Endo.

FERTILITY CONTROL IN MEN

Department of Internal Medicine

Grand Rounds

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I. The Normal Hypothalamic-Pituitary-Testicular Axis

II. Drugs that Inhibit Hypothalamic-Pituitary Function

III. Drugs and Other Agents that Affect the Testis Directly

IV. Drugs that Affect the Epididymis

V. Mechanical Interruption of Sperm Transport in the Vas Deferens

Effective reversible contraceptives for women have been available for decades. At the present time there is still no readily reversible effective contraceptive device for men. A number of explanations for this lag in the development of fertility control in men have been suggested (1). One possible explanation is that it intuitively seems easier to prevent the production of only one ovum per month in the female than to prevent the production of billions of sperm in the male. Even an 80 to 90 percent reduction in sperm density may not be sufficient to cause infertility. In addition, the processes of sperm migration from the vagina to the fallopian tubes, the development of the ability of sperm to fertilize an ovum (capacitation), fertilization itself, and implantation of the fertilized ovum in the uterus all take place normally only in the woman. Thus even some measures designed primarily to affect the sperm, such as attempts to inhibit capacitation (2), and attempts to block the subsequent processes, such as intrauterine devices, can be used in women but not in men.

Some investigators have suggested that prejudice may exist either among researchers or granting agencies awarding money for research about which sex should bear the responsibility of contraception (3). The proof that such a prejudice exists on such a large scale to explain the lag in male contraceptive development is lacking. An interesting alternative explanation is that there was not so much a lag in research in the male as that there was a large positive stimulus to research for a female contraceptive device (1). Thus the moral support, social pressure and financial aid of the feminist and birth control advocate Margaret Sanger and her friend, Mrs. Stanley McCormack, applied to a pioneer in reproductive endocrinology, Gregory Pincus, may to a certain extent explain the rapid early development of the oral contraceptive for women.

This review will update the avenues of research attempting to develop a safe, reliable, reversible technique for male contraception and focus particularly on the current status of the only effective and available method of fertility control in men, vasectomy.

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I. THE NORMAL HYPOTHALAMIC-PITUITARY-TESTICULAR AXIS

The testis consists of two components -- a system of tubules for the production and transport of sperm that empty into collecting ducts (rete testis) and ultimately into an excretory system (epididymis and vas deferens) (Fig. 1) and clusters of Leydig cells between the tubules that produce androgenic steroids (4). The basic unit by which the gland functions (5) is shown in Fig. 2. The Leydig cell contains a rich endoplasmic reticulum which is the location for testosterone biosynthesis. The basic components of the spermatogenic tubules are the germ cells and the Sertoli cells. The primordial germ cells, the spermatogonia, located adjacent to the boundary tissue, divide by mitosis to produce progeny that can enter into one of two pools, a regenerative pool of spermatogonia or a pool that

subsequently undergoes meiosis to begin the spermatogenic sequence that results in formation of mature sperm. The group of cells that enter the spermatogenic process become embraced by cytoplasmic extensions of the Sertoli cell (6).

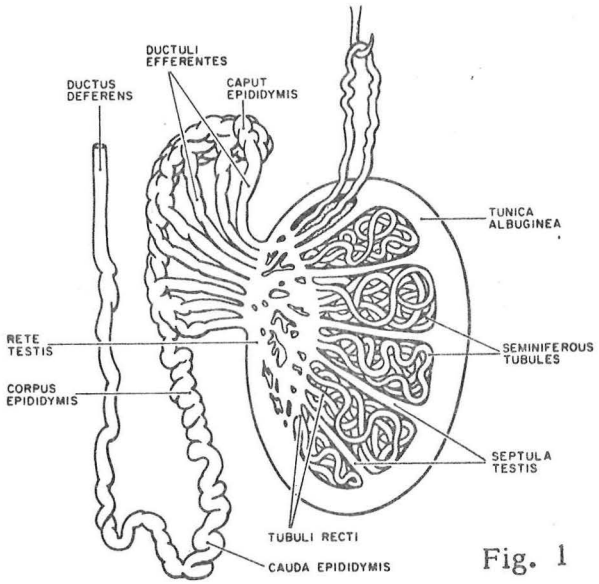
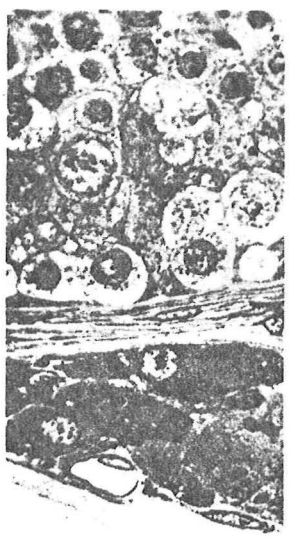


Fig. 1



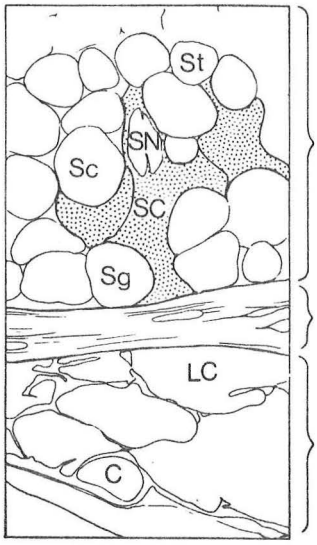


Figure 2. Photomicrograph of a normal adult human testis in which the proximity of the Leydig cell to the seminiferous tubule and the close association of the Sertoli cell to the germinal elements are demonstrated. The testis was perfused with glutaraldehyde (×L 1200). SC, Sertoli cell cytoplasm; SN, Sertoli cell nucleus; Sg, spermatogonia; Sc, spermatocyte; St, spermatid; LC, Leydig cell; C, capillary. (Courtesy: L. W. Kaler.)

