

PREFACE

There is enormous public interest in the successful use of endocrine therapy for the treatment of cancer. Newspapers and magazines daily extol the virtues of one product versus another. Tamoxifen is a household name and millions of people are now taking hormone antagonists in one form or another. This is the reason for writing this book.

We have lived through a revolution of translational research that, we believe, can be used as a model for future progress. The principle was simple—find a target in the cancer cell and attack a critical pathway for growth. But at the start, there was no guarantee of success. History is lived forward, but written in retrospect. We know the end before we describe the beginning and so we can never really recapture what it was like.

Thirty years ago, when we were starting our careers in endocrinology and pharmacology, the treatment of breast and prostate cancer was very different from what it is today. Patients were treated in the later stages of the disease based on clinical observations and experience accumulated over three generations. Strategies were not mechanism-based, although translational research had been important in defining the role of the ovaries and the testes in the growth of breast and prostate cancer, respectively.

In the case of breast cancer, radical mastectomy was the standard of care, with radiation therapy available to control recurrences. Advanced breast cancer was showing encouraging responses to combination chemotherapy, which led to the widespread belief among the medical community (that is still held by many today) that the appropriate cocktail of new and powerful chemotherapies would be found that would cure cancer. Adjuvant chemotherapy was not an option because the concept of destroying the last micrometastasis after “curative” surgery had not yet evolved into the lexicon of clinical trials. Although hormonal therapy had fewer side effects than any of the chemotherapies, the clinical studies in the 1950s and 1960s had proven, to the satisfaction of nearly everyone, that endocrine therapy was not a useful path for clinical investigation. High dose estrogen or androgen therapy showed advantages for about a year in one third of postmenopausal women with metastatic disease. Diethylstilbestrol produced higher response rates in prostate cancer, but most patients relapsed and many had serious cardiovascular complications caused by the therapy. The medical and scientific community concluded that hormonal approaches could not provide

any long-term benefits for patients. Rather than adding high doses of hormones, the other strategy was endocrine ablation to remove the ovaries, adrenal glands, or the pituitary gland. These approaches could be life-threatening and, more often than not, did not produce any beneficial response for the patient. Clearly, a test was needed to predict who to treat successfully, thereby avoiding unnecessary surgery.

The treatment of prostate cancer was also empiric. Although Professor Charles Huggins had received the Nobel Prize in 1966 for his contributions to the endocrine control of prostate cancer, it is fair to say that basic research on prostate cancer was at least a decade behind breast cancer research at this time. Nevertheless, the seeds for success had been sown that would develop into a molecular approach to drug treatment in the 1970s.

Elwood Jensen synthesized the first high specific activity tritiated estradiol and showed that it was localized and retained in the estrogen target tissues of immature rats. Jensen proposed the existence of an estrogen receptor (ER) that modulated estrogen action within different target cells. He thus established the molecular foundation for steroid endocrinology. But perhaps of greater importance, he also translated this knowledge to propose that the ER assay would predict the response of breast cancer patients to endocrine ablation. However, the concept that the presence of ER would predict endocrine responsiveness only became widely accepted following an NCI conference in Bethesda in 1974. Jensen had solved the important issue of targeting ablative therapy to those who were most likely to respond but perhaps more important, in our view, he identified a target for rational drug discovery. Unfortunately, in 1970, there was little or no enthusiasm for drug development in this area.

The first nonsteroidal antiestrogen was discovered serendipitously in the 1950s by Leonard Lerner and associates at the William S. Merrill Company, Cincinnati, but the analogs were not developed for cancer therapy because of toxicological concerns. One compound, clomiphene, was developed to induce ovulation in subfertile women, but the original enthusiasm that nonsteroidal antiestrogens would be effective “morning after” contraceptives had waned by the late 1960s. No one was suggesting research in antiestrogens as the way to a successful career. However, Arthur Walpole and Dora Richardson working at the laboratories of ICI Pharmaceuticals (now AstraZeneca) in Alderley Park, Cheshire, discovered a novel series of triphenylethylenes with reduced toxicity. In the patents, it was recognized that the drugs had the potential to regulate the reproductive cycle and to treat hormone-dependent cancers. The latter application alone, if it were achieved, would be a major advance as there

