Editorial

Introduction

Oestrogens are classically regarded as female sex hormones. Quite rightly so because they induce and regulate sexual development at puberty in women, most notably targeting the reproductive tract and the breast. However, the actions of oestrogen clearly stretch beyond this, having effects on bone, the cardiovascular system, the brain, skin and many other peripheral tissues in both men and women. Indeed, the challenge is to define an organ or system that is not influenced by such hormones. If oestrogens are crucial to normal development and function, aberrations in their synthesis, metabolism or action might be expected to lead to abnormalities, particularly in target tissues. Clinical observations and experimental data prove this beyond doubt, most notably in terms of the growth of cancers of the reproductive tract and the breast, and the development of precocious puberty.

Because of the central role of oestrogens in both normal physiology and disease, the biosynthetic pathway leading to these hormones has also attracted considerable interest. Oestrogens represent the endpoint of a chain of reactions in which the C27 sterol cholesterol is converted first to C21 steroids (progestins), then to C19 steroids (androgens) and, finally, to C18 steroids (oestrogens). The last step of the biosynthetic sequence introduces an aromatic ring into the steroid molecule, and the enzyme involved is known as aromatase. Because aromatase is uniquely responsible for oestrogen formation, attention has focused on (i) factors that regulate its expression and activity and (ii) agents that might inhibit these functions. It was this common interest that brought together some 300 scientists and clinicians in Prague in September 1998 to an International symposium entitled ‘Aromatase and its Inhibitors’. The current issue of *Endocrine-Related Cancer* represents its proceedings, and the following review puts into context the various contributions.

Aromatase and its regulation

Aromatase activities in the ovary, foeto-placental unit and adipose tissue are primarily responsible for circulating concentrations of oestrogen in premenopausal, pregnant and postmenopausal women respectively. However, the enzyme activity in other non-endocrine organs may be responsible for local tissue concentrations of oestrogen that may mediate important physiological events. For example, local oestrogen formation in bone cells may play a crucial role in the maintenance of bone mineralization in men and women. This concept is developed in the review of Simpson and colleagues, who suggest that oestrogen biosynthesis in sites such as mesenchymal cells of adipose tissue, skin, osteoblasts, bone vascular endothelial cells and numerous cell types within the brain has important physiological and pathophysiological functions. The regulation of aromatase expression in these tissues is also considered.

Mike Reed’s group show that prostaglandin E2, interleukin 6 (IL-6) and tumour necrosis factor α all stimulate aromatase in fibroblast cultures. Indeed, the effects of prostaglandins may be mediated via IL-6. The studies of Chen and colleagues indicate that transcription of aromatase switches from a glucocorticoid promoter (I.4) in normal breast tissue to cyclic AMP (cAMP)-stimulated promoters (I.3 and II) in breast cancers. They also propose that, in normal breast, adipose aromatase expression is primarily driven by glucocorticoid-dependent I.4, because I.3 and II promoters are suppressed by a silencer element. In breast cancers the silencer is not detectable, so transcription can occur from the cAMP-dependent promoters. This may also be the reason why, among peripheral tissues, breast cancers tend to have the greatest aromatase activity. Whether aromatase activity in breast cancers is capable of maintaining oestrogen-dependent growth factor remains a matter of debate. However, using a model system in which aromatase-transfected and non-transfected breast cancer cells were grown as xenografts in nude mice, Wei Yue and...
Aromatase inhibitors

Recent years have seen a major impetus to develop aromatase inhibitors, with the primary intention of treating postmenopausal women with breast cancer. The inhibitors fall into two classes: type I agents, which bind to the androgen substrate binding site of the enzymes (they are invariably androgen analogues that usually produce irreversible inhibition), and type II agents, which interfere with the cytochrome P450 prosthetic group of the enzyme (these drugs are non-steroidal, usually azoles and have reversible mechanisms of action).

Mitch Dowsett reviews the clinical development of these inhibitors and indicates that three novel drugs, letrozole, anastrozole (triazoles) and exemestane (steroidal) all inhibit in situ aromatase by more than 95%, without having significant effects on other endocrine pathways. The same inhibitors are capable of similar potent effects on aromatase activity in breast tissues (Miller) and, for example, neoadjuvant treatment with letrozole markedly inhibits in situ aromatase and reduces endogenous oestrogen concentrations in breast cancers. The biological changes before and after treatment with aromatase inhibitors have been examined in breast, endometrial and ovarian cancers by Sasano et al.; results indicate that the aromatase inhibitors can decrease proliferation and increase apoptosis in these tissues.

The effects of aromatase inhibitors, alone and in combination with anti-oestrogens, on the growth of breast cancer cells transfected with the aromatase gene and grown as xenografts in nude mice are reported by Angela Brodie’s group. Both aromatase inhibitors (letrozole and anastrozole) and antioestrogens (tamoxifen and ICI 182,780) inhibited tumour growth, but the combination of an aromatase inhibitor and an antioestrogen produced no greater effects than single agents. This suggests that the different endocrine agents should be used sequentially, rather than in combination.

In an interesting set of studies, Harada’s group examined the effects of steroidal and non-steroidal inhibitors on levels of aromatase mRNA and protein. After pretreatment with non-steroidal inhibitors, increased quantities of aromatase protein were detected by immunochemical staining; the inhibitors also appear to block degradation of the enzyme. It was suggested that non-steroidal, but not steroidal, inhibitors increase aromatase protein by stabilizing aromatase and reducing its turnover.