Tight junctions between Sertoli cells (Fig. 3) at some level between the spermatogonia and the primary spermatocyte serve to divide the germ cells by a poorly permeable barrier into two functional pools. As a consequence, the testis can be viewed as containing two distinct compartments -- the Leydig cells and outer layers of the tubules containing the spermatogonia as one compartment, and the inner two-thirds of the tubules containing primary spermatocytes and more advanced stages of spermatogenesis as the other compartment. The entire process of spermatogenesis from the beginning of differentiation of the primary spermatogonium to the completion of motile sperm takes approximately 70 days (7), and the transport of the maturing sperm through the epididymis and vas deferens requires an additional 12 to 21 days (8). The transport process is probably accomplished by a

combination of peristaltic movement, bulk fluid drag and intrinsic sperm motility. During the transport through the epididymis sperm maturation occurs with acquisition of enhanced motility and a variety of histological changes (9, 10).

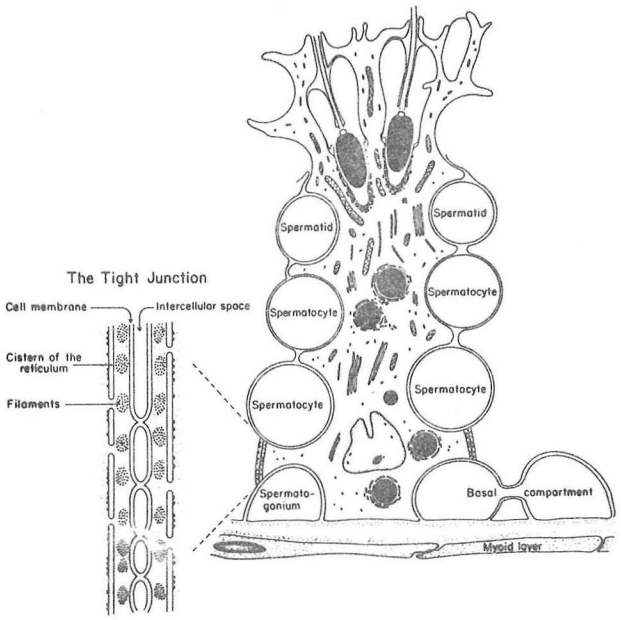


FIGURE 3

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Testosterone secretion is regulated largely by luteinizing hormone (LH) from the pituitary (Fig. 4). Follicle stimulating hormone (FSH) may also augment testosterone secretion (11), possibly by regulating the number of LH receptors on the plasma membrane of the Leydig cell (12). Testosterone feeds back on the

pituitary to alter the sensitivity of the gland to the hypothalamic releasing factor luteinizing hormone releasing hormone (LHRH) (13). Although the pituitary can convert testosterone to dihydrotestosterone and to estrogens, it is likely that testosterone itself is sufficient to regulate LH secretion (14). Whether testosterone also acts at the hypothalamus to regulate LHRH secretion is not clear.

Normal function of the seminiferous tubule is dependent on the proximity of the Leydig cells and the seminiferous tubule since testosterone as well as FSH is required for spermatogenesis. The major site of FSH action in the testis is the seminiferous tubule; indeed, almost all of the interaction of FSH with the tubule can be accounted for by binding to Sertoli cells (15). The seminiferous tubule is also a target for testosterone, and specific androgen receptors have been demonstrated in Sertoli cells (16). The entire process of spermatogenesis probably requires the concerted action of both FSH and testosterone; testosterone appears to be essential for the initial phases of spermatogenesis, whereas FSH is required for the terminal phases of spermatid development (17). However, once spermatogenesis has been initiated, it can be maintained after hypophysectomy by testosterone alone (18). The spermatogenic tubules, primarily the Sertoli cells in conjunction with maturing spermatids, produce a peptide hormone termed inhibin that feeds back on the hypothalamic-pituitary axis to selectively regulate the production of FSH (19, 20) (Fig. 4). Whether inhibin has effects on both the hypothalamus and pituitary is unclear, but it at least inhibits pituitary FSH production in the presence or absence of LHRH (20).

