INTRODUCTION
In the quest for appropriate family size, it is axiomatic that the male partners should be made to share both the benefits and risks of whatever contraceptive strategy the couple may choose (Waites, 1986). In the past several years, there has been renewed interest in developing methods for male contraception in particular. The impetus for this activity has in fact come from the consumer rather than from the scientific community. This is partly because of a sincere concern about possible adverse effects associated with the use of the 'pill' by women. There is also witnessed, over the past decade or so, a definite awakening, with menfolk, willing to share responsibility with women, for family planning. This changed scenario of contraception also emanated partly from the male desire to assume control over their own fertility (Paulsen, 1979). However, at present, there is a very restricted and far from satisfactory choice of contraceptive modalities for men. These include condoms, vasectomy, coitus interruptus and periodic abstinence.

(i) Condoms are effective, but all couples do not use them.

(ii) Vasectomy - voluntary male sterilization - though highly effective, involves surgery, is permanent in as much as its reversibility is not ensured.
(iii) Coitus interruptus or withdrawal has high failure rates.

(iv) Periodic abstinence can be effective only if the couple, specially the women, can monitor signs of the fertile period (Population reports, 1986).

So, although these methods except vasectomy and condoms have been used with questionable success, they are seemingly unaesthetic, inadequately effective or impractical. Hence, there is still a major need to develop safe, effective, reversible and acceptable fertility regulating agents for men (Waites, 1986). Since 1950, researchers have sought effective and acceptable newer methods of male contraception, in addition to vasectomy and condoms, which have been undoubtedly effective but are now losing popularity.

In contrast to the availability of successful oral contraceptives for the female, the search for an effective and reversible male contraceptive is still on - despite many optimistic reports, no breakthrough seems in sight yet. The male reproductive system seems less amenable to interference than does that of the female, because several phenomena work to maintain a reproductively intact and fertile state. Firstly, because the spermatogenic cycle is 74 days, and months pass before a drug is effective.
Secondly, because reproductive hormones are generally in a steady state in men and therefore interruption of cyclicity is not an effective contraceptive approach. Thirdly, because the testes are protected by a blood-testis barrier, many agents cannot reach the site of spermatogenesis (Alexander, 1986). So far, the continuing search for pharmacological agents capable of causing specific reversible inhibition of male fertility has not resulted in the emergence of an antifertility programme for men (Gomes, 1977). This is because most of the chemicals/drugs studied are either presumptive carcinogens or reportedly cause irreversible sterility or produce other serious side effects. It is doubtful whether majority of these will ever be used for the curtailment of male fertility unless these are tested for their toxic side effects.

So far, in the limelight are the following improved or new contraceptive methods:

(i) Man made analogues of LHRH which have the potential for suppressing ovulation and inducing menstruation in women as well as blocking the sperm production in men.

(ii) Vaginal ring and intracervical device which provide controlled local release of progestins which interfere with the sperm transport.
(iii) A vaccine against HCG or immunization against specific enzymes in spermatozoa.

(iv) A variety of hormones or combination of hormones in the form of pellet, implant and finally a contraceptive pill for men.

Until recently, work in the area of male contraception had primarily been directed towards understanding the fundamental control mechanisms involved in the hypothalamic-pituitary-testicular interaction. Interference with these mechanisms has not been seriously attempted.

So, there is clearly the need for a safe, anti-fertility pill for the male, capable of reversibly suppressing sperm production or sperm function without interfering, of course, with the libido and being free of any side effects. Inspite of a number of exciting developments in this area in the recent years, an ideal chemical or hormonal male contraceptive pill seems still a far cry.

Theoretically, for controlling male fertility, the numerous possible approaches available fall under three headings viz., (a) inhibition of spermatogenesis, a continuous and complex process of cell division and differentiation of long duration which is regulated by
pituitary gonadotrophins, (b) interference with sperm maturation, a delicate, complex and still incompletely understood biochemical process, taking place in the epididymis and (c) impairment of spermatozoal transport following ejaculation in the admixture of important secretory products from the prostate and seminal vesicle—the glands which provide the bulk of the semen (Waites, 1986). Broadly, the various areas of research for the development of a male contraceptive can be classified as—(i) hormonal suppression of spermatogenesis and (2) chemical interference at the sites of sperm production and maturation.