would now be little need for ablative surgery. Walpole was the head of the Fertility Control Program at ICI Pharmaceuticals throughout the 1960s and his work provided the basis for the development of tamoxifen for the induction of ovulation and for the treatment of advanced breast cancer in the 1970s. Unfortunately, Walpole died in July 1977 and never saw the full application of the results of his discoveries. He was an outstanding individual who was responsible not only for antiestrogens but also for the investigation of drugs that regulated gonadotrophin release. His contributions were essential to the progress we see today in the endocrine treatment of both breast and prostate cancer.



Nobel Laureate Dr. Charles Huggins, founding Director of the Ben May Laboratory for Cancer Research (left), and Dr. Elwood Jensen, his successor (right).

We are, therefore, both beneficiaries of Walpole's legacy. Walpole played an important role in our careers by encouraging us to develop our own ideas. One of us (VCJ) experienced Walpole "the PhD thesis examiner" in 1972 for a study of the structure activity relationships of nonsteroidal antiestrogens at Leeds University. Walpole subsequently approved the resources to conduct the first laboratory studies of tamoxifen (then ICI 46,474) as a treatment and preventative for breast cancer in laboratory animals. These studies by VCJ were conducted at the Worcester Foundation between 1972 and 1974 so the results could

be used to support clinical trials in the United States. Also, with the help of Elwood Jensen, then Director of the Ben May Laboratories at the University of Chicago, studies showed that tamoxifen blocked estradiol binding to human ER. Walpole subsequently strongly supported a Joint Research Scheme between Leeds University (VCJ) and ICI Pharmaceuticals (1975–1979). The results of this collaboration identified the potential of antiestrogens with high affinity for ER and the relationship between duration of tamoxifen treatment and the effectiveness of the antitumor actions. This was a key discovery for the future clinical application of tamoxifen as an adjuvant therapy.

One of us (BJAF) was recruited to ICI Pharmaceuticals in 1972 by Arthur Walpole to work in the Reproductive Endocrinology Group. His leadership and encouragement led to the discovery, with Dr. Anand Dutta, of the LHRH agonist, Zoladex, and its depot formulation with Dr. Frank Hutchinson. Although Walpole also supported strongly the antiandrogen project that led to the discovery of what is currently the leading antiandrogen, Casodex, sadly he did not live to see this triumph either.

Today, tamoxifen has reached its full potential as an endocrine agent used to treat all stages of breast cancer. Millions of women with breast cancer have benefited from the use of tamoxifen. Long-term adjuvant tamoxifen therapy is proven to save lives, and it can be estimated that 400,000 women are alive today because of this appropriate treatment strategy. The recognition that tamoxifen was becoming a “treatment of choice” encouraged the subsequent development of selective aromatase inhibitors and pure antiestrogens and pioneered the development of a whole new drug class: the selective estrogen receptor modulators (SERMs) to treat osteoporosis and to test in the prevention of coronary heart disease and breast cancer.

The lessons learned with tamoxifen were applied to prostate cancer with the development of nonsteroidal antiandrogens and luteinizing hormone releasing hormone (LHRH) superagonists to interrupt gonadotrophin release. These latter agents are used to treat both breast and prostate cancer.

The chapters in *Hormone Therapy in Breast and Prostate Cancer* describe the laboratory and clinical development of concepts that are now successfully applied for the treatment of breast and prostate cancer. We are pleased to thank our friends and colleagues who have contributed to the chapters and created a balance of history, laboratory discovery, and clinical practice. Our book is offered as a foundation and guide to progress for researchers and clinicians alike.

The clinical progress during the past three decades would not have happened but for the conceptual shift in reasoning that occurred in the early 1970s. The central role of steroid receptors in our story was the direct result of Elwood Jensen's seminal studies in translational research. We are honored that Professor Jensen generously agreed to write the Foreword for our book.

***V. Craig Jordan
Barrington J. A. Furr***

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V. CRAIG, J.; Furr, B.J.A. (Eds.)

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