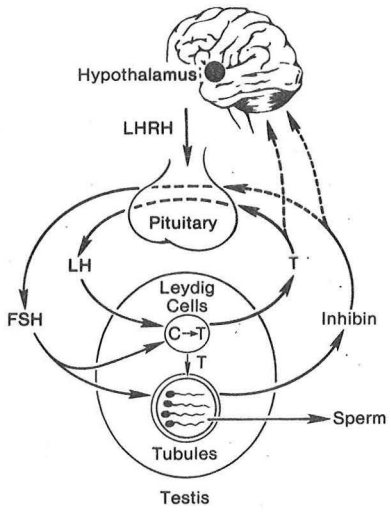

Fig. 4

The overall effect of this interlocking system in which two pituitary hormones regulate testicular function is to provide a delicate dual control mechanism by which plasma testosterone and sperm production can feed back independently upon the hypothalamic-pituitary system to regulate their own rates of production.

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II. DRUGS THAT INHIBIT HYPOTHALAMIC-PITUITARY FUNCTION

Since normal spermatogenesis requires normal gonadotropin levels, inhibition of the production of LH and FSH, either through a direct effect on the pituitary or indirectly through suppression of LHRH, will decrease sperm production.

A. Androgens Alone

The suppression of gonadotropins by any drug would be expected to result in inhibition of testosterone secretion and potential adverse effects on libido and potency. Thus, exogenous testosterone as the means of suppressing gonadotropins is attractive because its administration simultaneously replaces the deficiency in endogenous testosterone production. The only preparations currently available for administering testosterone safely are the long acting esters testosterone cypionate and testosterone enanthate. These preparations must be given intramuscularly, and testosterone enanthate is considered to have a somewhat longer effect with the optimal replacement dose considered to be 200 mg IM every 2 weeks (21). The oral androgen preparations available all have 17α-alkylation of the steroid to prevent inactivation by the liver. These preparations are not considered safe for testosterone replacement because of their potential for hepatotoxicity (reviewed in ref. 22).

Attempts of fertility control by administering replacement doses of testosterone enanthate (200 mg every 2 weeks) resulted in azoospermia in less than a fourth of men even after as long as 52 weeks. However, administration of 200 mg of testosterone enanthate every 7 to 10 days results in azoospermia in approximately half of men (Table I) (23-26). [Although severe oligospermia was achieved in additional men in these series, azoospermia is the only reliable criteria for success with this mode of therapy.] This weekly regimen resulted in an average 50 per cent increase in plasma testosterone levels above pretreatment values and suppression of plasma LH and FSH by 60 to 80% (23,25,26).

Table I. Effect of weekly injections of 200 mg testosterone enanthate on sperm density in normal men

Investigators (ref.)	No. of men	Duration (weeks)	% of men with azoospermia
Steinberger and Smith (23)	5	42	100
Paulsen et al. (24)	42	26	48
Cunningham et al. (25)	20	12	25
Swerdloff et al. (26)	17	16	59

The time course of changes in mean plasma hormone concentrations and sperm density in a representative study (26) are shown in Figs. 5 and 6.

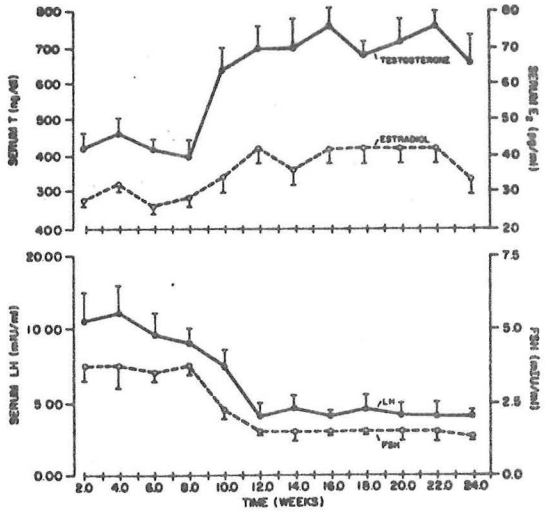

Fig. 5 Mean serum LH, FSH, T and E_2 in 17 subjects on weekly treatment with 200 mg of testosterone enanthate. Control values are seen on the left and the first 16 weeks of treatment on the right.

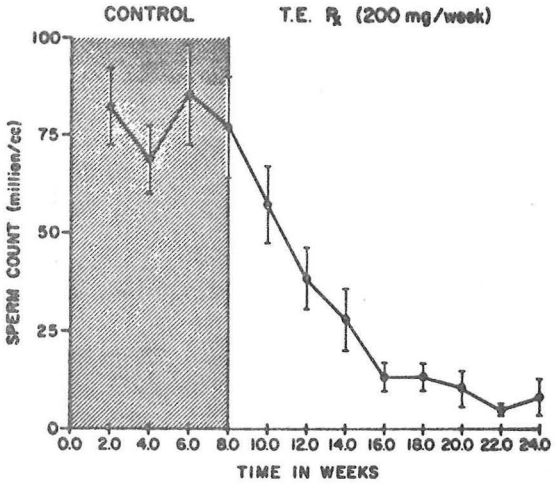

Fig. 6 Mean sperm count in 17 subjects on weekly treatment. (From Swerdloff *et al.* 1977, with permission).

The time required to achieve maximal suppression of mean sperm density was 8 to 10 weeks. The time to recovery of control sperm density on cessation of therapy is approximately 20 to 28 weeks (25). The side effects of weekly 200 mg testosterone enanthate injections are minor. Libido and potency are not altered. Mild weight gain is common. Many men develop or experience a worsening of acne, but this is usually mild (25,26). Rarely the acne has required that treatment be stopped (24).

