Male Contraception

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The provision of safe, effective contraception has been revolutionized in the past 40 yr following the development of synthetic steroids and the demonstration that administration of combinations of sex steroids can be used to suppress ovulation and, subsequently, other reproductive functions. This review addresses the current standing of male contraception, long the poor relation in family planning but currently enjoying a resurgence in both scientific and political interest as it is recognized that men have a larger role to play in the regulation of fertility, whether seen in geopolitical or individual terms. Condoms and vasectomy continue to be popular at particular phases of the reproductive lifespan and in certain cultures. Although not perfect contraceptives, condoms have the additional advantage of offering protection from sexually transmitted infection. The hormonal approach may have acquired the critical mass needed to make the transition from academic research to pharmaceutical development. Greatly increased understanding of male reproductive function, partly stimulated by interest in ageing and the potential benefits of androgen replacement, is opening up other avenues for investigation taking advantage of nonhormonal regulatory pathways specific to spermatogenesis and the reproductive tract. (Endocrine Reviews 23: 735–762, 2002)

I. Introduction

ACCESS TO EFFECTIVE contraception is a prerequisite of reproductive health (1). If the goal of ensuring that every birth results from a planned pregnancy is to be achieved, a wide range of methods of regulating fertility must be available. Because women literally are left “holding the baby,” family-planning organizations have traditionally concentrated on female methods. New developments in the last 10 yr, including new formulations of the oral contraceptive pill, medicated intrauterine devices, and subdermal implants, have provided for women a wide range of contraceptive choice (Fig. 1). In contrast, advances in male-directed methods have been confined to refinements in the type of condom and technique of vasectomy. It has been argued that research on new male-directed methods is unnecessary and that resources would be better directed toward making existing methods more widely available (2). Yet despite their limitations, up to 30% of couples worldwide use a male method of contraception (Fig. 2). Moreover, recent research has demonstrated that, in many societies, men are prepared to share the responsibility of contraception more equally with their partners (3). An individual’s requirements for contraception differ depending on their changing social circumstances. It is likely that the method of contraception that meets the requirements of an adolescent in an early exploratory relationship will differ radically from that which is suitable for a stable couple that has completed its family. Thus, the development of new, effective methods of male contraception has been identified as a high priority by international organizations including the World Health Organization (WHO; Refs. 4 and 5).

The male reproductive system offers a range of potential targets for new contraceptives (Fig. 3). Spermatogenesis is a continuous process involving the daily production of millions of mature sperm from spermatogonia. This process takes approximately 75 d and involves reduction of the chromosome number from 46 to the haploid number of 23 present in ejaculated spermatozoa. This process of meiosis only occurs in the gonad in the adult and is carefully regulated...
FIG. 1. Contraceptive prevalence by regions of the world. Data are percentages of married women currently using modern methods of contraception (male and female sterilization, intrauterine contraceptive device, the pill, injectables, hormonal implants, condoms, and female barrier methods) and vary from 8% in Western Africa to 80% in Eastern Asia, with narrower variation in the more developed regions. Modern methods account for approximately 90% of contraceptive usage in less developed areas but for 70% in more developed areas, with traditional methods, e.g., withdrawal and calendar rhythm methods, which require male involvement, accounting for 26% in developed regions compared with 8% in less developed areas. Data are from the United Nations Population Fund (323).

FIG. 2. Distribution of contraceptive usage by method in developed vs. less-developed regions of the world. Seventy percent of users in the more developed areas rely on short-acting, reversible methods (condoms, pills, traditional methods), whereas in the less-developed areas, 70% use longer-acting, clinic-based methods (injectables, sterilization, intrauterine contraceptive device). Data are from the United Nations Population Fund (319).
through a series of coordinated steps. Hence, it should be potentially possible to interfere specifically with key processes unique to the testis (6). Unfortunately, our knowledge of the physiological basis of spermatogenesis is still incomplete and, hence, developments of new methods still largely hypothetical. It has been known for more than 75 yr that normal testicular function is dependent on pituitary gonadotropins, the secretion of which is regulated by hormones secreted by the testis. The principle of hormonal contraception for men was established more than 60 yr ago when it was shown that man becomes azoospermic when injected every day with large doses of testosterone (7, 8). However, it is only recently that there has been a concerted effort to apply this knowledge to the development of a method that could be marketed as a practical contraceptive.

In this paper, we review briefly the methods of male contraception currently available and point out their advantages and limitations. We will concentrate on the development of new hormonal methods that at long last offer a realistic prospect of marketing within 10 yr. Other approaches stemming from basic research have been reviewed extensively elsewhere and offer great potential but are unlikely to yield a practical method in the next few years (6).

II. The Control of Testicular and Epididymal Function

This article is primarily concerned with the regulation of male fertility. Although some discussion of the physiological basis for male fertility is therefore required, the following section does not attempt to be comprehensive. The effects of abnormalities in gonadotropic regulation of testicular function have been recently reviewed (9), as has the regulation of FSH secretion (10). Focus will be on those aspects of male reproductive function that have been or may become targets for contraceptive action.
A. The regulation of gonadotropin secretion

The testis, like the ovary, has both endocrine and gameteogenic functions and is totally dependent on pituitary gonadotropins. Gonadotropin secretion is under the overall stimulatory control of GnRH, with inhibitory inputs consisting of steroidal and peptide hormone feedback from the testes and local regulatory factors. Mechanisms and pathways involved in the regulation of GnRH secretion and action are thus central to the hormonal approach to male contraception, both by the use of GnRH analogs, in particular antagonists, and by the use of steroids to override physiological feedback signals. The pattern of both LH and FSH secretion in the peripheral circulation is pulsatile (11, 12) and, in experimental animals, secretion of LH has been demonstrated to directly parallel that of GnRH into portal blood (13, 14). The pulsatile nature of GnRH secretion is believed to be crucial for the maintenance of gonadotroph responsiveness (15), preventing receptor down-regulation and subsequent fall in LH secretion. However, the absence of the COOH-terminal tail in the mammalian GnRH receptor, compared with other species, results in a much slower rate of receptor internalization, which may be of importance in the design of novel ligands (16).

Although testosterone is the major steroid secreted by the testis, it has been long recognized that other steroids may be involved in the regulation of gonadotropin secretion (17). Such steroids, such as estradiol, might be secreted directly by the testis (18) or produced by conversion from testosterone in extraglandular tissues. Testosterone inhibits LH secretion by acting at both the hypothalamus and anterior pituitary gland (19–24). Administration of dihydrotestosterone (DHT) has been widely used to investigate direct androgenic effects. High doses have generally been reported to result in suppression of LH concentrations (19, 25), whereas administration of more physiologically appropriate doses had little or no effect (17, 26, 27). The absence of an important effect of physiologically relevant amounts of endogenous DHT is suggested by the lack of effect of the 5α-reductase (5αR) inhibitor finasteride (28).

There is clear evidence that other steroids, including estradiol, are important in the regulation of gonadotropin secretion (17, 20). Estradiol infusion reduced LH secretion in response to pulsatile GnRH in men with idiopathic hypogonadotropic hypogonadism, whereas administration of a gonadotropin, an aromatase inhibitor, caused both an increase in LH secretion when administered alone in this model and a reduction of the inhibitory effect of testosterone (26, 29). The relative contributions of androgen and estrogen have been recently reinvestigated by comparison of the effects of aromatase inhibition and of biochemical castration by administration of ketoconazole, inducing a fall in both testosterone and estradiol concentrations (30). These results indicate differential regulation of the two gonadotropins by testosterone and estradiol, with the effect of testosterone on FSH being largely mediated by aromatization.

Despite the use of progestogens to inhibit gonadotropin secretion in male contraceptive studies for several decades (31), surprisingly few studies have directly investigated the effects of these drugs in men. Progesterone receptors are present in the hypothalamus and anterior pituitary of male rats and rams (32, 33). An inhibitory effect of progesterone in castrated rams has recently been demonstrated when given with a low dose of testosterone, whereas progesterone given alone was ineffective (33). Thus, it is possible that the effect of progesterone on serum LH requires the presence of testosterone and/or estradiol, analogous to the effects of estradiol in the female. Increased LH concentrations in male progestosterone receptor knockout mice suggest a possible physiological role (34). In normal men, the gestagen desogestrel caused a fall in LH, FSH, and testosterone concentrations over a 3-wk administration (35), with testosterone concentrations falling to approximately 35% of pretreatment values with 300 μg desogestrel. We have recently demonstrated that progestosterone administration to normal men reduces both LH pulse frequency and amplitude and also reduces FSH secretion (36). These effects were similar to those observed with desogestrel administration, indicating that the effects of progestogens on gonadotropin secretion are not solely mediated by the androgen receptor but are, at least in part, mediated by the progesterone receptor, with evidence for both hypothalamic and pituitary sites of action.

In addition to steroidal feedback control of gonadotropin secretion, there is an important nonsteroidal gonadal contribution. This was recognized and given the name “inhibition” by McCullagh (37), who observed the inhibitory effect of an aqueous testicular extract on the formation of castrate cells in the pituitary gland. After the purification of inhibin from follicular fluid (38, 39) and the development of immunoassays specific for the dimeric forms of inhibin A and B, the presence of inhibin B, but not A, in the male was demonstrated. Blood concentrations are lower in men with testicular disorders, and an inverse relationship between inhibin B and FSH concentrations was confirmed (40, 41). This relationship between inhibin B and FSH was also observed across the physiological range in normal men (42). These data strongly suggest that inhibit B is an important component of the afferent arm of the feedback loop from the testis, selectively regulating FSH secretion (10).

B. Testosterone production

Testosterone is produced by the Leydig cells of the testis, under the stimulatory control of LH. The biosynthesis and metabolism of testosterone have been recently reviewed (43). Because the hormonal approach to male contraception involves administration of testosterone, the question of the appropriate dose arises. Some androgen-dependent functions, such as sexual behavior, are normalized with subphysiological testosterone concentrations and do not increase with supraphysiological doses (44, 45), whereas muscle mass and hemoglobin concentration continue to increase with increasing testosterone concentrations and high-density lipoprotein (HDL)-C continues to fall (46). Currently available preparations are limited, particularly the availability of long-acting formulations (Table 1). Most current regimens involve coadministration of a second agent such as a gestagen or GnRH analog to induce gonadotropin suppression, with replacement of testosterone to augment the suppressive effect on gonadotropin secretion and prevent
androgens. The dose required should therefore approximate physiological replacement. Derivation from measurement of the metabolic clearance rate of radiolabeled testosterone gives a production rate of 6–7 mg/d (47, 48), although a recent re-investigation using stable isotope dilution indicated rather lower production rates of 3.7 ± 2.2 mg/d (49).