Clinical studies in breast cancer

Drugs that blockade the aromatase enzyme are an attractive treatment option for postmenopausal women with hormone-sensitive breast cancer, because major sites of oestrogen production (adipose tissue or breast tumours themselves) are not usually amenable to surgical or radiological ablation. Prototype drugs such as amino-glutethimide were not particularly powerful or specific. However, newer third-generation agents such as letrozole, anastrozole and exemestane are highly potent and selective inhibitors of the aromatase system. They are orally active, and in mg daily doses almost completely blockade aromatase in peripheral tissues and reduce circulating oestrogen to levels at the limit of detectability. The drugs are now being clinically tested, and results from phase I and II studies and randomized trials in patients with breast cancer are becoming available.

Experience in women with advanced breast cancer is reviewed by Buzdar. Randomized studies of these drugs in comparison with progestins or amino-glutethimide in tamoxifen-resistant disease have shown that anastrozole and letrozole have significant advantages in terms of both efficacy and tolerability. The drugs now represent second-line therapies of choice in patients whose cancer progresses on tamoxifen therapy. Studies are being performed in which the aromatase inhibitors are compared with tamoxifen as first-line treatment for advanced breast cancer. Results of similar trials using exemestane will shortly be published.

Because of these promising results in advanced breast cancer, it has been natural to use the inhibitors in earlier stages of the disease. Dixon and colleagues showed that both letrozole and anastrozole were highly effective.
agents when administered neoadjuvantly, dramatically reducing the size of oestrogen receptor-rich breast cancers after only 3 months of treatment. Randomized trials against tamoxifen are now required. Such studies have been established in the field of adjuvant therapy, and are recruiting patients so rapidly that the utility of the new generation aromatase inhibitors will be evaluated in considerably less time than it took to evaluate tamoxifen, the drug that aromatase inhibitors seek to replace (Baum).

Relative lack of toxicity is a major characteristic of aromatase inhibitors. This could be important if it were proven conclusively that oestrogen causes breast cancer and the drugs were then used as a preventative measure. In his paper, Santen hypothesizes that the metabolism of oestrogen generates free radicals, which cause genetic mutations and, ultimately, cancers. It is further suggested that in situ production of oestrogen within the breast accentuates this process, and aromatase inhibitors might prevent breast cancer by having a dual role in blocking initiation and promotion of breast cancer.

Many practical issues remain to be resolved in the clinical use of aromatase inhibitors. For example, what is the optimal dose and how best may efficacy be measured? These are addressed in the presentation of Ian Smith. Per Lonning considers whether there is crossresistance between different types of aromatase inhibitors. He reviews the clinical experience relating to the sequential use of different aromatase inhibitors either by adding a second inhibitor to a first-line inhibitor at relapse or by replacing one inhibitor with another on relapse. Further responses may be achieved in both study designs. These observations lead to other questions, such as what is the optimal sequence of endocrine therapy, and should aromatase inhibitors be used in combination with other forms of endocrine therapy? The first question is addressed by Charles Coombes, who concludes that sequential use of endocrine agents is likely to produce longer remissions. This view would seem to be supported by James Ingle, who indicates that combining aromatase inhibitors with other hormonal agents may have greater utility, especially if they were antioestrogenic in tumour cells, but oestrogenic in bone and other normal tissues. The plea for additional trials to identify the optimal endocrine therapy and sequence of available therapies is well-taken.

Aromatase inhibitors and other clinical conditions

Excess oestrogen production can result in several other clinical disorders that, although benign, may pose severe problems for those affected. These conditions include endometriosis, precocious puberty, gynaecomastia and hyperplastic breast lesions.

As oestrogen stimulates the growth of endometriosis and aromatase may be aberrantly expressed in endometriotic stromal cells, aromatase inhibitors represent a treatment option for the condition. Bulun reports the successful treatment of recurrent endometriosis in a postmenopausal woman using the aromatase inhibitor, anastrozole.

In McCune-Albright syndrome, precocious puberty results from oestrogen production in ovarian cysts. In her article, Penelope Feuillan reports that the aromatase inhibitor, testolactone, decreased the volume of cysts and reversed many of the signs of precocious puberty. Similar effects were noted in other cases of precocious puberty caused either by adrenal hyperplasia or familial conditions. Results using more potent and specific inhibitors of aromatase are awaited.

Braunstein reviews causes of gynaecomastia, which include increased peripheral or glandular aromatization of androgens to oestrogens. Despite this, the use of aromatase inhibitors to treat the condition is limited, and the newer more potent agents have hardly been used at all. There, therefore, may lie an opportunity to be exploited.

Using a model system, Tekmal and colleagues have demonstrated that overexpression of aromatase in the mammary glands of transgenic mice leads to hyperplasia and preneoplastic change, without evidence of increased concentrations of circulating oestrogens. Interestingly, these events could be completely negated by the administration of the aromatase inhibitor, letrozole. These results suggest that aromatase inhibitors have the potential to treat proliferative breast disease and prevent the development of neoplasia.

If aromatase inhibitors are to be more widely used in the preventative setting and used to treat patients with benign conditions, their cost-risk benefits need to be carefully assessed. In his review, Paul Goss summarizes both the side-effects and the benefits of aromatase inhibitors. The long-term consequences of intervention in
healthy women and patients already treated with endocrine agents are summarized.

Concluding perspectives
The symposium presented here reviewed the state of the art regarding the biology of aromatase and the clinical use of aromatase inhibitors. New data were forthcoming, but it was also clear that many questions remain to be answered - such as what is the role of low local activities of aromatase in the peripheral tissues of postmenopausal women and men, what factors influence aromatase expression at these sites, and will it be possible selectively to switch off oestrogen production in malignant tissues whilst leaving it switched on in normal tissue? What is the optimal dose, extent of administration and sequence of use of aromatase inhibitors? What will be the long-term consequences of prolonged use of such potent endocrine agents? Future research will address these issues, and it is hoped that the results will be presented at the next tumour aromatase symposium, scheduled for the next millennium, in Australia.

William Miller, Guest Editor