Hobson's Choice and the Need for Combinations of New Agents for the Prevention and Treatment of Breast Cancer

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The excellent article by O'Regan, Jordan, and colleagues in this issue of the Journal *(1)* highlights the "Hobson's Choice" currently available for clinical prevention or treatment of early breast cancer. In the 1600s, Thomas Hobson ran a large stable and rented horses at Cambridge University. He compelled customers to rent the one horse that happened to be nearest the stable door or go without—hence the term "Hobson's Choice." In current parlance, it has the connotation of an apparently free choice when there is no real alternative. Presently, we are faced with the clinical equivalent of a Hobson's Choice if we wish to use more than one experimental drug for prevention or adjuvant treatment of early breast cancer. In spite of numerous animal studies that indicate that treatment with combinations of two or more drugs is most effective, our current clinical choice appears to be the selection of a single experimental drug, not the opportunity to select experimental combinations that might offer a more promising outcome.

The article by O'Regan et al. *(1)* seeks an experimental answer, in the current clinical framework, to the question of how to treat women who have completed 5 years of tamoxifen therapy for early breast cancer in the adjuvant setting. It has been demonstrated conclusively that 5 years of adjuvant treatment with tamoxifen for postmenopausal patients with early-stage breast cancer results in greater reductions in breast cancer recurrence and mortality than do shorter treatments *(2)*. However, more than 5 years of adjuvant tamoxifen not only does not further improve outcome but substantially increases risk of endometrial cancer *(3,4)*. These postmenopausal women continue to be at risk for recurrence in the ipsilateral breast, for a second primary cancer in the contralateral breast, and for osteoporosis. One possible solution to this problem would be to substitute another selective estrogen receptor modulator (SERM), namely raloxifene, for tamoxifen at the end of 5 years. Like tamoxifen *(5)*, raloxifene has been shown to be clinically effective in lessening the risk for development of a first estrogen receptor (ER)-positive breast cancer in postmenopausal women *(6);* furthermore, raloxifene prevents osteoporosis and, unlike tamoxifen, does not appear to cause endometrial cancer *(6)*. The relative efficacies of tamoxifen and raloxifene for clinical prevention of primary breast cancer and endometrial cancer are currently under study in the Study of Tamoxifen and Raloxifene (STAR) trial sponsored by the National Cancer Institute.

As noted by O'Regan et al. *(1)*, the definitive answer to the usefulness of raloxifene after 5 years of adjuvant tamoxifen could be obtained in a very costly, lengthy, and impractical clinical trial. In their article, they have therefore used a suitable animal model to study this question. Unfortunately, the findings they report do not support an optimistic future for the use of raloxifene as a replacement for tamoxifen after 5 years of adjuvant therapy with the latter. In the mouse model used by the authors, and at the dose levels of drugs that were designed to mimic clinical usage, they found that neither raloxifene nor tamoxifen was effective in blocking the stimulatory effects of low-dose estrogen on human breast cancer cells that had been exposed to tamoxifen for more than 5 years. On the basis of their animal studies, they conclude that in women completing 5 years of tamoxifen, raloxifene may not further reduce the risk of breast cancer recurrence, although their experimental design does not address the question of whether raloxifene might be useful in this situation to prevent the development of a second primary cancer. Furthermore, they found no evidence that raloxifene offers any benefit in the treatment of human endometrial cancer cells (transplanted *in vivo*) that have previously been exposed to 5 years of tamoxifen in athymic mice, although again, their experimental design does not address the possibility that raloxifene could prevent the development of a primary endometrial tumor.

The conclusion to be drawn from these extensive animal studies is that adjuvant monotherapy with either tamoxifen or raloxifene has major limitations. In a broader sense, these studies emphasize the inadequacies of using single agents for either prevention or treatment of most common forms of carcinoma. Considering that the process of carcinogenesis, which results in invasive and metastatic disease, almost always involves multiple genetic and/or epigenetic lesions, it is unreasonable to expect that a single chemopreventive or chemotherapeutic agent will be optimal for controlling the pathological process. The process of carcinogenesis is multifocal and interactive, and therefore, its ultimate control will require the use of multiple agents to control the global cellular and tissue pathologies that are causative for carcinoma.

Novel pharmacologic approaches to cancer should be based on new advances in cell biology. As an example, a new view of the nucleus (clearly a site of critical genetic and epigenetic pathology during carcinogenesis) is emerging *(7)*. Rather than being a homogeneous, static organelle, the nucleus is now viewed as a structurally and functionally heterogeneous organelle with many components that are highly dynamic and interactive. Activation of gene expression requires remodeling of chromatin to allow assembly of the transcriptional machinery. Agents that remodel chromatin, whether they be histone deacetylase inhibitors *(8)* or agents that demethylate DNA *(9,10)*, thus can enhance the actions of other pharmacological agents *(11)* as diverse as the SERMs, selective peroxisome proliferator-activated receptor-γ modulators (SPARMs), retinoids, rexinoids (ligands selective for binding to retinoid X receptors), and deltanoids (ligands for the vitamin D receptor), all of which activate transcription fac-

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tors themselves. Likewise, many agents that impinge on signal transduction cascades, whether they be small molecules that are selective tyrosine kinase inhibitors or antibodies such as herceptin, modulate the genetic action of other transcription factors (e.g., by altering their phosphorylation) that may be critically involved in carcinogenesis. In addition to considering new agents that act directly on premalignant or malignant epithelial cells, attention needs to be focused on the importance of stromal–epithelial interactions, which are particularly germane to carcinogenesis in the breast. The new concept of "stroma as carcinogen" suggests that it will be possible to devise combinations of agents that will normalize the pathological communication between stroma and epithelium that contributes to the development of breast cancer *(12,13)*.

Although tamoxifen and raloxifene represent landmark achievements for the control of breast cancer, neither one is a new agent, and it is time to investigate new, more effective molecules, especially their use in combination. Experimental animal studies have shown that the addition of 9-*cis*-retinoic acid or one of the newer rexinoids can greatly potentiate the action of tamoxifen or raloxifene in prevention or treatment of ER-positive breast cancer in rats *(14–16)*. Moreover, 9-*cis*-retinoic acid or the rexinoid Targretin have been shown to be effective preventive agents in a mouse model of ER-negative breast cancer *(17,18)*. These first studies on prevention of ER-negative disease are particularly noteworthy and suggest that some drug combinations could be even more useful for preventing ER-negative disease than a single drug alone. Furthermore, new SERMs, such as arzoxifene, have been developed to have higher potency and better bioavailability than raloxifene *(19)*, again without the uterotrophic activity of tamoxifen, and to be less susceptible to the development of drug resistance *(20)*. Combinations of other agents with arzoxifene now need to be tested in experimental model systems for eventual use in the clinic.

Beyond the use of SERMs and rexinoids, at present, adjuvant treatment or prevention with combinations of agents can draw upon a wide array of new drugs that act by mechanisms known to be relevant to the control of breast cancer. This array includes experimental drugs, such as histone deacetylase inhibitors, SPARMs, and deltanoids, all of which are being studied intensively in animal models, as well as agents already in clinical use, such as herceptin, aromatase inhibitors, or cyclooxygenase-2 inhibitors.

There is a surfeit of options for potential combinations of agents. Innovation is needed to devise proper patterns of combinations tailored to mechanistic understanding of the pathogenesis of disease in individual patients. Although *primum non nocere* remains a cardinal principle, it is neither scientifically acceptable nor clinically desirable to confine ourselves to the Hobson's Choice of single preventive or adjuvant agents in the attempt to control breast cancer.

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NOTE

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