In hypogonadal men, standard regimens include 250 mg testosterone esters every 3 wk, i.e., approximately 5 mg testosterone per day, but with a large differential across the injection interval. Testosterone pellet and transdermal regimens are similar at approximately 5 mg/d (50, 51), with the pellets proving relatively stable concentrations, whereas the patches may mimic the physiological diurnal variation in testosterone production (52), the significance of which is unknown. These doses normalize prostate volume and maintain bone mass in hypogonadal men (53, 54); thus, approximately 5 mg/day appears appropriate for physiological replacement in contraceptive regimens.

C. The regulation of spermatogenesis

The involvement of the pituitary gland in the control of spermatogenesis was first described by Smith in 1927 (55). Using the classic endocrine technique of gland removal followed by replacement of the postulated active substances, he demonstrated the importance of pituitary factors in the stimulation of testicular growth and spermatogenesis in the rat by observing the effect of hypophysectomy and subsequent administration of pituitary extracts. It was subsequently recognized that two pituitary hormones are involved, with separate effects on the Leydig cells and on spermatogenesis (56). This finding provides the basis for current understanding of the dual control of the endocrine and spermatogenic functions of the testes by LH (via production of testosterone) and FSH.

There remain uncertainties regarding the importance of FSH in the maintenance of adult spermatogenesis (10). Inactivating mutations of the FSH β-subunit and FSH receptor have been identified in men (9) and in knockout models developed in mice (57, 58). Men with inactivating FSH receptor mutations showed qualitatively normal spermatogenesis and were in some cases fertile (59), whereas men with FSHβ mutations had a more marked phenotype and were azoospermic (60, 61), although there may have been coexisting abnormalities of Leydig cell function. The mouse knockout models for both the FSH β-subunit and receptor also showed qualitatively normal spermatogenesis (58, 62), whereas in the LH receptor knockout mouse, spermatogenesis was arrested at the round spermatid stage (63). In men who were administered supraphysiological doses of testosterone resulting in suppression of gonadotropins and spermatogenesis to azoospermia, subsequent administration of FSH resulted in a resumption of spermatogenesis (64). Conversely, administration of human chorionic gonadotropin or LH to men during testosterone-induced suppression (i.e., a model of selective FSH suppression) also resulted in reinitiation of spermatogenesis to sperm concentrations within the normal range, although lower than pretreatment concentrations for those men, despite FSH concentrations remaining suppressed (65, 66). Overall, these data indicate that FSH is not absolutely required for adult spermatogenesis, but it is required for quantitatively normal spermatogenesis to proceed. The testosterone regimen used in that and related studies investigating the effect of LH/human chorionic gonadotropin administration only induces azoospermia in a modest majority of Caucasian men (67), possibly related to the high testosterone concentrations achieved, which may directly support spermatogenesis in some men (65, 68).

Whether FSH would induce spermatogenesis in a model with more complete intratesticular testosterone deprivation is uncertain. Although data from nonhuman primates support the existence of an important role for FSH in the regulation of spermatogonial replication in the presence of well-maintained intratesticular testosterone concentrations (69), it is unlikely that a contraceptive approach based on selective FSH withdrawal would be successful. The present availability of recombinant gonadotropin preparations and potent GnRH antagonists opens this area to further detailed study. The recent development of a transgenic model based on the gonadotropin-deficient hypogonadal (hpg) mouse with transgenic FSH expression provides an opportunity to study the effects of FSH in isolation from LH (70): in the absence of FSH, spermatogenesis is arrested at the round spermatid stage and remains silent until the introduction of low levels of FSH following adenohypophysectomy (71).
of FSH, the germinal epithelium is disorganized with no tubular lumen and no spermatogonial progression beyond the pachytene stage, whereas in the presence of FSH such mice show near-complete spermatogenesis with a large number of round spermatocytes but few elongate spermatids, indicating lack of completion of spermiogenesis. This is similar to the testicular phenotype of the LH receptor knockout mouse (63), indicating the importance of FSH in the completion of germ cell meiosis.

A related finding is the effect of contraceptive steroid administration on inhibin B concentrations, as inhibin B is a Sertoli cell product reflecting both Sertoli cell number and the resident population of germ cells (71). Although initial studies using either testosterone alone (42) or testosterone with levonorgestrel (LNG; Ref. 41) demonstrated a fall in inhibin B concentrations, other studies using a range of testosterone/progestogen combinations have demonstrated that inhibin B concentrations can be maintained even in the face of induced azoospermia (72, 73). Despite FSH concentrations being generally suppressed to the limit of detection by such regimens, these data appear to suggest that Sertoli cell function is generally suppressed to the limit of detection by such regimens, indicating the importance of FSH in the completion of germ cell meiosis.

The concentration of testosterone within the testis is undoubtedly much higher than in the circulation, although the quantification of intratesticular testosterone concentrations has been the subject of considerable debate (76). The functional significance of such high concentrations remains unclear, as the androgen receptor present in the testis is believed to be identical with that expressed throughout the body (77). Of relevance to the present discussion, however, is the repeated observation that Leydig cells continue to produce some testosterone after hypophysectomy (78, 79). Although testosterone concentrations in the interstitial fluid are less than 5% of normal under those conditions, this remains similar to physiological concentrations in peripheral blood. Contraceptive approaches whose mechanism is predominantly through gonadotropin suppression are therefore unlikely to reduce intratesticular concentrations much lower than this. Such low concentrations may support spermatogenesis in some men, as antiandrogen administration results in a further decline in spermatogenesis (80). There are very limited human data on intratesticular testosterone concentrations under such circumstances, but weekly administration of testosterone propionate caused a fall in intratesticular testosterone concentrations to only double the total testosterone concentration in plasma (81). Similar data have recently been obtained in men undergoing testicular biopsy after treatment with testosterone enanthate (200 mg/wk) alone or with DMPA (75). Testicular testosterone concentrations declined to 2% of normal after 6 wk of treatment and were then similar to circulating concentrations of total testosterone. Because of the fall in sex hormone-binding globulin concentrations resulting from testosterone administration, the rise in free testosterone is considerably greater than that of total testosterone (68). The potential for a reverse gradient between the peripheral circulation and the testis therefore exists when high peripheral concentrations are achieved by exogenous steroid administration in the presence of suppressed LH secretion. An alternative approach to this question is the measurement of epitestosterone (EpiT; 17α-hydroxyandrost-4-en-3-one), a natural epimer of testosterone secreted predominantly by the testis (82, 83). Its excretion is suppressed by exogenous testosterone administration (84, 85) to approximately 10% of normal. EpiT remains detectable in all men during testosterone treatment, with concentrations several-fold higher than those found in hypogonadal men (83). These data suggest that there remains a low rate of steroidogenesis within the testis during testosterone treatment, consistent with data from hypophysectomized rats (78, 79).

Analysis of the effects and mechanism of action of testosterone within the testis is further complicated by the potential for conversion to other steroids, particularly DHT and estradiol. The ability of rat testicular tissue to convert testosterone to DHT in vitro has long been recognized (86, 87) and is differentially distributed with greater activity in the seminiferous tubules than in the interstitium (86). 5αR activity has also been demonstrated in the human testis (88, 89), and there appeared to be an increase in activity at the expected time of puberty (90). The presence of mRNA for both isoenzymes of 5αR has been demonstrated in the human male reproductive tract (91, 92). Although mRNA and enzyme activity levels were very low in human testis, the presence of enzyme activity at pH 5.0, but not 7.0, is consistent with the presence of the type 2 enzyme (91). Conversely, the type 1 isoenzyme is the predominant isoform in the rat testis (92, 93). There may therefore be significant species difference in the testicular expression of 5αR isoenzymes. DHT can quantitatively support spermatogenesis in rats at lower doses than are required with testosterone (94, 95). Under physiological conditions, i.e., in the presence of an apparent vast excess of testosterone within the testis, what the potential role of the amplification of testosterone action by conversion to DHT might be is unclear. However, when intratesticular testosterone concentrations are low, such as during gonadotropin suppression, the amplification of androgen signaling may become of importance in supporting spermatogenesis. This has been investigated using the 5αR inhibitor L675-272 (80, 96) in rats after induction of hypogonadotrophic by administration of testosterone and estradiol implants. In that experimental model, testosterone administration results in dose-dependent stimulation of spermatogenesis. Co-administration of the 5αR inhibitor resulted in a reduction of the ability of lower testosterone doses to restore spermatogenesis. Detailed morphological analysis demonstrated a reduction in the progression of round sper-
matids through mid spermiogenesis as well as in the number of elongate spermatozoids produced (80). The two isoforms of 5αR also appear to be differentially regulated in the testis, with 5αR1 negatively regulated by testosterone and 5αR2 positively regulated by FSH (97). Although data regarding 5αR isoforms in the testis are not available for the human, it has been demonstrated that intratesticular DHT concentrations do not fall after gonadotropin suppression in men (75). This further illustrates the potential importance of 5αR1 in conditions of reduced intratesticular testosterone concentrations, although attempts to exploit this using the 5αR inhibitors finasteride have been unsuccessful (98, 99).

The second major metabolic pathway of testosterone metabolism is conversion to estradiol by the enzyme aromatase. Aromatase activity is high in the Sertoli cells of the immature testis but decreases thereafter (100) and is also present in both Leydig and germ cells (101, 102). Human testicular venous blood contains higher estradiol concentrations than are found in the peripheral circulation (18). The study of the role of estradiol in the testis has received a considerable stimulus by the identification of a second estrogen receptor, ERβ, and the demonstration of the expression of ERβ receptors by many cell types, including germ cells, within the male reproductive tract (reviewed in Ref. 102). Analysis of the effects of ERα knockout mice gave rise to the novel finding of a major physiological role for estrogen/ERα in the regulation of epididymal fluid transport, whereas ERβ knockout mice have apparently normal reproductive function. Analysis of the physiological role of ERβ is complicated by the recent identification of several variants of the receptor, some of which may not be active as transcription activators and are expressed by human testicular germ cells (103). Further study of ERβ receptor function may give rise to novel insights on the steroidal control of spermatogenesis.