Although plasma estradiol levels increase 50 to 80% (25,26), gynecomastia was reported in only one man in the four series in Table I (24). The mean concentration of hemoglobin increased about 1 g/dl (25,26) but polycythemia was not detected. Testis volume decreased about 20% (27).

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B. Progestagens

Progestational agents inhibit pituitary gonadotropin secretion in women and men and have thus been considered a potential means of fertility control in men. Since the suppression of plasma LH would be expected to lower testosterone levels, progestagens have primarily been used only in conjunction with androgens. The most extensively studied combination is the injection of depo-medroxyprogesterone acetate and testosterone enanthate. Unfortunately all of these trials have used a monthly injection regimen which is known not to be optimum for the antifertility effect of testosterone enanthate. The results of three such studies are summarized in Table II. The usual time to lowest sperm density is 2 to 3 months (28). An initial loading dose of medroxyprogesterone acetate of 1000 mg was given in two of the studies (28,30) which may account for their apparent greater success in inducing azoospermia. The higher dose of testosterone enanthate in the third trial did not seem to improve the response. Of interest is the observation that some escape from the suppression of spermatogenesis seemed to occur in five men in the first study when followed for several months after achieving azoospermia (28). The importance of achieving azoospermia for contraception with this drug combination is proven by the report of five pregnancies in the partners of men receiving this regimen whose sperm densities were less than 1 million/ml (31).

Table II. Effect of monthly injections of medroxyprogesterone acetate (MPA) and testosterone enanthate (TE) on sperm density in normal men.

Investigators (ref.)	No. of men	Dose (mg)	Duration (months)	% of men with azoospermia
Alvarez-Sanchez et al. (28)	20	MPA 150-300 TE 250	9	70
Brenner et al. (29)	14	MPA 100-150 TE 200	4	14
Faundes et al. (30)	10	MPA 150 TE 500	6	80

The length of time for recovery of sperm density to pretreatment levels following cessation of monthly MPA and TE injections may be as long as 1 year (30). Since medroxyprogesterone acetate is available as an oral preparation, one group tried combining it with an oral androgen, methyltestosterone. However, even the highest dosage combination of these two agents tried (20 mg each daily) was ineffective at producing anymore than mild oligospermia (32).

The side effects of the MPA and TE monthly injection regimen were mild acne and gynecomastia in a few patients. Most patients gained weight; in one study the average was 6 kg (30). Some men reported decreased libido. A possible explanation for this might be that plasma testosterone measured one month after the injection was only 10 to 30% of baseline in the third study in which the highest dosage of TE was given (30). Presumably the depomedroxyprogesterone acetate has a longer duration and leads to persistent gonadotropin suppression after exogenous testosterone is depleted.

Cyproterone acetate is an antiandrogen progestational agent not available in this country. A number of studies have attempted fertility control in men trying to take advantage of its combined effect of gonadotropin suppression and impairment of androgen action at the testis or epididymis (33-35). These studies did not include the addition of testosterone administration with the expected adverse effect of lowering plasma testosterone levels. With this single drug regimen cyproterone acetate is ineffective in lowering sperm density below the normal range in most patients, and only one patient developed azoospermia.

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C. LHRH Analogues

The decapeptide structure of LHRH was determined in 1971 and has subsequently proved amenable to chemical modification. As a result a family of analogues (both agonists and antagonists) has been synthesized. The LHRH agonists modified at positions 6 and 10 are more potent than the native hormone (36). Prolonged administration of these agonists causes a paradoxical inhibition of gonadotropin secretion (37). Recent studies of the mechanism of this inhibition of gonadotropin secretion suggest the changes in gonadotroph receptor number as well as alteration in post-receptor events may be involved (38). In rats LHRH agonist analogues have an additional site of action to decrease testosterone production. The agonists appear to decrease LH receptors in the testis and inhibit steroidogenesis by partially blocking the activity of the 17-hydroxylase and 17,20-desmolase enzymes (37). This direct inhibition of testicular function in the rat has been shown to be mediated by LHRH receptors in Leydig cells (39). Furthermore, in hypophysectomized-castrated rats LHRH agonists appear to partially inhibit testosterone action directly since testosterone-induced increase in weights of ventral prostate and seminal vesicles are diminished in rats given analogue with testosterone (40).

One LHRH agonist studied in man is D-Ser(TBU)^{6}-EA^{10}-LHRH (Hoe 766). The administration of 5 µg of this analogue subcutaneously each day to normal men acutely (one week) (41) and chronically (17 weeks) (42) lowered LH, FSH and testosterone levels. However, sperm density and potency were not significantly affected in 4 men treated for 17 weeks (42). The reason for the lack of effect was probably that mean decreases of the three plasma hormones were less than 50 per cent while receiving the therapy. Interestingly, this same agent was also administered as a single intranasal dose of 500 µg to six normal men (43). Plasma LH and FSH temporarily increased and returned to normal in 8 to 12 h after administration of the analogue. Following a brief elevation plasma testosterone and several of its precursors decreased to 50% of baseline values for the subsequent three days (43).

