

PREFACE

The sharp decline in ovarian steroidogenesis occurring at the time of the menopause results in immediate adverse events that impair quality of life. These can include vasomotor instability and urogenital atrophy, as well as more long-term sequelae such as increased morbidity and mortality from cardiovascular disease and osteoporotic fractures. Hormone replacement therapy (HRT) with estrogen and progesterone (in the presence of an intact uterus) is clearly effective in alleviating symptoms of hot flashes and urogenital atrophy. Case control and cohort studies have also indicated that HRT reduces the risks of cardiovascular disease and osteoporotic fractures. However, results from the Heart and Estrogen/Progestin Replacement Study (HERS), which failed to demonstrate a benefit in cardiovascular mortality in women with established heart disease, emphasize the difficulty in drawing conclusions from epidemiological data. Despite its proven or implied benefits, HRT is associated with a variety of significant drawbacks that include increased risks of breast cancer, uterine cancer, deep vein thrombosis, gallbladder disease, and breast enlargement/tenderness. Because of these disadvantages, HRT is restricted to a relatively small fraction of postmenopausal women, and long-term compliance with treatment is estimated to be only 15–40%.

Agents that retain the benefits of estrogens but at the same time avoid the risks are urgently needed to provide postmenopausal women with an optimal form of HRT. Selective Estrogen Receptor Modulators (SERMs) are a class of drugs with mixed estrogen agonistic/antagonistic activity that holds promise in fulfilling this need. Tamoxifen, the first and most studied of these compounds, has been in clinical practice for over 20 years in the treatment of women with hormone-responsive breast cancer. As a result of its antiestrogenic action in the breast, tamoxifen may, indeed, be effective as a chemopreventive agent for hormone-responsive breast cancer, while its partial estrogen agonistic effects on the skeletal system and on serum lipoproteins may offer protection from osteoporosis and cardiovascular disease. Although demonstration of these clinical benefits is still preliminary or lacking (e.g., reduction in heart disease risk), such mixed agonistic/antagonistic properties of tamoxifen provide proof of principle for the feasibility of developing new SERMs with an improved pharmacologic and therapeutic activity profile. A possible improvement in this regard may have been the introduction of raloxifene, which, in contrast to tamoxifen, has minimal estrogen-like activity in the uterus. As a result, its use has not been associated with an increased risk of endometrial cancer.

Over the last several years, our knowledge of the basic cellular mechanisms governing estrogen action has grown exponentially. The simple model of estradiol binding to its cognate receptors (ER) followed by binding of the complexed receptor to estrogen-responsive elements of target genes has significantly expanded to include multiple additional interactive components. Several chapters in the Basic Studies section address in detail the cellular mechanisms of action of estrogens and SERMs, focusing on important aspects such as distinct ligand-dependent conformational changes in the ER that play a

critical role in the recruitment of coactivators and corepressors and the bidirectional crosstalk between estrogen receptor and growth-factor signaling. Differences in tissue distribution and function of ER- α and - β are also reviewed and discussed. Understanding of these basic mechanisms is critical for the design of new SERMs with improved tissue-specific estrogen agonistic/antagonistic activity resulting in maximal health benefits and minimal risks. The chapters in the Basic Studies section will provide a comprehensive updated review of the preclinical studies with currently available SERMs focusing on their effects on critical target organs such as the cardiovascular system and the brain.

The Clinical Studies section will compare and contrast the influence of estrogens and currently available SERMs (primarily tamoxifen and raloxifene) on the major clinical endpoints, such as incidences of breast cancer, cardiovascular disease, osteoporosis, and cognitive impairment. Based on our current state of knowledge, a tentative approach to menopause-related health issues will be provided both for normal women as well as for women with a previous diagnosis of localized breast cancer. We believe that *Selective Estrogen Receptor Modulators: Research and Clinical Applications* will be of interest to basic scientists in endocrinology, tumor biology, and pharmacology, as well as a wide range of clinicians, including endocrinologists, medical oncologists, gynecologists, and family practitioners. We wish to thank the many contributors, who are distinguished leading experts in their fields and without whose major efforts this book would not have been possible.

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