D. The epididymis

The essential role of the epididymis is the maturation of spermatozoa, including the capacity for motility and fertilization. Although spermatozoa can be used for in vitro fertilization after surgical recovery before passage through the epididymis, fertilization rates are low without intracytoplasmic sperm injection. The epididymis secretes proteins that modulate spermatozoal function (104) and has absorptive and secretory functions. The major problem with the consideration of the epididymis in this regard is the identification of cellular processes specific to the epididymis that could be used as potential targets without toxicity in other organs. Advances in molecular biology and proteomics are likely to improve identification of epididymis-specific regulatory pathways (105–107).

E. Conclusion

In summary, the adult testis is controlled by a feedback system involving the hypothalamus, anterior pituitary, and testis. The main testicular components of the feedback loop involve testosterone, inhibin B, and estradiol, secreted directly or arising by aromatization of testosterone in peripheral tissues. Testosterone and possibly DHT have important effects on spermatogenesis directly within the testis as well as systemic effects maintaining libido and sexual function. Testosterone suppresses LH secretion by acting directly at both the hypothalamus and anterior pituitary. FSH secretion is mainly controlled by the action of inhibin and estradiol. Progesterone and synthetic gestagens suppress the concentrations of FSH and LH, although the role, if any, of progesterone in the physiological regulation of gonadotropin secretion in men is unknown. Because spermatogenesis is dependent on gonadotropins, an obvious contraceptive approach is suppression with exogenous steroids.

III. Currently Available Male Contraceptive Methods

A. Condoms

Condoms have been in use since antiquity. Their initial use was predominantly to provide some protection from sexually transmitted disease (STD), an issue that has come full circle with the emergence of HIV. Condom usage is the only method, other than lifelong mutual monogamy, that can reduce the risk of HIV infection and other STDs, with other contraceptive methods, particularly female hormonal methods, possibly increasing susceptibility to STD acquisition (108–110). In the United States, one in five adults has an STD, and many go untreated; thus, approximately 15 million new sexually transmitted infections occur annually in the United States (111). The great majority of condoms are made from latex rubber and undergo testing for water leakage, tensile strength, and longevity. Possible improvements to these tests include testing with viral particles, which have demonstrated the potential for viral penetration in approximately 2% of condoms (112). However, the volume of semen contamination from such holes is very low, orders of magnitude lower than for not using the condom and probably of little significance compared with slippage and breakage.

The effectiveness of condoms is influenced by the nature of the product; variation in use of the product by individual users, including variation between users, as to risk of pregnancy or STD acquisition; and characteristics of the population being studied, including background prevalence of STDs. There are two pertinent aspects of the nature of condoms: 1) by providing a physical barrier to semen, the effectiveness of condoms will depend on the proportion of acts of intercourse during which they are used (i.e., correctly and consistently); and 2) they are prone to physical complications, particularly breakage and slippage. The term “efficacy” is used to denote the protection afforded by usage under ideal conditions, and “effectiveness” is the term used to describe the protection afforded under real conditions. Effectiveness therefore includes the contribution of the user as well as that of the device. The great majority of studies that have investigated the effectiveness of condoms have been observational in design with inherent risk of confounding bias. Another major source of bias is the necessity for reliance on self-report for much of the information to be gathered, including the occurrence of slippage and breakage, although more objective tests are being developed (113–115). These factors have all contributed to uncertainties in establishing
whether condom usage really provides protection against STDs.

1. Prevalence of condom usage. The usage of all methods of contraception is limited by availability. This in itself is not only a societal issue but is relevant at the level of the individual. Thus, many aspects of contraceptive use and failure are partly determined by relative poverty and its associated barriers (116), in addition to inherent method differences. Condoms are very widely used by men at some point in their lives, with up to 90% of respondents in a survey across different cultures reporting usage of the condom at a rate higher than that for any other method (3). There have also been large increases in the use of condoms over the last two decades; these increases are associated with increased awareness of HIV and public information campaigns (117, 118). Usage by women in the United States aged 15–44 yr increased from 12% in 1982 to 20% in 1995 (119), with higher usage in the young and unmarried. Reported usage of condoms by men aged 15–19 in all acts of intercourse also increased from 33% in 1988 to 45% in 1995, with a halving to 9.5% in the proportion of men reporting never having used condoms (120). The prevalence of HIV infection in some high-risk groups, however, remains very high (121), resulting in concern that the perceived risk of HIV has diminished, perhaps as a result of the increasing effectiveness of antiretroviral therapy.

Recent data from the United Kingdom indicate that the proportion of family-planning clinic attendees using condoms rose from 6% to 35% over the yr 1975 to 2000–2001, whereas the proportion using the combined contraceptive pill fell from 70% to 42%. Condoms were the most widely used method of contraception by partners of girls under age 16 yr, with more than 50% of those attending family-planning clinics using this method. The proportion using the pill was, however, greater than that using condoms in all other than the youngest age group and was highest in the 20- to 24-yr age group (122).

Usage and attitudes about condoms vary greatly among different societies. As part of a recent survey of attitudes regarding male contraception, condom usage was found to differ by more than 3-fold among men in Cape Town and in Hong Kong. Men in Hong Kong were found the most likely to currently use condoms (62% of subjects; Ref. 3) and, compared with men in other locations, appeared to rate the convenience of condoms highly while being least likely to think that they provided effective protection against pregnancy; they were also the least enthusiastic about novel male methods.

2. Protection from pregnancy. Estimates of the pregnancy rate during condom usage vary greatly according to the population studied. With near-perfect use, pregnancy rates as low as 3% have been reported, although national data probably more closely reflecting typical use show a rate of 14% in the first year (116). Condom usage is generally highest in the young, which, by their high fecundity, accentuates the problems of the learning curve: the pregnancy rate is approximately 50% lower in the second year of use than in the first (123). This is paralleled in the data for slippage and breakage, which are also related to user experience and knowledge (124). Data from recent prospective studies (125–127) indicate that slippage occurs on 0.6–1.3% of occasions and breakage on 0.4–2.3% of occasions. Although these data may be taken to reflect the overall difficulties with the method (i.e., the relative ease of misuse and nonuse), they also show that very good contraceptive protection can be obtained when condoms are used consistently and correctly (128).

3. Protection from STDs. STDs include bacterial, viral, and parasitic infections, may be ulcerative or nonulcerative discharge diseases, and may be clinically overt or asymptomatic. A large number of these and other microbiological, physiological, and behavioral factors contribute to the risk of disease acquisition, including the coexistence of other STDs (129) and, for the female partner, the hormonal status of the vaginal and cervical epithelium. These and the methodological issues mentioned previously complicate interpretation of the available data. However, the results of meta-analysis of the 12 studies, which were regarded as sufficiently informative, of the potential protective effect of condom usage on HIV transmission clearly show a reduction in risk of infection with condom usage of approximately 87% (130). Among those reporting consistent usage of the condom, HIV incidence was 0.9 per 100 person-years, compared with 6.8 per 100 person-years for male-to-female transmission and 5.9 per 100 person-years for female-to-male transmission in those who reported never using condoms.

The data on protection against other STDs are more limited, and a recent workshop concluded that the data showing a protective effect was only consistent for HIV for both men and women and for gonorrhea for men (131). The available epidemiological studies pertaining to other infections were either inconsistent or regarded as methodologically flawed; thus, it was considered impossible to give an accurate estimate of the degree of potential protection offered by condom usage. However, the panel also concluded that there was strong laboratory-based evidence for protection against gonorrhea for women and against chlamydia and trichomoni-asis, and that condom use might reduce the risk of human papillomavirus-associated diseases including genital warts and cervical neoplasia. Since that report, additional prospective studies have indicated protective effects of condoms against transmission of herpes simplex virus type 2 from men to women but not from women to men (132) and against transmission of several STDs in a study of Kenyan prostitutes (110).

4. New developments in barrier male contraceptives. Developments in condom manufacture include the use of polyurethane, styrene ethylene butylene styrene (125, 133), and hypoallergenic latex (134). These are useful for those with latex allergy, and although most men found the polyurethane condom gave increased sensitivity, it had higher slippage and breakage rates (relative risks of 6.0 and 6.6, respectively) than latex (125). In a randomized trial comparing latex with two new materials, two thirds of both male and female participants preferred one of the synthetic condoms (133). No information is available regarding protection from STDs, and there are only limited data on protection from pregnancy (126).
A separate line of development is in the microbicidal coating of condoms. At present, many condoms are coated with lubricant containing the nonionic detergent nonoxynol-9 (N9). This was originally introduced as a spermicide, but it became apparent that this and similar compounds had antiinfective (including antiviral) activity by disrupting cell membranes (135). N9 decreased the rate of simian immunodeficiency virus transmission to monkeys (136) and has also been suggested to reduce HIV transmission in women in one epidemiological study (137). However, by virtue of the same cell membrane activity responsible for its antimicrobial activity, it also has irritant activity on the epithelia of the penis and vagina with changes in approximately 50% of women administered N9 suppositories 4 times per day for 2 wk (138). It has been suggested that the use of N9 and related compounds might actually increase the risk of HIV infection; evidence to support this was found in a study of female sex workers in Kenya who used vaginal sponges containing N9 (139), but additional large studies are required for confirmation. There is, however, probably a dose threshold below which N9 has no significant detrimental effect, and there is no evidence that this effect is relevant to the doses involved in condom use. A recent randomized, controlled study comparing condom use with and without N9 in more than 1000 women at high risk for STD (but excluding sex workers) showed no difference in the rate of urogenital gonorrhea and chlamydial infection (140). There is currently much interest in the development of combined spermicides and microbicides that may come to have a major role in both contraception and prevention of STDs. Although these are generally considered in terms of female application, they may also be used in condom lubricants.

B. Vasectomy

Division and/or occlusion of the vas deferens (vasectomy) is a highly effective method of contraception that has been shown to be extremely cheap and cost effective (141). Between 40 and 60 million couples (about 7%) in the world depend on vasectomy as their method of contraception (Ref. 142 and Fig. 2). Although it is usually regarded as permanent, the pregnancy rate reported after reversal by trained surgeons using microsurgical techniques is as high as 50% (143). The international incidence of vasectomy varies greatly and within each country by ethnic origin, socioeconomic status, age, and marital status. For example, in United States, the incidence of vasectomy rises from 1% in men aged 20–24 yr to 20% in men aged over 40 yr (144), although it has been becoming relatively less popular than female sterilization over the last four decades (145). In Great Britain in 1992, nearly 30% of couples over 35 yr old were using vasectomy as their contraceptive method compared with approximately 20% choosing female sterilization (146). Vasectomy was found to be more popular in men who are better educated, more affluent, and who are currently married. Cultural factors also influence the popularity of vasectomy: in Europe, less than 1% of French men are vasectomyzed (147), whereas it is particularly common in New Zealand (148). Thus, it would appear that cultural and socioeconomic factors are more important than concerns about safety and efficacy in determining the popularity of vasectomy.