The only partially successful trial of an LHRH agonist as a male contraceptive was a study of the agonist D-Trp^{6}-Pro^{9}-N-ethylamide-LHRH. In this study eight normal men were given 50 μg of agonist subcutaneously daily for as long as 10 weeks (44). The mean levels of plasma testosterone, LH, and FSH for basal, nadir, and peak recovery are shown in Table III. Testosterone values declined by over 90% while gonadotropins decreased only about 50%.

Table III. Mean levels of testosterone, luteinizing hormone (LH), and follicle stimulating hormone (FSH) during basal period, at nadir of LHRH agonist therapy, and at peak during the recovery period (ref. 44).

Hormone	Basal	Nadir	Peak Recovery
Testosterone (ng/dl)	471	24	618
LH (mIU/ml)	10.9	5.4	17.3
FSH (mIU/ml)	4.7	2.9	5.6

Agonist treatment was discontinued after 6 or 7 weeks in five of the eight subjects because of impotence. Libido and potency returned two weeks after stopping agonist therapy. Of three subjects who completed 10 weeks of therapy, one was azoospermic. The time course of the changes in plasma hormone concentration and sperm density in this man is shown in Fig. 7. Recovery of spermatogenesis occurred within 10 weeks of cessation of therapy in all but the one azoospermic man who recovered after 14 weeks.

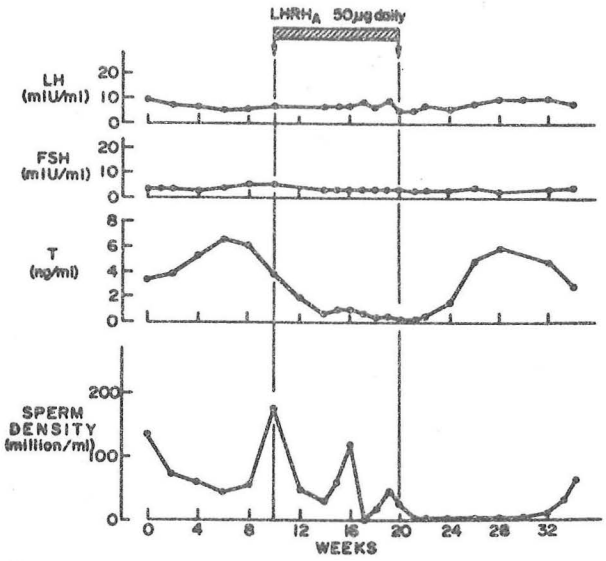

Figure 7. Levels of Luteinizing Hormone (LH), Follicle-Stimulating Hormone (FSH), and Testosterone (T) and Sperm Density in Subject 7 during the Basal Period, Treatment Period (LHRH$_A$), and Recovery Period.

The diminished libido and impotence are a significant drawback to the use of LHRH agonists alone as male contraceptive agents. Thus, just as with

progestational agents, the logical next step would appear to be trials of a combination of LHRH agonists and testosterone enanthate to replace the decreased endogenous testosterone. Rabin et al. have reported such an initial attempt combining daily 50 μg injections of agonist with bimonthly injections of 100 mg of testosterone enanthate (45). The degree of oligospermia observed in 6 subjects was similar to that reported following agonist alone, and azoospermia was not achieved in any subject (45). Dr. Ronald Swerdloff believes that the reason for this lack of success is that the dose of agonist chosen was too low and that it was combined with a dose of testosterone enanthate which, by itself, did not suppress spermatogenesis. Trials are now in progress of a higher dose of agonist combined with a dose of testosterone enanthate previously demonstrated (26) effective in suppressing spermatogenesis (R. Swerdloff, personal communication).

Although we must await the results of these studies, published observations of such combination therapy in animal models suggest that synergism exists in suppressing gonadotropins in castrate rats (46) and inhibiting spermatogenesis in intact animals (47). The intratesticular total sperm counts of groups of rats either given vehicle alone, testosterone, LHRH agonist, or the combination of testosterone and agonist at 40 and 60 days are shown in Table IV.

Table IV. Effect of testosterone and LHRH agonist on spermatogenesis in rats (ref. 47).

Group	Intratesticular sperm counts (mil/testis) day 40	day 60
Control	145 ± 7	169 ± 13
Testosterone	156 ± 15	122 ± 16
LHRH Agonist	62 ± 10	44 ± 10
Agonist plus Testosterone	34 ± 7	9 ± 1.6

Although these results appear impressive, studies of testosterone and LHRH analogues in the rat are complicated. First a "subsuppressive" dose of testosterone must be used since testosterone has a biphasic dose effect in the rat with an initial dose-related suppression followed by a stimulation of spermatogenesis and return of sperm counts toward control levels as the dose is increased (18). Such a phenomenon has not been observed in man. Also, since the addition of testosterone in this study in rats (47) seemed to primarily be effective by lowering the elevated gonadotropin levels induced by agonist, a major effect of LHRH agonist in the rat may be at the level of the testis. Based on the studies of agonist alone in man (44), the primary effect seems to be at the pituitary level. Thus one cannot immediately assume that synergism of LHRH agonist and testosterone in suppression of spermatogenesis will exist in man.

