The role of androgens in menopausal hormone replacement therapy (HRT) is an area of great controversy. Clinicians range in opinion from those who believe adding androgens is a dangerous and regrettable practice to those who believe that androgenic input is key in maintaining premenopausal energy levels, cognitive function, and libido. The debate is often passionate and dominated by anecdotes rather than a cogent mastery of the available literature. We attempt here to briefly review the available data and formulate practical recommendations.

We feel obliged to state our bias in the matter from the onset. Our view is that androgen homeostasis is altered in menopause. For the majority of women, estrogen replacement resolves the symptoms that arise at menopause. In rare exceptions, certain symptoms persist despite adequate estrogen replacement. In these instances, the addition of androgenic preparations may be of assistance. Unfortunately, androgen therapy is associated with side effects that are metabolic, cosmetic, and psychological in nature.

Principles of Androgen Endocrine Physiology

Androgens were initially described as compounds that induce development of male secondary sex characteristics. Such compounds generally demonstrate a 19-carbon structure (Figure 26.1). There are three clinically relevant groups of androgens: precursors, testosterone, and androgen metabolites. Precursors include dehydroepiandrosterone (DHEA), dehydroepiandrosterone sulfate (DHEAS), and androstenedione. Testosterone is the classic androgen; it has multiple metabolites, including dihydrotestosterone.

Androgens are produced through the steroid synthesis pathway (Figure 26.2). They thus constitute an important link in the production of estradiol itself, through aromatization. There are three main sites of production for androgens: the ovaries, the adrenal glands, and peripheral adipose tissue that truly functions as an endocrine synthetic organ (Figure 26.3). The metabolism of androgens occurs principally in the liver and at the tissue level (Figure 26.4). Testosterone can either be aromatized to estradiol or acted upon by the 5α-reductase enzyme and converted to dihydrotestosterone. The kidneys are responsible for the excretion of androgens.

Androgen physiology in menopause has been reviewed in Chapter 1. We concentrate here on the role of androgenic compounds in HRT.

Pharmacological Agents Available

Testosterone taken orally is rapidly metabolized and inactivated by the liver. For this reason, testosterone must be modified to be
given orally or it must be administered through another route. In this respect, it is similar to estradiol.

The serum half-life of testosterone is 10 to 20 minutes. To have clinical application it must therefore be given as a sustained release preparation. This is accomplished by placing it in a heavy injectable vehicle, such as sesame oil. Alternately, it can be embedded in slow-release pellets. Another approach is to modify its chemical structure, resulting in compounds such as testosterone enanthate. Adding a methyl or fluorinated residue to testosterone protects it against hepatic degradation. Methyltestosterone and fluotestosterone are therefore effective when given orally. Table 26.1 provides a partial listing of available testosterone preparations.

In North America, oral, depot-injectable, and subcutaneous implants are the most widely used methods of testosterone adminis-