Vasectomy almost always involves occlusion and/or division of the vas under local anesthesia (149). The vas can be accessed either by traditional surgical incision or by the “no-scalpel” technique using a specially designed sharp, pointed forceps (150). Occlusion of the ends of the tube by cautery, sclerosing agent, or interposition of fascia are more effective than simple division and ligation. A number of modifications of the technique, including possible reversible methods, have been investigated, including insertion of rubber plugs into the vas or injection of styrene polymer, the latter having the advantage of administration by injection (151). Assessment of efficacy is not easy. Short-term failure is usually defined as the presence of sperm in the ejaculate at some arbitrary time after operation (3–6 months) or after 23–25 ejaculates (141). There are always some sperm present in the initial ejaculates, although after 4 wk the number and quality in the majority of men is probably insufficient to achieve fertilization. In practice, a significant proportion of men fail to provide postvasectomy ejaculates for examination, and failures are identified only after an unexpected pregnancy in the partner. Late failure can occur at any time after vasectomy and is thought to be due to recanalization of the vas. The pregnancy rate in partners whose fertility status is unknown is only an indirect measure of efficacy. The apparent failure rate is inversely related to the age of the partner because of the marked decline in fertility of older women. In one study, the cumulative pregnancy rate after 10 yr was only 1.9 per 100 when the woman was over 40 yr at the time of vasectomy, as compared with 12 in 100 cases when the wife was 25–29 yr (152). Common sense dictates that vasectomy should be more successful when performed by experienced surgeons using a technique that involves occlusion and division of the vas. Case series by individual surgeons report failure rates of 0–2%. In one prospective series, 2250 men were followed up for at least 1 yr after at least two postvasectomy samples had no sperm (153). In the first year, 15 men had sperm in the ejaculate, 4 in the second, and only 1 in the third. All the men had sperm counts less than 0.1 million/ml, and there were no pregnancies reported. The same clinic reported only 9 failures that resulted in pregnancy in more than 30,000 vasectomies performed between 1970 and 1999. The low failure rate (1 in 2000) is probably an underestimate due to underreporting. However, there are no published prospective studies equivalent to those for female sterilization [e.g., Collaborative Review of Sterilization (CREST); Ref. 154] in which the incidence of failure can be assessed in relation to these factors. It is likely that the effectiveness, as judged by the number of unplanned pregnancies, is lower than the results of these individual series would suggest.

Vasectomy under local anesthesia has few serious side effects. Perioperative complications include bleeding and hematoma, the prevalence of which is related to the experience of the surgeon and the type of procedure (155). Incisional vasectomy is associated with a higher complication rate than no-scalpel techniques (156). Although sperm granulomas at the site of occlusion occur in 15–40% of vasectomies, they are usually asymptomatic. Although long-term complications such as chronic pain and epididymitis are rare (157), it is
important that prevasectomy counseling includes information about these risks.

The majority of men develop antisperm antibodies that persist in the circulation for several years (158, 159) and may lead to continuing infertility even when the patency of the vas has been reestablished by surgical reversal (160). The interval between vasectomy and reversal is also an important predictor of success, as are the techniques of both surgical procedures. Initial reports of a high incidence of atherosclerosis in monkeys after vasectomy have not been confirmed (161, 162). Epidemiological surveillance fails to demonstrate any increase in cardiovascular disease in vasectomized men (163). Case control and cohort studies investigating the incidence of carcinoma of the prostate and testis in vasectomized men have given conflicting results (141, 164, 165). Interpretation of these studies is complicated by the difficulty of removing confounding factors, especially detection bias. A recent review (165) concluded overall that there was no association between vasectomy and cancer of the prostate or testis.

In summary, vasectomy is one of two existing methods of contraception available to men. It is more effective than the condom and has the advantage that it does not rely on compliance at the time of coitus to be effective. However, it provides no protection against STD, and reversal is expensive and only partially successful. The fact that men in many countries choose vasectomy reflects their commitment to sharing the burden of fertility control with their partners and is an indication of the potential demand for new methods of contraception.

IV. The Hormonal Approach to Male Contraception

Whatever the precise mechanisms of actions of the two gonadotropins and their relative importance in maintaining spermatogenesis in the adult may be, it is clear that suppression of gonadotropin secretion will result in a fall in sperm production, which is the basis of the hormonal approach to male contraception. Suppression of testicular steroidogenesis is therefore also a consequence of endocrinological male contraception, requiring coadministration of androgen to prevent the symptoms and consequences of hypogonadism. Suppression of gonadotropin secretion can be achieved by overriding the physiological negative feedback control mechanisms at the hypothalamus and pituitary gland by administration of exogenous steroids, or perhaps more directly, the effect of GnRH on the pituitary may be prevented by administration of a GnRH analog or by a combination of such agents. The requirement for androgen to provide replacement for the secondary hypogonadism will also provide a physiological feedback signal at the hypothalamus, preventing increased GnRH secretion, which may increase the effectiveness of a coadministered GnRH analog. The major issues are the need for rapid, consistent, and sustained suppression of spermatogenesis to a level that will give adequate contraceptive efficacy, potential adverse effects of administered steroids or other agents, and the need for appropriately acceptable drug formulations. Conversely, there is the potential for noncontraceptive health benefits as well as risks from such alterations in the hormonal milieu, as with the female combined contraceptive pill.

A. Testosterone alone: demonstration of contraceptive efficacy

The potential of this concept is far from new; the demonstration that administration of testosterone resulted in suppression of spermatogenesis dates back to 60 yr ago (7, 8, 166). These initial observations and subsequent studies (Ref. 167 and Fig. 4) demonstrated that testosterone could induce fully reversible azoospermia using the short-acting ester testosterone propionate. The development of the longer-acting testosterone enanthate (TE) allowed investigation of the effect of varying dosage and administration frequency, par-
particularly to reduce exposure to supraphysiological doses of testosterone, and introduced a distinction between frequent administration for induction followed by a reduced-frequency maintenance phase (168). These and similar studies involving varying injection intervals (169, 170) were encouraging, with near-azoospermia maintained during TE injections at 10- to 12-d intervals, although longer injection intervals resulted in partial recovery.

These studies illustrated the side effects associated with testosterone administration, e.g., weight gain and acne in some men, but the degree of spermatogenic suppression was sufficiently encouraging to lead to the initiation of two large international studies sponsored by WHO to investigate the true contraceptive potential of this approach. The regimen investigated was 200 mg im TE weekly, and subjects used no other contraceptive for 12 months once their sperm concentration had fallen below the set threshold. In the first study (171), the threshold was azoospermia, and 137 men (70%) entered the efficacy phase. Only one pregnancy resulted. However, this large study clearly demonstrated the variable degree of suppression of spermatogenesis achieved, with only two thirds of men achieving azoospermia within 6 months of TE treatment. This relatively low proportion, however, allowed the investigation of the contraceptive efficacy of induced oligozoospermia (67, 172), which may carry a very different risk of pregnancy from that observed in subfertile men (173). Initially, the threshold for entering the efficacy phase was 5 × 10⁶/ml, which was later reduced to 3 × 10⁵/ml after an interim analysis that identified that three of five pregnancies at that stage had occurred among men with sperm concentrations greater than 4 × 10⁵/ml. Inadequate suppression of spermatogenesis to preclude entry to the efficacy phase occurred in only 8 (2.2%) of the 357 men who completed the suppression phase. Four pregnancies occurred during the 49.5 person-years of exposure in the oligozoospermic (0.1 to 3.0 × 10⁵/ml) group, with none in 230 yr of exposure in the azoospermic group. These data gave an overall pregnancy rate of 1.4 (95% confidence interval, 0.4–3.7) and of 8.1 (95% confidence interval, 2.2–20.7) in the oligozoospermic group alone. These landmark studies clearly demonstrate the contraceptive efficacy of hormonally induced azoospermia. Although induced oligozoospermia also appears to offer contraceptive efficacy similar to other male methods, i.e., condoms, the number of pregnancies involved was very small and, thus, the confidence intervals wide. In vitro studies have also demonstrated the fertilizing ability of residual spermatozoa during TE-induced suppression (174).

The relationship between spermatogenic suppression and contraceptive efficacy raises the issue of the degree of efficacy required from a hormonal method. All existing methods of contraception have a failure rate, and although some recently introduced methods are more effective than sterilization, the range is wide. Condoms have an important place in contraceptive practice despite their evident shortcomings. Thus, it cannot be assumed that a male contraceptive that does not offer near-100% contraceptive efficacy will have no place in global provision. However, the skepticism still associated with the introduction of a hormonal male method (2) is such that the first method to be introduced should be as efficacious as possible.

These WHO studies also identified significant ethnic differences in the proportion of men who achieved azoospermia, being greater in Chinese (91%) than Caucasian (60%) men (171). High azoospermia rates in Asian men have been confirmed in subsequent studies using both testosterone alone (175, 176) and androgen/progestogen combinations (177). The basis for this is uncertain and could not be explained on the basis of body size or pretreatment endocrine or seminal differences in data from the WHO study (178). Overall, men achieving azoospermia had slightly higher pretreatment FSH concentrations and showed a gonadotropin rebound in the recovery phase (178).

On the basis of investigation of men taking part in the second WHO study (172), it had been suggested that the maintenance of oligozoospermia was associated with higher 5αR activity than in men achieving azoospermia (48, 179). As discussed above, inhibition of 5αR activity in the rodent testis has been demonstrated to reduce the supportive effect of low-dose testosterone on spermatogenesis (80, 96), and intratesticular DHT concentrations are maintained during gonadotropin suppression (75). Differences in 5αR activity between Caucasian and Chinese men and women have been identified (180) in parallel to the greater suppression of spermatogenesis in Asian men. The possible importance of 5αR in supporting low rates of spermatogenesis in some men has been investigated in two studies involving administration of the 5αR inhibitor finasteride. One protocol involved selective administration of finasteride to men once incomplete suppression had been identified (98), and the second protocol involved administration to men from the initiation of suppression using a submaximal regimen of testosterone with the oral progestogen desogestrel (99). In both studies, no additional effect of finasteride was demonstrated. However, because it is likely that 5αR type 1 is the predominant isoform in the testis and finasteride has preferential activity on the type 2 isoform, it is possible that more selective inhibition of the type 1 isoform may be more effective.

