6. SUMMARY AND CONCLUSIONS

1 Two sets of formulations were standardized for the purpose of transdermal delivery of testosterone. The first consisted of a polymer blend and testosterone dissolved in an iso-propyl alcohol vehicle, which cast a film on skin when dispensed on the surface. The second series was formulated as an "adhesive-dispersion" transdermal patch using a commercially available pressure-sensitive adhesive.

2 Optical microscopy of films cast from different grades of the liquid formulation indicated that the presence of the polymer in the crystallizing bed imparted a characteristic morphology to the crystal bed. This effect was observed to depend on the ratio of the polymer to testosterone. Laser diffractometry of particles extracted from these beds indicated the presence of a population of particles that were not observed in a sample of pure T prepared the same way. Scanning electron microscopy of both sets of delivery systems revealed the presence of "small" particles (<3 μm in size) that could not be found in the source material, and did not appear to have the monoclinic dimensions associated with testosterone crystals.

3 The presence of polymeric excipients had a marked effect on the particle size distribution of testosterone in both the formulations. Such differences are extremely likely to induce alterations in the diffusion behavior of testosterone from the delivery systems.

4 Both sets of formulations showed a biphasic pattern of drug release in *in vitro* diffusion experiments, with a prominent early burst and a sustained phase of release after the burst was resolved. The burst could be attenuated or enhanced by formulation factors, but the release profiles were all biphasic in nature.
Bioavailability studies on these formulations in castrated rats and in monkeys immunized against gonadotropin-releasing hormone revealed a biphasic pattern of variation in serum testosterone with time. An initial peak was observed within 2 hrs and a subsequent maximum was observed 6-8 hrs after application.

The TD systems were found to maintain prostate weights in castrated rats if supplementation was initiated immediately after castration. This confirmed their efficacy as androgen preparations.

Continuous administration of the film-casting formulation for 4 wks to monkeys immunized against GnRH did not alter their oligospermic status over one cycle of spermatogenesis. This is in agreement with the current theory that testosterone alone is not sufficient to (re-) initiate spermatogenesis, and also indicated the feasibility of using these systems as components of a contraceptive regimen employing the GnRH vaccine. Supplementation with androgen would be required in case of such vaccinees to overcome the effects of androgen deprivation on metabolism and behavior.

The possibility of using a biphasic profile of testosterone release to feedback inhibit the pulsatile activity of the hypothalamus-pituitary-gonad axis was investigated by a mathematical modeling approach. This exercise indicated that such a profile could have advantages over the current paradigm of inducing inhibition by administering massive doses of androgens. The biphasic profile was found to induce perturbations in pulsatile behavior with a much smaller dose. This observation prepares ground for investigating the feasibility of using these systems as a "stand-alone" male contraceptive regimen.

The novel pharmacokinetics of T from these formulations offer investigators an opportunity to evaluate the effects of pulsatile versus continuous administration of T using a non-invasive delivery system for in vivo studies.