It is emphasized that any method of male fertility control must take into consideration all the fundamental physiological changes that normally occur between the male gonads and other organs. Studies on the various changes at cytological or biochemical levels in the testis alone are thus not sufficient. The accessory reproductive glands are vitally important in the male reproductive functions and hence deserve consideration while formulating any strategy of male contraception. If progress towards a male analogue to the female pill is to be made, it may well derive from efforts to interrupt sperm maturation or interfere with the accessory glands, rather than through suppression of spermiogenesis (Potts, 1986).
The accessory male reproductive organs and their secretions not only add to the volume of semen, but also constitute the physiological environment of the spermatozoa. After the spermatozoa are swept into the epididymis from the testis, through the efferent duct, they spend 5-20 days in the epididymis depending upon the species (Orgebin-Crist, 1969; Waites and Setchell, 1969). During this span, the spermatozoa undergo a series of changes in their morphology, membrane permeability, composition, metabolism and above all acquire motility as well as fertilizability (Bedford, 1966; Igboeli and Foote, 1968; Orgebin-Crist, 1969 and Mann and Mann, 1981).

The accessory reproductive glands are known to secrete into the genital tract, a large variety of substances ranging from ions and small molecules to proteins including various enzymes in most mammalian species (Mann, 1964; Mann and Mann, 1981). In mammalian species, a large contribution to the volume of semen is made by the seminal vesicles and prostate. It has also been suggested that the longevity of spermatozoa also depends upon the composition of the seminal fluid (Anon, 1969). This is indicative of the importance of these organs in overall male reproductive physiology. Maintenance of the
sex accessory glands, secondary sexual characteristics and libido, deserve particular attention while formulating male chemical contraceptives (Flickinger, 1978).

For male contraception, the goal of a 'male pill' remains still elusive. Recent researches have focussed attention on various possibilities which include the use of gossypol, LHRH analogues, long acting steroids and inhibin for this purpose. But to-date none of these approaches has yet qualified in clinical trials (Prasad, 1981).

Gossypol derived from the cotton plant Gossypium (Family-Malvaceae) interferes with sperm production. However, recent clinical trials have found that gossypol has two major side effects: (1) some men develop hypokalemia (Lee et al., 1982) and (2) reversibility of damage is questionable (Kalla, 1982; Prasad and Diczfalusy, 1982; Segal, 1984). As a result, clinical trials with gossypol are now jeopardized. Efforts are being made to find a non-toxic component/analogue of gossypol which could be more effective as a male sterilant yet reversible in action (Diczfalusy, 1986; Waites, 1986). A wide variety of other compounds that directly interfere with sperm production have been tested but discarded because of
their toxicity (Rabe et al., 1985; Vickery et al., 1986; Waites, 1986) and irreversibility.

Another approach to male contraception is the use of chemical analogues of LHRH. These analogues interfere with the action of LHRH, a peptide synthesized in the hypothalamus that stimulates the release of FSH and LH by the pituitary. These hormones, in turn, trigger the production of testosterone and other steroids that are essential for sperm production. Over thousand LHRH analogues have been developed, some even more potent than the natural hormone, but none completely inhibits spermatogenesis in men.

It is unlikely that LHRH analogues will come into use in the next decade. First, the best analogue and the most appropriate dose have not yet been established. Secondly, the male users are required to receive continually exogenous testosterone along with the analogues to prevent impotence and loss of libido (Steinberger, 1981; Fraser, 1982). Third, the best delivery system is yet to be determined. LHRH analogues and testosterone are not active orally. Injections and nasal sprays are possible but may not provide the constant blood levels necessary and hence the desirability of sustained action release over long periods.
Empirical screening of numerous steroidal compounds has resulted in the discovery of some natural and synthetic steroids such as androgens, estrogens and progestins which possess antifertility effects in the male. These have been tried singularly and in combinations to arrest or alter the functions of the testis (Frick, 1973; Segal, 1973; Flickinger, 1977 a,b; 1978). This type of chemical contraception enjoys preference over the surgical methods because of its reversibility and wide acceptance.

Studies indicate that testosterone or its esters (propionate, cypionate or ananthate) alone may also suppress spermatogenesis to azoospermic levels (Swerdloff et al., 1978; Steinberger et al., 1978), and simultaneously maintain androgenic effects. The onset of azoospermia is slow and occurs as a result of reduced gonadotrophin secretion (Pryor, 1982). However, azoospermia does not always occur and in some patients there is evidence of escape from the androgen-induced inhibition of gonadotrophin secretion. The use of androgens is not without risk and side effects (Farell et al., 1975; Westaby et al., 1977; Falk et al., 1979).