Other reproductive differences between Caucasian and Asian men include differences in feedback sensitivity to testosterone (181) and in rates of germ cell apoptosis (182). A recent analysis of differences in androgen production and metabolism between Caucasian and Chinese men concluded that, although there were differences, they were largely due to dietary/environmental rather than genetic factors (183). Although there are several possible contributory factors to the increased sensitivity of Asian men to steroidal suppression of spermatogenesis, none have been clearly demonstrated to be of direct importance.

These two WHO studies (171, 172) demonstrated conclusively that hormonal suppression of spermatogenesis sufficient for contraceptive efficacy was possible. The main drawbacks of the TE preparation used were the need for frequent injection; the relatively high proportion of men not achieving azoospermia and, thus, the need for identifying nonresponders; and side effects due to the high dose of testosterone administered. The influence of the testosterone formulation has been demonstrated using testosterone pellets. These pellets consist of fused crystalline testosterone, which is usually
inserted sc using a trocar, with the patient under local anesthesia, into the lower abdominal wall at a dose of 800 mg (4 × 200 mg pellets, each releasing 1.3 mg/d), providing hypogonadal replacement for approximately 5 months with good acceptability and reproducibility (184). Although the pellets may occasionally be extruded, their long duration of action with near-zero-order pharmacokinetics make them an excellent prototype preparation for long-acting injectable preparations with similar properties that are yet to be developed. Their use allows considerable reduction in the dose of testosterone required for gonadotropin and spermatogenic suppression (98, 185), resulting in a reduced prevalence of side effects while maintaining similar efficacy to TE. The absence of supraphysiological testosterone concentrations, while also avoiding diurnal fluctuations, may also contribute to spermatogenic suppression (68). We have recently investigated the effect of repeated administration of testosterone pellets in combination with a gestagen; the findings in these studies are discussed in Section IV.B.

A variety of other testosterone preparations, particularly longer-acting injections and, more recently, transdermal formulations, have also been investigated. The data from investigations in which these preparations have been in combination with other suppressive agents are discussed below. Injectable testosterone preparations are 17β-esters, slowly absorbed from the site of injection then rapidly hydrolyzed in the circulation (186), with the speed of absorption being related to the length and hydrophobicity of the side chain (187).

The longest-acting ester tested as a potential contraceptive thus far is testosterone buciclate, which has a duration of action of 3–4 months (188). Single administration of 1200 mg to a small group of men resulted in encouraging spermatogenic suppression, with three men becoming azoospermic (189), but this androgen has not been available for further investigation due to difficulties with formulation and potential toxicity. More information is available regarding injectable preparations of testosterone undecanoate (TU), different preparations of which have been developed in China and Europe. Pharmacokinetic analysis of the Chinese preparation, in which the TU is dissolved in tea seed oil, indicated that administration of 500 mg provides replacement for 6–8 wk (190). A subsequent study investigating contraceptive potential demonstrated that 500 mg every 4 wk resulted in azoospermia in 11 of 12 men, and a higher dose of 1000 mg per 4 wk resulted in azoospermia in all 12 men, although there was some accumulation of testosterone (176). A large efficacy study using this preparation involving 308 men demonstrated that only 9 failed to suppress spermatogenesis to a sperm concentration of $3 \times 10^6$/ml or lower within 6 months, and that there were no pregnancies among partners of men whose sperm concentration remained below that threshold for an additional 6 months (191). As with the WHO studies, most contraceptive exposure was with azoospermia, and pregnancies were reported in partners of the small number of men whose sperm concentration showed a partial recovery to above $3 \times 10^6$/ml. The 8-ml injection volume appeared to be well tolerated: although it is reduced in the preparation developed by the pharmaceutical company Jenapharm (Jena, Germany) in which the drug is dissolved in caster oil with improved pharmacokinetics (192), the diluent volume required for 1000 mg TU remains 4 ml. This preparation has also been investigated as a potential contraceptive: 1000 mg TU administered every 6 wk resulted in azoospermia in 7 of 14 men (193). It appears from studies of repeated administration in hypogonadal men (194) that this injection interval can be significantly increased, and this is therefore a promising development in testosterone therapy with contraceptive potential, particularly when combined with another gonadotropin-suppressing agent.

Transdermal testosterone preparations including scrotal and nonscrotal patches and gels are becoming widely available (Refs. 51, 195, 196 and Table 1). Because their main value is in maintaining physiological testosterone concentrations, data so far on their potential in contraception have been as components of a combination preparation (72, 197, 198), in which the degree of spermatogenic suppression achieved has been surprisingly low. This may, in part, reflect poor compliance because the transdermal patches currently available are irritant to the skin (199, 200).

In summary, the studies described illustrate the development from proof of concept that testosterone-based regimens could provide efficacious contraception in at least a proportion of men to newer preparations with improved pharmacokinetics allowing for significant dosage reductions. However, the long-term side effects (and low efficacy in Caucasian populations) associated with this approach make it unlikely that testosterone alone will be developed as a male contraceptive.

B. Testosterone-progestogen combinations

The ability of progestosterone and synthetic progestogens to suppress spermatogenesis has long been recognized, with azoospermia being achieved in all 19 men administered 50 mg progesterone im or 30 mg daily of one of three synthetic progestogens administered by mouth (31). The administration of the progestogens alone resulted in loss of libido; thus, these potent suppressors of gonadotropin secretion have been widely investigated in combination with testosterone to allow a reduction in testosterone dosage while potentially augmenting the degree of spermatogenic suppression (Fig. 5). In addition to suppression of gonadotropin secretion, progestogens may have additional intratesticular effects. Inhibitory effects on Leydig cell steroidogenesis, specifically on 17β-hydroxysteroid dehydrogenase activity, have been identified (201), as well as inhibitory effects on LH receptor expression and function (202), possibly mediated by a nonclassical progesterone receptor also identified in spermatozoa (203). Both effects might be important in a gonadotropin-depleted state, by further reducing Leydig cell steroidogenesis and, thus, intratesticular testosterone concentrations.

The following section describes the current status of several combination approaches (see Table 2). It will be immediately recognized that many of these studies have involved only small numbers of subjects (see Fig. 5). Interpretation is further complicated by the use of different criteria for spermatogenic suppression (thresholds of 1, 3, or $5 \times 10^6$/ml) and variation in the ethnic background of subjects. Few studies
have involved drug administration for longer than 6 months; thus, very limited information is available as to the effects of these regimens in the medium term.

1. Medroxyprogesterone acetate (MPA). Early studies sponsored by the International Committee for Contraceptive Research of the Population Council in the 1970s investigated the effects of megestrol acetate, norethindrone, and norgestriene with testosterone (204–206). Azoospermia was achieved in approximately 50% of men, and these studies were followed by a series of studies investigating the combination of DMPA with testosterone (207). These studies demonstrated suppression of spermatogenesis to sperm concentrations of less than 1 × 10^6/ml in the majority of men and provided some information regarding the potential contraceptive efficacy of these regimens (208). The additive effect of DMPA on the degree of suppression achieved with the synthetic androgen 19-nortestosterone was also suggested, although it was not demonstrated in direct comparative studies (209, 210), and multicenter studies in Indonesia were undertaken by WHO to compare testosterone and 19-nortestosterone with DMPA (177). This demonstrated the high efficacy of this combination, with 97–98% of men achieving azoospermia with both androgens, although androgen-only groups were not included. As discussed above, azoospermia is more readily achieved in Asian men, and the dose of testosterone (100 mg/wk) used in this WHO study resulted in 100% azoospermia in a small study in Indonesia when administered alone (175), compared with much lower efficacy in Caucasian populations (211). Investigation of this combination also highlighted potential adverse effects on serum lipoproteins (212). The combination of DMPA with testosterone pellets has also allowed the clear demonstration of the additive effect of that progestogen to testosterone with single-dose administration (213), although no data are at present available regarding repeated administration of this combination. The efficacy, ready availability, and economy of DMPA mean that it continues to be the subject of ongoing investigation, with a large study investigating the contraceptive efficacy of testosterone pellets/DMPA, i.e., a dual depot regimen, underway (D. J. Handelsman, personal communication). It appears, from a recent study with only small numbers of men, that the speed of spermatogenic suppression with testosterone/DMPA is similar to that with testosterone alone (75). There are also concerns regarding potential delay in restoration of spermatogenesis due to accumulation of DMPA in adipose tissue (214).

![Fig. 5. Comparison of spermatogenic suppressive efficacy in a number of recent studies of testosterone-only and combination regimens. Data indicate percentages of subjects achieving azoospermia (solid columns) and oligozoospermia (open/shaded columns). Open columns indicate threshold of less than 3 × 10^6/ml, and shading indicates less than 1 × 10^6/ml. Numbers within base of column indicate numbers of subjects. T, Testosterone (precise preparation specified at base of figure); DSG, desogestrel (oral); ETO, etonogestrel (implant). Horizontal lines indicate groups of columns to which the text refers. Numbers immediately below columns indicate doses (see text for details). Reference numbers are indicated at the base of the figure below the appropriate columns.](image-url)

### Table 2. Progestogens currently investigated as potential components of a hormonal male contraceptive regimen

<table>
<thead>
<tr>
<th>Progestogens</th>
<th>Formulations</th>
<th>Special notes</th>
</tr>
</thead>
<tbody>
<tr>
<td>MENT acetate</td>
<td>Oral, daily or injection every 2–3 months</td>
<td>Low androgenicity</td>
</tr>
<tr>
<td>LNG</td>
<td>Oral, daily or implant: months/years</td>
<td>Significant metabolic effects, e.g., lipoproteins</td>
</tr>
<tr>
<td>CPA</td>
<td>Oral, daily</td>
<td>Antiandrogenic activity, hepatotoxicity</td>
</tr>
<tr>
<td>Desogestrel/etonogestrel</td>
<td>Oral, daily or implant: months/years</td>
<td>Significant metabolic effects, e.g., lipoproteins</td>
</tr>
<tr>
<td>NET enanthate</td>
<td>Injection every 2–3 months</td>
<td>Complex metabolism, including estrogenicity</td>
</tr>
</tbody>
</table>
MPA can also be administered orally and has been investigated in combination with early percutaneous testosterone preparations (215, 216). Although effective suppression of spermatogenesis could be achieved (216), absorption of the testosterone by the female partners was troublesome (217). This would not be anticipated using current transdermal testosterone preparations, although their use results in a very high incidence of allergic reaction (199), which can be severe (200). Transdermal testosterone with oral LNG or desogestrel induced dose-dependent suppression of spermatogenesis (72, 197), although this was not complete, and significant numbers of subjects withdrew because of skin irritation.