Studies of rat pituitary LHRH receptors may provide insight into potential mechanisms of synergism of LHRH agonists and testosterone at the pituitary level in intact animals (48). Pituitary LHRH receptor binding was increased by agonist treatment alone at 20 days and returned to control levels at 40 and 60 days of treatment in parallel to the observed changes in serum LH. Testosterone administration alone decreased pituitary LHRH receptor binding. Combined LHRH agonist and testosterone administration prevented the initial increase in pituitary LHRH receptor binding observed with agonist alone (48).

Studies of the effect of the LHRH agonist $(DNal_2)^6$-LHRH on gonadotropins in normal men from Dr. Swerdloff's group are now in press. Two doses of agonist, 10 μg and 100 μg, were given to two groups of seven men for 10 days. Administration of the agonist resulted in a dose-related inhibition (higher doses more effective) of the integrated LH, FSH, and testosterone responses to agonist on day 10 vs. day 1 (49). These studies demonstrated that stimulation of gonadotropins and testosterone by LHRH agonist in man is transient following daily agonist treatment and is completed by 10 days, when inhibitory effects are manifest. The gonadal response to hCG (measured as increase in plasma testosterone) was tested in the control period and the day after the last LHRH agonist injection. While basal levels of testosterone were lower following the treatment with agonist, plasma testosterone increased after hCG in a parallel fashion to that of the pretreatment test (49).

The effect of the addition of 200 mg of testosterone enanthate given intramuscularly on day 1 to the 100 μg daily injections of LHRH agonist was evaluated in 4 men. Daily mean basal levels of LH and FSH were always lower in the LHRH agonist plus testosterone enanthate group when compared to agonist alone (50). FSH was more effectively suppressed than LH by combined administration with all FSH values undetectable on the 10th and 11th day after beginning treatment. The integrated plasma LH and FSH concentration (calculated as mIU-h/ml) for the 24h period after the first and last LHRH agonist injection are shown in Figure 8 (50). Combined treatment of testosterone enanthate with 100 μg of agonist leads to enhanced inhibition of LH as well as FSH secretion on day 10. The effect of combined treatment on plasma FSH levels is understated since most values were undetectable and were given an arbitrary value at the lower limits of assay detectability.

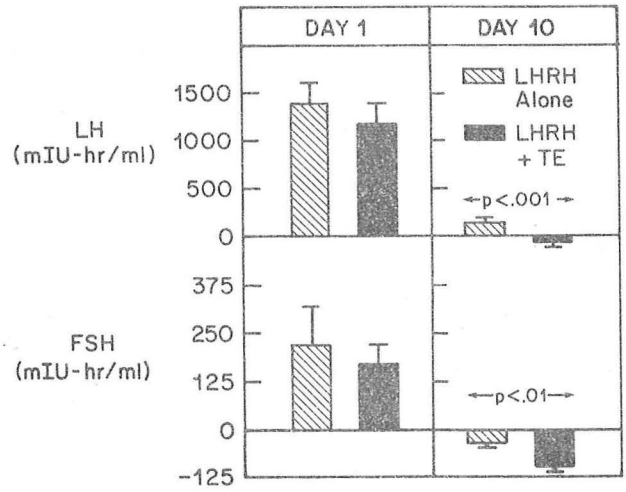

Fig. 8

These last two studies thus offer promise of a synergism of LHRH agonist and testosterone in fertility control in men. They also suggest that the primary site action of the agonist is at the pituitary level in man in contrast to the at least dual effect at the pituitary and testis level in the rat. However, the proof of the effectiveness in man is not yet available. Dr. Swerdloff feels that there is even greater hope for a successful combination of testosterone with one of the new group of LHRH antagonists (51) since the length of time an effect is seen after administration is more prolonged than with the agonists (personal communication).

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47. Heber D, Swerdloff RS: Gonadotropin-releasing hormone analog and testosterone synergistically inhibit spermatogenesis. Endocrinology 108:2019-2021, 1981.

48. Heber D, Dodson R, Stoskopf C, Petersen M, Swerdloff RS: Pituitary desensitization and the regulation of pituitary gonadotropin-releasing hormone (GnRH) receptor following chronic administration of a superactive GnRH analog and testosterone. Life Sci. 30:2301-2308, 1982.

49. Heber D, Bhasen S, Steiner B, Swerdloff RS: Stimulatory and inhibitory effects of $(DNal_2)^6$GnRH in reproductive hormonal function in man. J. Clin. Endocrinol. Metab. (in press).

50. Bhasin S, Heber D, Steiner B, Swerdloff RS: Enhanced inhibition of gonadotropin secretion in man by combined GnRH agonist and testosterone. J. Clin. Endocrinol. Metab. (in press).

51. Rivier C, Rivier J, Vale W: Antireproductive effects of a potent gonadotropin-releasing hormone antagonist in the male rat. Science 210:93-95, 1980.

