocin.[11] Finally, will adolescents really swallow enough pills to amount to 75 mg per kilogram in three divided doses every day? For an adolescent of average weight, this represents 1 to 2 g of the drug three times daily. Such a burdensome regimen is itself an open invitation to noncompliance and the development of heart disease. Ominously, 10 percent of the patients in the trial reported by Olivieri et al. did not comply with the regimen.

Given these concerns, clinical studies of deferiprone that last for several years and enroll at least 100 patients will be required before physicians can advise patients with thalassemia to dispense with nightly subcutaneous administration of deferoxamine and instead swallow a handful of capsules every eight hours. Patients who are unable or unwilling to use deferoxamine and for whom there are histocompatible donors available will have to weigh the unknown risks of defer-

Despite questions about the long-term efficacy and safety of deferiprone in the management of thalassemia, Olivieri and her coworkers are to be congratulated for rescuing the drug from a shaky start and for performing a careful initial study that moves the field forward. Whether deferiprone proves to be useful and safe will be known in the fullness of time. Whatever further studies of the drug reveal, it is comforting to know that the search for a better life for patients with thalassemia is in reliable hands.

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CLINICAL IMPLICATIONS OF BASIC RESEARCH

TELOMERES, CANCER, AND IMMORTALITY

NUMEROUS genetic accidents, including the activation of proto-oncogenes and the loss of tumor-suppressor genes, can result in the stimulation of cell division. However, mammalian cells have evolved an intricate set of checks and balances against uncontrolled cellular proliferation. One of these is cellular suicide, or apoptosis, triggered by the p53 gene in the presence of aberrant growth signals. Another appears to be the progressive shortening of the ends of chromosomes, or telomeres, that accompanies normal cell division and may contribute to cellular aging. Support for this concept comes from a recent article in *Science* by Kim and coworkers,[1] reporting a dramatic correlation between cancer and the expression of telomerase, an enzyme capable of preventing the shortening of telomeres. This finding suggests that virtually all cancers must activate telomerase in order to overcome a biologic clock, and it points to a potentially important new therapeutic target in the fight against cancer.

Telomeres are thought to be critical in maintaining chromosomal integrity.[2] In humans they are composed of a sequence of six nucleotides (thymidine, thymidine, adenosine, guanosine, guanosine, and guanosine, or TTAGGG) repeated from a few hundred to a thousand times. These sequences are synthesized by telomerase, a ribonucleoprotein enzyme (composed of both RNA and protein). The RNA component contains nucleotides that are complementary to those present in the telomere (Fig. 1, inset). By reverse transcription, telomerase makes a DNA copy of its own RNA sequence, which is then fused to the 3′ terminus of the chromosome. The extension of telomeres by telomerase is required to counter the normal shrinkage of chromosomes that occurs after each round of DNA replication. Normal replication of a linear DNA strand by DNA polymerase is initiated from the site of a bound primer and can proceed only from 5′ to 3′. Since no primer is bound at the extreme 5′ end of each chromosome, there is a gap in replication, leading to a progressive shortening of daughter strands with each round of DNA replication. The length of a telomere is thus determined by the balance between the number of cell divisions and the activity of telomerase.

The importance of preserving the length of telomeres in continuously dividing cells has been clearly demonstrated in yeast and in the protozoan tetrahymena, in which the inactivation of telomerase results in the shrinking of telomeres, chromosomal loss, and eventually cell death. In humans, germ cells express telomerase and maintain their telomere length (along with their ability to divide) throughout life. In contrast, somatic tissues do not have telomerase activity, and they progressively lose telomere length. In a given person, the telomeres in skin and blood cells are shorter than those in germ cells, with an estimated loss of 15 to 40 nucleotides per year.[3,4] Patients with progeria, the premature aging syndrome, have pronounced shortening of telomeres.[5] These observations have led to the hypothesis that telomere length serves as a biologic clock regulating the life span of normal cells (Fig. 1). In a manner consistent with this model, cultured normal human fibroblasts undergo a finite number of cell divisions, after which they enter a state of senescence or terminal arrest of growth. The number of cell divisions correlates well with the initial length of the telomeres, and progressive loss of telomeres is observed in culture: 50 to 200 nucleotides are lost with each cell doubling, and some 4000 nucleotides are lost by the time of senescence.[5,6]

In contrast to normal cultured cells, tumor-derived cell lines that can grow indefinitely in vitro express telomerase, and their telomeres do not progressively shrink. Thus, cancer cells have appropriated a gene whose normal function may be to allow germ cells to avoid the mortality of somatic cells. The aberrant expression of telomerase in cancer cells may result from a mutation in the sequences that normally regulate its expression, and the timing of that mutation may be inferred from the length of the telomere itself. Primary ovarian tumors expressing telomerase were found to have very short telomeres, suggesting that they had undergone many cell divisions before telomerase was activated and telomere length stabilized.[7] Thus, the activation of telomerase may not be the initial transforming event leading to cancer, but rather a late genetic event that allows the cancer to progress by conferring immortality on cancer cells that are already transformed.

The recent study by Kim et al.[1] has demonstrated the widespread expression of telomerase in cancer cells, implying that telomere stability is critically important for the progression of cancer. Since the telomerase gene in humans has not been isolated, the authors used a sensitive and reliable polymerase-chain-reaction (PCR) assay of telomerase enzymatic activity. Ninety of 101 specimens from primary tumors, representing 12 different types of cancer, contained telomerase activity, whereas none of 50 normal tissues had detectable activity. Similarly, 98 of 100 cancer-derived cell lines expressed telomerase, as compared with none of 22 cultures derived from normal tissues. Benign tumors such as leiomyomas and colonic adenomas did not express telomerase, and only 1 of 10 specimens of tissue affected by benign prostatic hyperplasia showed such expression. This striking correlation suggests that the expression of telomerase may be a common pathway leading to cancer.

Does this study suggest potential diagnostic or therapeutic options that would be applicable to a wide range of cancers? The extreme sensitivity of the PCR-based enzymatic assay allows the detection of 1 cancer cell expressing telomerase among 10^4 normal cells. However, this assay, involving the PCR amplification of a synthetic telomere-like DNA target elongated by endogenous telomerase activity, will need to be adapted for general use before its applicability in the diagnosis

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