2. Cyproterone acetate (CPA). CPA is an orally active antiandrogen and progestogen that is widely used in the treatment of hirsutism in women and prostate cancer in men. Its potential use in male contraception is therefore perhaps surprising, but some very informative data have been obtained. Initial studies demonstrated that high doses (200 mg/d) resulted in marked suppression of spermatogenesis, with five of six men reaching sperm concentrations less than 1 × 10⁶/ml, two of whom became azoospermic (218). Gonadotropin secretion in that study was estimated using urinary analysis. The lack of change in gonadotropin excretion was interpreted to indicate a direct effect within the testis, and although subsequent studies of the effects of lower doses (5–30 mg daily; Refs. 219 and 220) using more accurate gonadotropin assays demonstrated that gonadotropin secretion was indeed suppressed, the possibility that intratesticular effects contribute to the efficacy of CPA remains.

The high prevalence of side effects of even the low doses of CPA (219–221), including loss of libido and fatigue, precluded further studies without androgen supplementation. A series of studies have more recently been carried out re-investigating oral CPA with TE (222, 223). These studies, although involving small numbers of men in each group, suggested that the combination of CPA in doses of 25–100 mg/d with 100 mg TE per week resulted in the rapid onset of azoospermia in all subjects, whereas that dose of TE alone was less effective. The antiandrogenic effect of CPA appeared to be reflected in a dose-dependent fall in hemoglobin concentration and hematocrit and also in body weight, despite the mildly supraphysiological dose of testosterone. CPA with oral TU offers the potential for complete self-administration; suppression of spermatogenesis was achieved in all eight subjects, and one became azoospermic despite the relatively low dose of 12.5 mg CPA (224). Although this approach remains attractive, it is likely to require novel oral androgens to become a more realistic method.

It is possible that the high efficacy of CPA may reflect antagonism of the effect of residual testosterone concentrations within the testis. The available data on residual androgen concentrations in the human testis during gonadotropin withdrawal suggest that intratesticular testosterone concentrations are similar to physiological peripheral concentrations during testosterone administration (75, 81), and measurement of the testicular steroid EpiT indicates that there continues to be a low rate of testicular steroidogenesis (84, 85). The potential enhancement of spermatogenic suppression with other antiandrogenic compounds as part of a contraceptive regimen therefore remains an attractive area for further investigation.

3. LNG. LNG, as with the other progestogens previously discussed in this review, is widely used in female contraception both orally and as the Norplant device (Wyeth, Philadelphia, PA). Initial studies using LNG alone or in combination with testosterone showed only modest suppression of spermatogenesis (225, 226), with no subjects achieving azoospermia when administered 500 μg LNG orally with 200 mg TE monthly. Oral LNG at that dose does induce improved suppression with a higher dose of TE (100 mg/wk), with 12 of 18 men becoming azoospermic, compared with 6 of 18 with TE alone, with more rapid onset of azoospermia (211). Titration of the dose of LNG downward to 125 μg daily demonstrated the continuance of good, although incomplete, spermatogenic suppression but with reduced metabolic effects (227). The importance of the dose of testosterone is demonstrated by comparison of these studies involving weekly administration of TE with the earlier study (226) involving less frequent administration of TE and with a recent study of the combination of LNG with transdermal testosterone patches in which only 2 of 11 men became azoospermic (72); thus, maintenance of serum testosterone concentrations appears crucial to prevent escape of gonadotropin secretion and, thus, spermatogenesis. Conversely, when high doses of testosterone as injectable testosterone undecanoate are administered with oral LNG (228), no additive effect of the gestagen on suppression of spermatogenesis was observed, with only 50% of subjects achieving azoospermia, although suppression of serum lipoproteins was greater in the combination group.

LNG is also formulated as an implant. The potential advantage of sustained-release preparations include avoidance of reliance on the subject’s compliance, and as with the testosterone pellets (185), a dose-sparing effect may be evident. Administration as a two-rod implant, each rod containing 75 mg LNG, with TU (250 mg/month) resulted in azoospermia in 6 of 16 men in a Chinese study, but sperm concentrations remained in the normal range in 4 men (229). Higher doses of either the progestogen or androgen may improve on these results (198).

4. Desogestrel and etonogestrel. Promising results have been obtained with the oral progestogen desogestrel (35, 73, 230–232). Desogestrel is a potent progestogen with 300 μg oral desogestrel daily in combination with 50 mg im TE weekly (35). This study also demonstrated the apparent narrow dose-response relationship with this combination: either decreasing the dose of desogestrel to 150 μg or a higher dose of testosterone (100 mg/wk) resulted in a lower apparent incidence of azoospermia, although the groups were of small size. Comparable results were obtained in a similar study (230), although the combination of 150 μg desogestrel with 100 mg TE per week resulted in azoospermia in all eight subjects. The differences in prevalence of azoospermia between these two studies highlight the need for caution in interpreting data based on very small subject groups.
In a dose-finding study using testosterone pellets with oral desogestrel, 300 μg desogestrel resulted in greater spermatogenic suppression than 75 or 150 μg (73). We have recently demonstrated that this combination resulted in azoospermia in all subjects investigated in both Scotland and Shanghai (231) using a dose of testosterone designed to give no more than physiological replacement (400-mg testosterone pellets every 12 wk, i.e., 4.8 mg/d at steady state after repeated administration). This is reflected in the serum testosterone concentrations, which fall slightly but remain within the normal range during repeated administration (231). Similar results have also been obtained in a study involving African men in South Africa and Nigeria (232). The stability of serum testosterone concentrations with this regimen may be more than compensate for the dose being lower than in previous combination studies of testosterone. It is similar, however, to transdermal administration that delivers 5 mg/d, but with significant diurnal variation (51), and appears to be markedly less effective in inducing spermatogenic suppression in combination with an effective dose of progestogen (72). The low rate of spermatogenic suppression during administration of transdermal testosterone has recently been confirmed using oral desogestrel as the progestogen in doses up to 300 μg (197). Thus, comparison of the degree of spermatogenic suppression achieved with the various testosterone regimens used with oral desogestrel clearly illustrates the overriding importance of formulation as well as dose, as both the testosterone pellets and transdermal methods deliver approximately 5 mg/d: 300 μg desogestrel daily with testosterone pellets resulted in azoospermia in 100% of subjects (231), but with transdermal testosterone, only 57% of men became azoospermic (197). The significant dose-sparing effect with the use of testosterone pellets probably results in serum testosterone concentrations straying neither into the supra-physiological range, inducing side effects and possibly supporting spermatogenesis, nor into the hypogonadal range, allowing escape of gonadotropins from effective suppression. This applies equally to combination as to testosterone-only regimens (185).

As with other testosterone/gestagen preparations, weight gain and HDL-C suppression are reported and demonstrated to be dependent on the doses of both desogestrel and testosterone (230), although there was no weight gain in the study by Wu et al. (35). The speed of onset of azoospermia is also high with desogestrel/testosterone combinations, with 23 of 28 men achieving azoospermia within 12 wk (231). Although slowness of onset is perceived to be a potential drawback of the hormonal approach, these results approach those achieved after vasectomy.

Etonogestrel implants have recently been developed for female contraception, with a single implant (Implanon, Organon, Cambridge, UK) providing effective contraception for 3 yr and acting by inhibition of ovulation (234). The implants release approximately 50 μg etonogestrel per day; thus, by comparison with oral dosages of desogestrel (73), it would be expected that a minimum of two implants would be required for spermatogenic suppression when given in combination with testosterone pellets, the logical choice as the longest-acting testosterone preparation available. We have recently completed a study of this combination, comparing one with two implants, both with testosterone pellets (235). In the two-implant group, sperm concentrations were reduced to less than 0.1 × 10^6/ml in 14 of 15 men, with more variable suppression in the single-implant group. It is possible that the efficacy of etonogestrel is mediated by direct intratesticular effects, as gonadotropins were not suppressed to the same extent as with high-dose TE (68), yet suppression of spermatogenesis was more rapid and consistent. As discussed previously for testosterone pellets compared with other preparations, these data indicate the dose sparing achieved with depot/implant preparations. The avoidance of exposure of the liver to high concentrations after gastrointestinal absorption may also account for the reduced effect (<10% fall) in HDL-C concentrations compared with that observed with oral desogestrel.

5. Norethisterone (NET). NET enanthate is formulated as a depot contraceptive for women, with 200 mg being administered every 8 wk. NET is a relatively androgenic progestogen, binding to the androgen with approximately 45% of the affinity of testosterone, resulting in approximately 15% of the androgen action of testosterone (236). It is also metabolized to ethinyl estradiol and 5α-NET. In postmenopausal women, the production of ethinyl estradiol is approximately 6 μg per milligram of NET (237); thus, the resulting estrogenicity will be expected to contribute to suppression of gonadotropins. The low receptor affinity of 5α-NET results in an antiandrogenic effect in the rat prostate (238). Analysis of its overall effects is therefore complex and will differ between androgen-dependent organs, e.g., the pituitary, prostate and testis, with potentially advantageous effects at each site. Despite the long time it has been available, it is surprising that it has been relatively little studied in men, although azoospermia was reported in all five men administered NET acetate orally with percutaneous testosterone (216). A recent pharmacokinetic investigation of NET enanthate demonstrated marked gonadotropin suppression (239), and subsequent administration of 200 mg NET enanthate with injectable TU (1000 mg), both administered every 6 wk demonstrated very high efficacy, with 13 of 14 men becoming azoospermic compared with 7 of 14 men receiving TU alone (193). Interestingly, although spermatogenic suppression was more rapid in the combination group, the maximal degree of suppression was not seen until wk 24 of the study, with the final drug administration having been at 18 wk.

C. Estrogens in male contraception

The increasing recognition of the importance of estrogen in male reproductive physiology has been discussed in the previous sections. In particular, much of the feedback effect of testosterone on FSH secretion is mediated by conversion to estradiol (30). Administration of implants containing LNG and estrone, without testosterone supplementation, resulted in variable suppression of spermatogenesis (240). This approach has been recently reinvestigated using sc implants of both estradiol and testosterone (241), demonstrating increased spermatogenic suppression with addition of estradiol, but a very narrow therapeutic window before estrogenic side effects, particularly gynecomastia, became
problematic. This combination is therefore attractive in theory but of limited practical benefit at present, although the potential development of ER modulators with high selective activity at the gonadotroph might reopen this avenue of investigation. It is also pertinent to the potential effects of synthetic androgens, which, if not subject to aromatization to active estrogenic compounds, may have reduced activity at suppressing gonadotropins, in particular FSH, and may not adequately mimic the effects of testosterone on bone metabolism.