D. Inhibin

Since the peptide hormone inhibin is thought to be the primary mediator of feedback inhibition of spermatogenesis on FSH secretion, it would appear to be a suitable site of intervention in the hypothalamic-pituitary-testicular axis for fertility control in men (52). One might postulate that administration of inhibin or an analogue of it might selectively suppress FSH and thereby block spermatogenesis. However, inhibin has not been purified to homogeneity, and administration of even large amounts of the purest preparations available only suppress FSH levels about 70 to 80% (19,52). In addition, even if FSH levels could be completely suppressed, it is likely that spermatogenesis once initiated could be maintained by testicular testosterone secretion (18). Thus, a combination of inhibin plus testosterone replacement would probably be necessary. No such studies have been reported.

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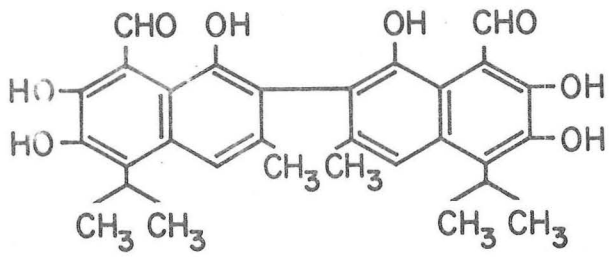
In summary in regard to attempts at fertility control by drugs that inhibit hypothalamic-pituitary function: Long-acting testosterone enanthate must be injected once a week to result in azoospermia in a significant fraction of men. Side effects are minimal. The addition of progestational agents to testosterone enanthate do not seem to offer a clearcut improvement as studied to date and may increase the frequency of side effects. The LHRH agonists appear to be ineffective alone. Even if they can eventually be given intranasally, it appears that the simultaneous administration of parenteral testosterone will be necessary. The theoretical synergism of such a combination over testosterone alone has not been shown. Inhibin therapy is purely theoretical at present and would no doubt require combination with androgen. Since the likelihood of men adhering to a regimen that requires weekly intramuscular injections seems remote, fertility control in men with agents aimed at pituitary inhibition does not seem promising. Perhaps the subcutaneous implantation of silastic capsules filled with testosterone could overcome this injection problem, but the calculated size of the capsule to provide the required testosterone release also seems prohibitive.

III. DRUGS AND OTHER AGENTS THAT AFFECT THE TESTIS DIRECTLY

Sperm production can be inhibited through a direct effect on the testis. A number of antineoplastic drugs and other relatively toxic compounds have been shown to impair sperm production. Most of these compounds have associated unacceptable toxicity in other tissues. This section will concentrate on the relatively new oral agent gossypol, review some recent studies with other drugs, and describe physical and immunological methods to inhibit spermatogenesis.

A. Gossypol

In the late 1950's Chinese investigators noted that where crude cottonseed oil was used in cooking there were usually more cases of infertility. In the late 1960's animal experiments in China showed that the effective antifertility agent in crude cottonseed oil was gossypol. Gossypol is a yellow substance which occurs in various parts of the cotton plant. Its chemical structure is a naphthol phenol (Fig. 9).



GOSSYPOL

Fig. 9

Clinical trials of gossypol as an antifertility agent in men have been going on in China for almost 10 years and have included by now almost 10,000 volunteers (53,54). The effect of gossypol on the testis in general appears to be limited to the spermatogenic tubules with little effect seen in the Leydig cells. In the clinical studies men were initially given an oral dose of 20 mg daily for 60 days ("loading period"). This causes the sperm in the ejaculate to become immotile, decreased in number, and often totally absent. The Chinese investigators used a criterion of a sperm density of less than 4 mil/ml as being indicative of "infertility" and claim this was achieved in 99.9% of men. Since gossypol affects sperm motility, the need for azoospermia may not be the same as for drugs that inhibit pituitary function. Neither of the clinical reports describe actual assessment of fertility in men receiving gossypol (53,54). Once "infertility" was achieved (usually 60 days) the dose of gossypol was decreased to one third the original dose for maintenance of the antifertility effect. Most volunteers did not complain of any symptoms. Some noted temporary fatigue, decreased libido and altered appetite. Recovery of normal sperm density after stopping gossypol occurred within three months in over 90% of men who took the drug for a year, but in less than 70% of men who took the drug for 2 or 3 years (54).

During chronic therapy the only major side effect of gossypol, hypokalemia, was encountered in some provinces of China. In some groups of volunteers receiving gossypol chronically the incidence of symptomatic hypokalemia was as high as 4.7% while in other groups it was not detected (55). Initial fatigue and muscle cramps was followed by frank hypokalemic paralysis in a few subjects. Limited studies of affected men suggest decreased total body potassium with renal

potassium wasting (55). Dietary histories of men in regions with frequent occurrence of the side effect of gossypol reportedly disclosed a diminished dietary potassium intake presumably predisposing them to hypokalemia. Studies of salivary sodium to potassium ratios were felt to be inconsistent with aldosterone excess as a mechanism for the renal potassium loss (55). These authors cite a paper in the Chinese literature indicating that gossypol may have a direct affect on the Na-K ATPase. They also report that symptomatic hypokalemia was prevented by the simultaneous administration of supplemental potassium.

