GnRH is a decapeptide, secreted from the hypothalamus in a pulsatile fashion, that regulates the synthesis and secretion of pituitary gonadotropins (1–9). In contrast, synthetic GnRH agonists or antagonists inhibit gonadotropin secretion and subsequently gonadal function (10, 11). Since synthetic agonist analogs were shown to suppress gonadotropin secretion after an initial phase of stimulation (12–17), several studies were performed aiming toward modulation of androgen secretion and the development of a male contraceptive (18–24). GnRH agonists can effectively suppress secretion of gonadal steroids (25–28), but during the initial 2–3-week period of administration a transient stimulation of LH release occurs, resulting in an increase in gonadal steroid levels, which can in some cases induce a flare of the underlying disease. Agonists failed, however, to effectively and consistently suppress spermatogenesis (29–32). Oligospermia was achieved by most men in these studies, but only very few men reached azoospermia (33). This failure of GnRH agonists can be attributed to incomplete suppression of serum FSH immunoreactivity and bioactivity (34) and to the fact that, during long-term agonist administration, FSH serum levels tend to return toward baseline (35).

Antagonist analogs of GnRH inhibit pituitary and gonadal function by competing with endogenous GnRH for binding to gonadotrope receptors and suppressing mRNA levels of both α- and β-subunits of gonadotropins (36–40). Induction of suppression is potentiated by a decrease in the biological potency of the FSH and LH molecules (41–46). Administration of GnRH antagonists induces rapid and sustained pituitary and gonadal suppression in humans (46–53), with no initial stimulatory phase as is the case with GnRH agonists. Therefore, antagonists should be the agents of choice for all clinical situations that require rapid and effective induction of gonadal suppression. Development of GnRH antagonists, however, has been slow because of low potency of early analogs (54), and histamine-like side-effects caused by more potent analogs (55–57). A potent GnRH antagonist, synthesized by Drs. J. Rivier and W. Vale...
at the Salk Institute, and relatively free of side effects (48, 58), has permitted us to study the pharmacology of GnRH antagonists in men and evaluate their antigonadal and antispermatogenic properties.

Clinical Pharmacology

In the first studies the Nal-Glu antagonist, [Ac-D2Nal¹, 4ClDphe², D3Phe³, Arg⁵, Dglu⁶ (AA), DAla¹⁰]GnRH, was given as single doses to normal men, and immunoreactive FSH, LH, and bioactive LH decreased significantly after all doses of the antagonist. Testosterone levels, shown in Figure 18.1, decreased with the same rate after all doses of Nal-Glu, reaching nadirs of 78.5 ± 4.0%, 86.8 ± 2.6%, and 90.9 ± 2.8% after the 1-, 5-, and 20-mg doses, respectively. The duration of T suppression rather than the nadir reached was dose-dependent. Estradiol levels also decreased from mean baseline levels of 17.6 ± 2.0 pg/mL to a nadir of 4.2 ± 1.4 pg/mL 36 h after Nal-Glu administration. Serum FSH decreased by 28.9 ± 5.4%, 38.2 ± 7.9%, and 44.5 ± 3.6%, while IR-LH decreased by 39 ± 13.8%, 53.2 ± 10%, and 53.1 ± 14.4% after the 1-, 5-, and 20-mg doses, respectively. Bioactive LH levels, shown in Figure 18.2, decreased significantly after the 20-mg dose and reached a nadir of only 12.2% of baseline 16 h after Nal-Glu administration. The B/I ratio of LH (Fig. 18.2) decreased from 0.93 ± 0.026 during baseline to a nadir of 0.2 ± 0.02 at 16 h, where it remained for at least 36 h.