Pharmacology and clinical uses of testosterone

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1 Historical background of testosterone therapy

The first experimental proof that the testes produce a substance responsible for virility was provided by Berthold (1849). He transplanted testes from roosters into the abdomen of capons and recognized that the animals with the transplanted testes behaved like normal roosters: "They crowed quite considerably,
often fought among themselves and with other young roosters and showed a normal inclination to hens”. Berthold concluded that the virilizing effects were exerted by testicular secretions reaching the target organs via the bloodstream. Berthold’s investigation is generally considered the origin of experimental endocrinology (Simmer and Simmer 1961). Following his observation various attempts were made to use testicular preparations for therapeutic purposes. The best known experiments are those by Brown-Sequard (1889), who tried testis extracts on himself (which can at best have had placebo effects). The first testicular extracts with demonstrable biological activity were prepared by Loewe and Voss (1930) using the seminal vesicle as a test organ. Finally, the groundstone for modern androgen therapy was laid when steroidal androgens were first isolated from urine by Butenandt (1931), testosterone was obtained in crystalline form from bull testes by David et al. (1935) and testosterone was chemically synthesized by Butenandt and Hanisch (1935) and Ruzicka and Wettstein (1935).

Immediately after its chemical isolation and synthesis testosterone was introduced into clinical medicine (unthinkable if it had happened today) and used for the treatment of hypogonadism. Since testosterone was ineffective orally it was either compressed into pellets and applied subcutaneously (see chapter by Handelsman 1990) or was used as 17α-methyltestosterone. In the 1950s longer acting injectable testosterone esters (Junkmann et al. 1956) became the preferred therapeutic modality, prevailing until today. In the 1950s and 1960s chemists and pharmacologists concentrated on the chemical modification of androgens in order to emphasize their erythropoetic or anabolic effects (Kopera 1985). These preparations never played an important role in the treatment of hypogonadism. In the late 1970s the orally effective testosterone undecanoate was added to the spectrum of testosterone preparations clinically used (Coert et al. 1975, Nie­schlag et al. 1975).

Today, oral and injectable preparations are used in the clinic. However, the available oral and injectable testosterone preparations fall short of being ideal in the substitution treatment of hypogonadism and in recent years the quality of substitution therapy has received more attention. In addition, hormonal methods for male contraception require new testosterone preparations with improved pharmacokinetic profiles. This prompted a search for new testosterone preparations. As a result, several new modalities are being developed or are almost ready for clinical use, such as long-acting testosterone esters, injectable testosterone microspheres, oral testosterone cyclodextrines or transdermal testosterone preparations.

This chapter provides an overview of the various conventional and new testosterone preparations and discusses the clinical and experimental uses as well as the abuses of testosterone. Some aspects will be expanded in the following chapters.