D. Testosterone with GnRH analogs

The combination of a progestogen with testosterone thus allows a reduction in the dose of testosterone while also increasing the proportion of men achieving azoospermia. However, these combinations continue to have significant side effects, including weight gain and alterations of lipoprotein metabolism. Metabolic effects may be inevitable with a method that relies on interference with steroidal negative feedback on gonadotropin secretion. A potentially more elegant method would be to abolish gonadotropin secretion by interference with the action of GnRH on the gonadotrophs; thus, testosterone would be required solely for the prevention of hypogonadism. The elucidation of the structure of GnRH opened new possibilities for the manipulation of reproductive function, many of which have come to fruition in both the male and the female.

1. GnRH agonists. Administration of GnRH agonist analogs results in an initial increase followed by suppression of gonadotropin secretion, and the contraceptive potential of this approach in men has been investigated in approximately a dozen trials (reviewed in Ref. 242). These studies have involved D-Trp6, buserelin, and nafarelin and a total of more than 100 men treated with doses between 5 and 500 μg/d both alone and in combination with androgen. However, even the most successful of these studies induced azoospermia in only a minority of subjects (243), rather less than when the androgen was administered alone. It became clear that the predominant mechanism for this lack of efficacy was the escape of gonadotropins, in particular FSH, from continuing suppression (244), and this area has not been pursued further.

2. GnRH antagonists. GnRH antagonists prevent the action of GnRH on the gonadotroph without inducing the initial stimulation of gonadotropin secretion characteristic of the agonist analogs (245). Despite promising results in primate models (246, 247), relatively few clinical studies have been carried out with sufficient duration to assess the effect on spermatogenesis. This reflects problematic histamine-like allergic reactions at the site of injection, the need for daily administration by injection, and the difficulties and expense of manufacture. However, the clinical studies that have been performed have been promising, and new antagonists have fewer side effects. In two initial studies in which testosterone replacement was delayed for the first 2 wk of administration of the antagonist Nal-Glu, azoospermia was induced in 1 of 14 men (248, 249). Neither study included a testosterone-only arm, precluding clear demonstration of the additive effect of the antagonist. Such an arm was included in a study using the relatively high dose of TE, 200 mg/wk (250), as in the multicenter WHO studies. Azoospermia was induced in 7 of 10 men in the antagonist-plus-TE group, compared with 6 of 9 in the TE-only group. Although this study did not have sufficient power to allow a clear comparison of the two regimens, it provided no evidence for an additive effect of the antagonist. It is possible that this reflects the high dose of TE: if the relatively low prevalence of azoospermia induced by this dose reflects a direct stimulatory effect on spermatogenesis in some men, it is unlikely that any greater suppression of gonadotropins by the GnRH antagonist would have an appreciable effect. Although these studies are therefore promising, the small study groups preclude the conclusion that GnRH antagonists can result in a higher prevalence of azoospermia with less metabolic impact than the progestogen-based regimens.

The practical difficulties with these drugs has, however, had the effect of stimulating research into biphasic administration protocols, with one drug regimen for the suppression phase followed by a lower-dose maintenance phase. Administration of Nal-Glu with TE for 16 wk induced azoospermia in 10 of 15 men; subsequent TE-only maintenance for 20 wk sustained suppression in 13 of 14 subjects, with only 1 showing escape (251). This dose of 100 mg TE/wk alone is relatively ineffective in inducing azoospermia in Caucasians (211). A second study used the GnRH antagonist cetrorelix in combination with 19-nortestosterone (200 mg every 3 wk) (252). All six men became azoospermic with the combined drug regimen, but when cetrorelix was discontinued and the androgen continued alone, spermatogenesis was restored. This may have resulted from inadequate androgen dosage or too prolonged a dosage interval and was associated with a strikingly rapid but transient increase in gonadotropin concentrations into the normal range on cessation of cetrorelix. Selective metabolism of 19-nortestosterone compared with testosterone results in relatively low estrogenic activity, which may contribute to the lack of suppression of gonadotropins. Limiting GnRH treatment to the induction phase may reduce costs as well as drug exposure, a potentially important issue with these compounds. However, the overall advantages of GnRH antagonists in the primary outcome, i.e., suppression of spermatogenesis to near-azoospermia, have yet to be clearly demonstrated. Orally active nonpeptide GnRH antagonists have also been described (253), but no data relevant to the present discussion are yet available.

E. Adverse effects and long-term considerations

Many of the side effects of the regimens previously discussed in this review were largely predictable on the basis of testosterone concentrations rising above the physiological range, if intermittently. These include acne and weight gain with high-dose TE (254) and may be prevented by appropriate physiological testosterone replacement in a combination regime, although some may be induced by a progestogen component. Other potentially serious adverse effects are either difficult to accurately determine in relatively short-term studies, e.g., effects on bone (231) and prostate function
(255), or are merely markers for complex disease processes, e.g., changes in serum lipoproteins as indicators of future risk of cardiovascular disease (212, 256). Limitations of interpretation are increased by many studies effectively being observational pilot studies inadequately powered even to detect differences in the prevalence of azoospermia between regimens, an increasing problem with the improved efficacy of recently investigated regimens. Thus, the apparently reassuring lack of changes, e.g., in prostate volume or markers of bone metabolism, may be unreliable although appropriate at this stage of development when a wide range of potential drugs and regimens are being studied without any one being clearly better than others. Although biochemical measurements can only be indirect markers of the long-term risk of disease, the ideal regimen should be at worst metabolically neutral and should at best reduce the incidence of cardiovascular and prostatic disease.

In conclusion, the combination of testosterone with progestogen is currently the most promising approach to hormonal male contraception. The progestogen component allows a reduction in the dose of testosterone with, at least in the case of certain progestogens, more rapid and effective spermatogenic suppression. Results of studies using newer progestogens, e.g., desogestrel, are encouraging, and there continue to be advances in progestogen development that may be of value (257). Several recent studies have compared different doses of various progestogens, particularly levonorgestrel and desogestrel (Fig. 5). Although these studies have demonstrated the dose dependency of the effect of the gestagen, they have also served to highlight the importance of the testosterone formulation that is likely to be of greater importance to the efficacy of the combination than relatively minor differences between the gestagens. It is to be hoped that more direct comparisons between androgen preparations will be performed in the near future. Advances in testosterone formulation, by providing longer-acting preparations with nearer zero-order absorption, will no doubt increase the effectiveness of these combinations even further, as illustrated by data from studies using testosterone pellets. The appropriate dose of testosterone also needs to be more rigorously determined: it is unclear whether small overall increases or decreases in testosterone may have adverse or even beneficial effects and, thus, whether they may have health benefits.

F. Future directions in androgen delivery

In many of its physiological roles, testosterone acts as a prohormone. This is well illustrated in the several experiments of nature involving abnormalities of testosterone metabolism, most strikingly in the phenotypes of individuals with 5αR deficiency (258) and mutations of ERα (259) and the enzyme P450 aromatase (260). Individuals with these abnormalities have normal circulating testosterone concentrations, but phenotypic abnormalities include incomplete development of the external genitalia and prostate (5αR deficiency) or unfused epiphyses and osteoporosis (ER and aromatase mutations). Furthermore, different androgen-dependent tissues and responses such as sexual function and muscle mass have different testosterone dose-response relationships (46). Synthetic androgens subject to selective metabolism might therefore have the advantages of tissue selectivity and improved risk-benefit ratios. Increased potency would also require a smaller quantity of drug, which might allow improved transdermal administration or implant formulations with longer duration of action. 7α-Methyl-19-nortestosterone (MENT) is a synthetic androgen that is approximately 10 times more potent than testosterone in anabolic bioassays and as a suppresser of gonadotropin secretion, but it is resistant to 5α reduction (261) and thus has relatively low potency in bioassays such as stimulation of prostate size in castrated animals (262, 263). MENT can be converted by aromatase to an active estrogen (264); thus, it may be effective in the maintenance of bone mass, although this has yet to be demonstrated. This androgen was initially developed many years ago (265), but detailed human data remain limited to pharmacokinetic and pharmacodynamic studies (266). MENT is not bound by sex hormone-binding globulin and is rapidly cleared from the circulation. MENT acetate can, however, be prepared in the form of implants for SC insertion, thus giving the potential for long-term replacement therapy or treatment. These implants have recently been demonstrated to support mood and sexual behavior in hypogonadal men in a fashion similar to conventional testosterone replacement (267) and to suppress gonadotropin secretion in normal men (268). MENT also has progestogenic activity, which might be advantageous in the context of male contraception, and longer-term studies of spermatogenic suppression are underway. The use of DHT as androgen replacement has the theoretical advantage of increased potency relative to testosterone. Because the effect of testosterone is normally amplified by conversion to DHT in the prostate, this will be avoided; thus, DHT may be paradoxically regarded as prostate sparing (170). This has been confirmed by the demonstration of no change in prostate volume in a placebo-controlled study in older, partially androgen-deficient men during transdermal administration of DHT (269). However, investigation of DHT gel with LNG implants showed very limited suppression of spermatogenesis (270), with no men achieving azoospermia and only 33% showing suppression to less than 20 × 10⁶/ml. These results may reflect the limited effect of DHT on gonadotropin suppression, in particular FSH, which is likely to reflect the lack of aromatization. It remains possible that DHT will be of value as replacement in combination with the use of a GnRH antagonist.