Estrogens no doubt suppress spermatogenesis quite effectively, but even with androgen supplementation, feminizing symptoms such as gynaecomastia do appear which are undesirable.
In the recent years, androgen and progestin combinations have attracted more attention, obviously because of the fact that either of the hormones compensates for the adverse effects of the other. Different progestagens have been used in combination with testosterone in clinical trials for male fertility control: norethisterone, medroxy progesterone acetate (MPA) and depot-medroxy progesterone acetate (DMPA), 17-hydroxyprogesterone capronate and megestrol acetate. Some of these combinations have shown very promising results both in terms of suppression of spermatogenesis and the seriousness of side effects. The male libido and potency have also been maintained.

For several decades, scientists have been studying inhibin, a peptide hormone found in the gonads. Research in animals suggests that inhibin suppresses the release of FSH from the pituitary and thus could prevent sperm production. However, inhibin does not seem to reduce release of LH, and so does not affect the production of testosterone. In other words, inhibin feedback hormone appears to be the ideal candidate for suppression of spermatogenesis because it specifically inhibits FSH secretion and does not affect androgen production (Alexander, 1986). Currently, the isolation and purification of the hormone are on, but have yet to be standardized for yielding
consistent results (Nieschlag et al., 1981; Paulsen et al., 1982; Negro-Vilar and Lumpkin, 1983). An inhibin-like substance has been isolated from reproductive tissues as well as from ovarian follicular fluids of various animal species, however, these inhibin peptide preparations have been reported to inhibit not only FSH but also LH secretion (Braunstein and Swerdloff, 1977). Even if this is achieved the problems of appropriate delivery system for long-term administration of this peptide substance has yet to be devised.

Other possible approaches for male contraception include administration of new long-acting steroids and immunization against FSH (Nieschlag et al., 1981; Wickings et al., 1982). Immunization against FSH so far has failed to suppress sperm production at least in the monkeys (Nieschlag, 1986). Another approach – the induction of antisperm antibodies – currently appears more feasible in women than in men (Alexander, 1986; Goldberg and Sheldon, 1986).

Progestins of the 19-nortestosterone group are considered potent as contraceptives. Norethisterone enanthate has been found to be an effective contraceptive in females and has scored over DMPA in effect-reversibility and longevity of effects. Also 19-nortestosterone
derivatives have higher binding affinity with androgen receptors. It would not be unwise to probe into the effects of this compound in the male.

Considerable attention has been paid in recent years to the study of non-steroidal compounds which inhibit gonadal activity and other associated endocrine functions (Fridhandler and Pincus, 1964; Kncli et al., 1965; Nelson, 1965). Clomiphene 1-[p(diethylaminoethoxy)-phenyl]-1,2-diphenyl-2-chloroethylene, a non-steroidal triphenyl derivative of chlo-octriamene, has varied biological effects in animals and men. It is known to inhibit endogenous gonadotrophic activity and to reduce fertility in rats and rabbits (Prasad et al., 1965; Davidson et al., 1965; Prasad and Kalra, 1967; Flickinger, 1977). Furthermore, administration of clomiphene to immature male rats suppresses development of the sex accessory glands and Leydig cell functioning as it alters spermatogenesis (Nelson and Patanelli, 1962; Kalra and Prasad, 1967). Clomiphene also impairs/retards the blood-testis barrier when administered to young male rats (Vitale et al., 1973). It has been suggested that very low doses of clomiphene stimulate gonadotrophin release while higher doses suppress it (Roy et al., 1964).
In view of a number of lacunae in the literature regarding the contraceptive action and efficacies of steroids and non-steroids and physiology of reproductive organs under changed hormonal milieu, the present study was designed to investigate primarily the changes which may occur in the testis and various segments of the reproductive tract of the male rat following combined administration of (i) a progestin and an androgen; and (ii) a combination of a non-steroidal compound and an androgen. Testis, epididymis and accessory sex glands were subjected to various histological and biochemical investigations at different treatment intervals with a view to determine the time of onset of spermatogenic arrest, effect of the drugs on the target cells, degree and nature of histopathological lesions, extent of physiological alterations and biochemical lesions in the testis and accessory sex glands and finally to understand the mechanism of action of the sterilants employed. The work also embodies quantitative analysis of some of the enzymes and metabolites of the blood serum for assessing physiological liver functioning.