well established that LH exerts both acute and trophic effects on the growth and functional differentiation of Leydig cells. The acute effects of LH include stimulation of synthesis/activity of enzymes involved in steroidogenesis, while trophic effects consist of stimulation of Leydig cell division and maintenance and biogenesis of SER. The results of the present study on the effect of LH deprivation on SER proteins of Leydig cells and on 17-α-hydroxylase activity provide biochemical evidence for such a conclusion; in addition, it may be suggested that the proteins which are found only in the SER of adult and hCG-treated immature rats may be representing some other enzymes or associated factors as well as protein involved in the biogenesis and maintenance of SER in Leydig cells.

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Use of androgens for contraception in men

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Androgens have been used for treating hypogonadism for several years. Experimental evidence suggests that in normal men intramuscular injections of androgens suppress sperm production while maintaining normal libido and accessory reproductive organ functions. The findings strongly support the view that the development of potent orally active androgens could provide an effective antifertility agent for men.

AN effective, safe and reversible antifertility drug for men is yet to be developed. The development of a good chemical contraceptive for men would add a new option for regulating family size and population growth. The mode of control of fertility in men could be through chemicals which can directly affect the testis and disrupt spermatogenesis and sperm formation, or through hormonal interference of testicular spermatogenesis. Though some chemicals like gossypol[1] showed promise in blocking the process of spermatogenesis, due to its adverse side effects, the use of this drug in the control of fertility appears to be remote. Similarly, agents which may cause selective interference with maturation of spermatozoa have not yet been found. Among the hormonal methods for the control of fertility, selective interference with the circulating levels of follicle stimulating hormone by specific antibodies[2] or by blockage of gonadotropic hormones of the pituitary

appears to be promising[3,4]. In this article the latter possibility is discussed.

Use of androgens for the treatment of infertility

Testosterone was used for the treatment of impotency and for improving sperm count as early as in 1950. Heller *et al.*[5] and Charny[6] used therapeutic doses of testosterone in infertile men with oligospermic sperm counts to improve the number of spermatozoa. In these treatments it was observed that the spermatozoa counts were totally reduced with symptoms of azoospermia. After stoppage of treatment the sperm count gradually increased to the level seen before the start of treatment while in some cases a slight improvement was also obtained. The observation that azoospermia preceded recovery phase in these patients was exploited for the development of a method for contraception by using testosterone[7].

Testosterone as an injectable contraceptive

Reddy and Rao[7] injected seven normal men in the age group of 23 to 38 years with 25 mg/day of testosterone propionate for 60 days. The subjects showed gradual decline in the sperm count, reducing to oligospermic levels at 45 days and complete suppression of spermatozoa at 60 days. When this treatment was discontinued, there was a gradual recovery of spermatogenesis after 60 days. At 90 days the spermatozoa were in the range of 3–8 million increasing to about 35–70 million after 120 days of stopping treatment. By 150 days there was complete recovery of the number of spermatozoa in the ejaculates, which was comparable to pre-treatment levels. The motility of spermatozoa after recovery was normal. The libido and potentia of these patients during the treatment and recovery periods was also normal. There was no change in the volume of semen during the entire period of the experiment. This study, for the first time, demonstrated that in normal men a hormonal method for the control of fertility is possible.

In studies using testosterone propionate, the main drawback has been the need for administering the hormone. Hence a long acting ester, testosterone enanthate, was used for suppression of spermatogenesis. It was observed that frequency and dose of testosterone enanthate are critical for maintaining spermatogenic suppression[8–11]. In order to maintain adequate inhibition of spermatogenesis, weekly injections of testosterone enanthate were necessary. In these studies with intramuscular injections, azoospermia was achieved between 16–20 weeks of starting the treatment in a majority of the subjects while in a few, oligospermia to the level of about 5 million or less was noted[10–12].

Since testosterone enanthate presented advantage over testosterone propionate and since the mode of administration of this hormonal preparation as a weekly injection was more convenient, a multicentric study was done in seven countries to assess the contraceptive efficacy of this drug[13,14]. Intramuscular injections of testosterone enanthate caused azoospermia in 157 healthy men after 120 days of treatment. In this study it was concluded that this method can maintain suppression of spermatogenesis by continuing testosterone injections. After treatment cessation, recovery of spermatogenesis to a mean sperm concentration of 20 million/ml of semen was achieved after 3–7 months. This study further supports the idea that testosterone can be used as an effective contraceptive for the control of fertility in males. Recently a long acting testosterone preparation 20 AET-1 was shown to yield a normal plateau of circulating testosterone for 3–4 months after a single injection[15,16]. Hence such a preparation may become more suitable as an injectable testosterone for the control of fertility in males.

Oral androgens as contraceptive agents

Though testosterone esters have proved to be effective in inducing azoospermia, their mode of administration being through injection, an easier method of administration is necessary. Orally active fluoxymesterone and mesterelone were not effective in suppressing spermatogenesis[17]. The other orally active androgen, methyltestosterone was shown to impair liver function[18]. Recently an orally effective androgen, testosterone undecanoate, has become available for clinical use. Nieschlag *et al.*[19] treated seven normal men with this androgen to suppress spermatogenesis. A dose which is twice or thrice more than that required for the treatment of hypogonadal men did not cause azoospermia. The failure of this preparation in suppressing spermatogenesis was found to be due to its short half-life in circulation and due to considerable individual variations[20]. A more effective testosterone preparation which is orally active would be an ideal agent compared to injectable testosterone esters.

Gestagen–androgen combinations for fertility regulation

It was suggested that the dose of androgen used for suppression of spermatogenesis can be reduced by the combined use of progesterone and androgens for contraception[7]. Progesterone alone was shown to suppress spermatogenesis[21] but this resulted in loss of libido and potentia. Since progesterone is well known to suppress gonadotropic hormones in females, the same principle can be applied for suppressing both luteinizing hormone and follicle stimulating hormone. Several progestational compounds have been tried to see the effect of proge-

sterone in combination with testosterone[22]. In these studies it was demonstrated that silastic capsule filled testosterone implants can maintain libido and potentia while daily oral administration of progesterone caused suppression of spermatogenesis. However, in a majority of the 191 men treated, only oligospermia was achieved. In addition to this study, danazol–testosterone combination and medroxy–progesterone acetate testosterone combination treatment[12,23] were also shown to be effective in suppressing spermatogenesis while maintaining libido and potentia. In all studies involving progesterone and testosterone combinations, there was recovery of spermatogenesis, though in some instances it took a longer period for such a recovery[22]. In all of the above studies while progesterone was administered orally, testosterone was either injected intramuscularly or was given as a silastic implant. The latter mode of administration of testosterone still needs to be replaced. An orally acting progesterone with less side effects along with an orally active testosterone which would cause reversible suppression of spermatogenesis while maintaining libido and potentia would be an ideal contraceptive for men.

Conclusions

The available experimental evidence suggests that androgens are potentially good chemicals for the control of fertility in human males. It is possible to develop a combination drug with a combination of progesterone and testosterone. Since an orally active ester, testosterone undecanoate, is now available with no known adverse side effects, it is possible that this androgen or some other derivative, in combination with minimal amount of a suitable gestagen would be effective in causing reversible azoospermia without any side effects. Such studies need to be carried out.

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