A group of molecules has been recently identified that has selectivity and specificity for the androgen receptor (271), and further modification of these selective androgen receptor modulators may lead to them displaying agonist, antagonist, or partial effects (272). Not only may this be of great benefit in the area of male hormonal contraception, but this discovery may also have more widespread clinical applications in the treatment of hypogonadism, androgen-dependent malignancy, and in the development of hormone replacement therapy in ageing men. Similarly, the development of nonsteroidal progesterone receptor ligands (273) may replace conventional progestogens as an adjuvant in male contraceptive strategies.
V. Nonhormonal Testicular and Posttesticular Agents

The nonhormonal and posttesticular approaches have a number of potential advantages over the hormonal approach. These include potential rapidity of onset and lack of interference with nonreproductive androgen-dependent function. The meiotic division and dramatic differentiation of spermatogonia into motile spermatozoa with subsequent release from the Sertoli cell make spermatogenesis potentially vulnerable to specific intervention. Progress has been hampered by lack of understanding of the molecular regulation of spermatogenesis; however, potential targets are emerging. These include interference with the adhesion of germ cells to Sertoli cells (274), but none are in clinical development. The few nonhormonal agents investigated clinically include gossypol, a phenolic compound found in the seed, stem, and roots of the cotton plant, whose antifertility effects were first identified in the 1950s. Gossypol inhibits lactate dehydrogenase, found only in the testis, and inhibits spermatogenesis and sperm motility without affecting Leydig cell function. Large clinical studies carried out in China and involving more than 8000 men demonstrated the ability of gossypol to induce oligozoospermia in more than 90% of men (275, 276). However, azoospermia was found to be irreversible in approximately 20% of men who had taken gossypol for prolonged periods (277). Other serious side effects were also reported, including hypokalemia and occasional periodic paralysis (278). These effects of gossypol are dose dependent, and recent data indicate that low doses may provide effective yet reversible inhibition of spermatogenesis (279). Conversely, the irreversibility of the effect of gossypol has been proposed as providing a chemical alternative to vasectomy (280). Gossypol also shows activity as a vaginal contraceptive (281), and its effects on cell cycle regulation and antitumor activity are being investigated for the treatment of malignant conditions including refractory breast cancer (282).

The Chinese herbal medicine *Trypterigium wilfordii* is used in the treatment of arthritis and psoriasis. Multiglycosides extracted from this plant result in infertility in the rat, an effect initially attributed to an epididymal site of action as its major impact was on sperm motility, which was reversible without apparent toxicity (283). Similar effects were noted in a small group of men (284), and subsequent to a systematic approach to fractionated extracts (285), triptolide was isolated, administration of which to rodents resulted in rapid declines in sperm motility and fertility with later effects on spermatogenesis. Testicular volume was markedly reduced after 80 d of administration, and irreversible infertility resulted (286, 287). Triptolide has immunosuppressive activity, probably accounting for its activity in skin and joint disease (288). It remains unclear whether triptolide at lower doses will result in a selective postmeiotic effect, but both gossypol and triptolide indicate the potential for novel approaches to male contraception.

The location of the testes in the scrotum maintains them at lower than core body temperature. Even short-term scrotal heating has marked effects of spermatogenesis in the rodent (289, 290) with increased germ cell apoptosis, and although testosterone concentrations are maintained, higher LH levels indicate a greater drive to the testis (291). This has been explored in clinical studies but with variable results (292–294). In one study, azoospermia was achieved in all 14 subjects and was maintained for 1 yr. Full reversibility was indicated by recovery of sperm density in the ejaculate and by successful pregnancy thereafter (293). In a second study, 21 men wore one of three variants of polyester-lined athletic supports for 52 wk (294). These supports modestly increased scrotal temperature toward core temperature but had no effect on sperm concentration or function. The application of heat has been demonstrated to increase the degree of suppression of spermatogenesis in rats during testosterone administration, with the two effects acting at different stages of spermatogenesis (295), but this “two-hit” concept has yet to be tested in a clinical trial.

Spermatozoa undergo a maturation process in the epididymis, where they are stored before ejaculation. Interference with epididymal function could be a useful approach to contraception. Within the epididymis, contraceptive effects could be mediated on the spermatozoa directly, via the epididymal epithelium on epididymal fluid composition or on epididymal peritubular muscle. All three of these aspects of epididymal function have been investigated as potential contraceptive targets, but none have thus far been translated into clinical studies. Identification of novel receptors specific to the epididymis provides a further target for pharmacotherapy (296). Attempts to influence epididymal epithelium function have included the inhibition of *α*-glucosidase, reducing epididymal carnitine concentrations, and immunological approaches to specific proteins secreted by the epididymis. Interference with acidification of the epididymal fluid is also a possible target (297). The potential for successful interference with maturation of spermatozoa within the epididymis is suggested by the effect of the c-ros tyrosine kinase knockout in mice (105). This results in failure of development of the proximal epididymis and infertility, with the mice being otherwise normal. The spermatozoal flagellum shows a marked angulation similar to that observed in association with infertility in some species of domestic animals (“Dag Defect”; Ref. 298), which may reduce sperm functional motility although *in vitro* motility assessment appears normal.

The most widely clinically studied agents acting on the epididymis are the 6-chloro-6-deoxysugars and *α*-chlorohydrin (299). The antifertility activity of these and related compounds such as ornidazole (300) has been shown to reside in the chlorinated side chain (301). These compounds act on epididymal spermatozoa by inhibition of glycolytic activity taking advantage of the inability of spermatozoa enzymes to distinguish between chlorinated and phosphorylated compounds (302). Glyceraldehyde-3-phosphate dehydrogenase is inhibited limiting ATP production from glucose, thus reducing sperm motility. Neurotoxicity was, however, a problem with these compounds in both mice and nonhuman primates (303), limiting further development. However, the significant differences between sperm glycolytic enzymes and those found elsewhere in the body mean that the development of compounds that specifically target these processes remains a possibility.
A cation channel specific for sperm motility has recently been identified and demonstrated to be specifically expressed on the sperm tail, targeted disruption of which reduced spermatozoal motility and abolished the ability of sperm to penetrate the zona pellucida and fertilize the egg but had no other apparent effect (304). This or similar molecules would be ideal candidates for pharmacological or immunological contraception.

A. Immunological approach to male contraception

The concept of harnessing the power of the immune system to the development of contraception has parallels in nature, as antispem antibodies may contribute to subfertility in both men and women. Immun contraception using antispermatozoal antigens may be effective in both men and women; alternatively, immunoneutralization can be used to prevent the trophic effects of hormones. Indeed, the first immuno contraceptive to reach clinical studies has been an anti-β chorionic gonadotropin vaccine for women (305). This approach also avoids the potential pitfalls of steroid administration, although the safety considerations are, if anything, greater. Potential targets for male-directed contraception include FSH and GnRH, specific sperm antigens, and epididymal proteins. The application of microsequencing methodology has the potential to identify numerous sperm-specific proteins that may be candidates for immun contraception (107). However, few have been developed to the stage of clinical testing. The possibility that anti-FSH immunization might result in selective antispermatogenic activity without affecting testosterone production by the testis was investigated in nonhuman primates. Although it was clear that testosterone alone could maintain spermatogenesis in the rat, the evidence in the human was unclear and to some extent remains so (Section II.C). Passive immunization resulted in a decline in sperm concentration but did not lead to azoospermia (306, 307), confirming the importance of FSH in the maintenance of spermatogenesis in the adult primate. Active immunization, however, also showed incomplete efficacy, with some monkeys achieving inconsistent azoospermia but sperm concentrations in others remaining within the normal range (306, 308). More recent studies using an ovine FSH vaccine have indicated fewer nonresponders (309) and lower fertility than might have been anticipated on the basis of the degree of oligozoospermia induced.

A pilot study of active immunization against ovine FSH in humans demonstrated antibody production in all five subjects and resulted in a decline in sperm concentrations (310). Although the study appears not to have been of sufficient duration to fully investigate the degree of achievable suppression of spermatogenesis, the reported decline (33–65%) is much less than achievable by hormonal suppression. No adverse effects were reported. Future work may improve the consistency and titer of antibody production, but at present it appears unlikely that this approach will result in the consistent degree of suppression of spermatogenesis required for effective contraception.

Immunization against LH might be expected to be similarly efficacious, although by reducing testosterone production, this approach requires the concomitant administration of testosterone to prevent hypogonadal symptoms, as with the hormonal approach. Marked inhibition of spermatogenesis was achieved in nonhuman primates by active immunization against ovine LH (311). Muscle wastage was apparent in some immunized animals, to a greater extent than was expected based on the decline in testosterone concentrations, and this approach has not been further pursued.

The possibility that GnRH might prove to be a more effective antigen and might avoid the difficulties due to the incomplete spermatogenic suppression with FSH, immunoneutralization has been investigated (reviewed in Ref. 312). Clinical trials in subjects with prostate cancer have been conducted, and infertility has been induced in nonhuman primates, although data are scanty (313). Frequent administration of the antigen was also required.

A number of spermatozoal antigens have been investigated as immunological targets in animal models, some with promising results (314). Immunization against one such antigen, PH-20, induced reversible infertility in all male guinea pigs treated, with infertility lasting longer than 1 yr in some cases (315). Some spermatogenic antigens are proteins acquired by the spermatozoa during their passage through the epididymis and may be required for fertilization (316). The identification of human proteins with similar roles (317) raises the possibility for clinical studies in both men and women. The identification of these specific epididymal proteins and elucidation of their functions also raises the possibility for targeting the epididymis. One problem specific to epididymal antigens is that the blood-testis barrier may prevent adequate titers from reaching the epididymal lumen. However, it appears that sperm antibodies (and other proteins) do in fact accumulate within the epididymis after systemic administration (318), although the prolonged time required reduces the potential advantage of this approach to targeting the epididymis.

Thus, although there is no shortage of potential targets for immunization to prevent pregnancy, the immunological approach to contraception has not been enthusiastically pursued by either the public or private sector. Concerns include the possibility of provoking autoimmunity, variability in both the degree and duration of response among individuals, and reversibility. In addition, political concern over the potential abuse of long-term methods has made it unlikely that the immunological approach will be the basis of a product for commercial development.
Male Contraception

Contraception differs from most medications in that it is used by healthy individuals for prevention rather than cure. Tolerance of side effects is therefore low. The apparent saturation of the market in developed countries by cheap, effective, hormonal female-based methods obscures the high rate of method change, which is a clear index of dissatisfaction. Furthermore, perhaps surprisingly, use of traditional, often male-oriented methods is in fact higher in developed than in developing countries (319). Developing countries have an overwhelming need to increase usage of methods to control fertility. Coupled with changes in gender roles, the time appears ripe for the introduction of a novel male method. The hormonal approach appears close to producing a real product, and the pharmaceutical industry has at last made a small if tangible contribution to development. However, it may well be that the current explosion in our understanding of the molecular basis of reproductive function will reveal the real fruits and allow men to contribute more equally to the freedom from excessive fertility.

VII. Conclusions

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Table 3. Percentages of men and women who would definitely/probably use a male contraceptive pill

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<thead>
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<th>Edinburgh</th>
<th>Cape Town</th>
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<td></td>
<td>Black</td>
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<tr>
<td>Men n =</td>
<td>436</td>
<td>153</td>
<td>169</td>
<td>171</td>
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<tr>
<td>Women n =</td>
<td>416</td>
<td>267</td>
<td>152</td>
<td>87</td>
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Data are from Refs. 3 (men) and 321 (women).


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