Another disturbing aspect of the clinical reports is that 6 to 11% of men complained of decreased libido. Although the initial report (53) states that potency was not impaired and recovery usually followed reassurance, the second report notes that plasma testosterone levels in 18 men with loss of libido dropped from 710 ng/dl to 442 ng/dl on therapy while it was unchanged in another group of 10 men who did not experience a decrease in libido (54). Individual data and sampling techniques are not given to know whether this change within the normal range is significant.

Studies of animals treated with gossypol suggest that the drug not only affects spermatogenesis but sperm maturation in that motility is strikingly impaired (53, 56-58). While the antifertility affect of the drug is similar in rats, hamsters and monkeys, the rabbit is apparently quite resistant to any impairment of sperm production or fertility (56). The only detailed study of the effects of gossypol on a subhuman primate, the cynomolgus monkey, provide detailed ultrastructural analysis of the ejaculated sperm (58). The major finding accounting for impaired motility is a disruption of the axial complex. At lower gossypol doses there was primarily a disruption of radial arms while at higher doses the entire axial complex was destroyed associated with grossly distorted midpiece region and mitochondrial breakdown. This study of seven monkeys did not detect any change in serum potassium and found not only normal basal testosterone levels but normal response to LHRH injection.

The observation that gossypol inhibits sperm motility has led to studies of the possible mechanism of action by incubations with sperm in vitro (59-61). Gossypol in the μM range inhibits sperm mitochondrial metabolism blocking fructose utilization, significantly decreases sperm calcium and magnesium activated ATPases, and appears to be a selective inhibitor of the sperm-specific lactate dehydrogenase-X. Since the ability of gossypol to inhibit sperm motility persists in the presence of cervical mucus (59), the possibility of its use as a vaginal contraceptive was suggested. Even crude cottonseed oil emulsions were shown to be effective in inhibiting sperm motility (62).

53. National Coordinating Group on Male Antifertility Agents: Gossypol --A new antifertility agent for males. Chinese Med. J. 4:417-428, 1978.

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56. Chang MC, Gu Z, Saksena SK: Effects of gossypol on the fertility of male rats, hamsters and rabbits. Contraception 21:461-469, 1980.

57. Bozek SA, Jensen DR, Tone JN: Scanning electron microscopic study of spermatozoa from gossypol-treated rats. Cell Tissue Res. 219:659-663, 1981.

58. Shandilya L, Clarkson TB, Adams MR, Lewis JC: Effects of gossypol on reproductive and endocrine functions of male cynomolgus monkeys (macaca fascicularis). Biol. Reprod. 27:241-252, 1982.

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61. Lee C-Y, Malling HV: Selective inhibition of sperm-specific lactate dehydrogenase-X by an anti-fertility agent, gossypol. Fed. Proc. 40:718, 1981.

62. Tso W-W, Lee C-S: Cottonseed oil as a vaginal contraceptive. Arch. Androl. 8:11-14, 1982.

B. Other Drugs

Other classes of drugs than antineoplastic agents or gossypol that have antispermatogenic activity in animals are the nitrofurans, thiophenes, diinitropyrroles and bis-(dichloroacetyl)-diamines (63). Of these only the last was not so toxic in other tissues to reach clinical trials in human subjects. Although apparently effective in decreasing sperm density, studies were abandoned when an antabuse-like effect was discovered on ingestion of alcohol. Thioglucose (64) and cyclohexanol (65) are two additional agents investigated recently in animals which appear unlikely candidates for studies in man because of the variable reversibility of the effect on spermatogenesis and the toxicity in other organs, respectively.

Indazolecarboxylic acids and more specifically lonidamine (AF 1890) (Fig. 10) appear to be the only new drugs with some potential for fertility control in men with a site of action at the testis (66). These chemicals have a selective action on the testicular germinal epithelium of rats, rabbits and rhesus monkeys with no apparent side effects at effective dosage levels. In addition spermatogenesis returns to normal when the drug is discontinued. Interestingly, the site of action of lonidamine appears to be the Sertoli cells with the first detectable effect being a decrease in androgen binding protein (ABP) production with a secondary rise in plasma FSH as spermatogenesis is interrupted (66).

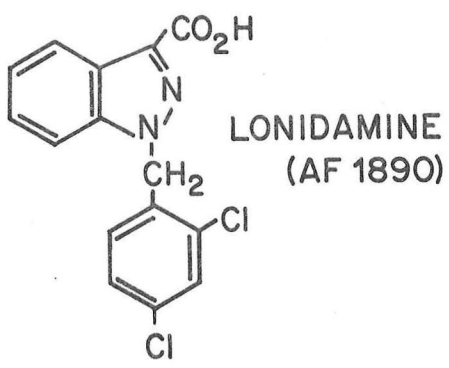

Fig. 10

63. Jackson H: Antispermatogenic agents. Br. Med. Bull. 26:79-86, 1970.

64. Davies AG, Meanock SJ: Potential of 5-thio-D-Glucose as an agent for controlling male fertility. Arch. Androl. 7:153-158, 1981.

65. Dixit VP, Gupta RS, Kumar S, Joshi BC: Reversible chemical sterilization: effects of cyclohexanol administration on the testes and epididymides of male rabbit. Indian J. Physiol. Pharmacol. 24:278-286, 1980.

66. Lobl TJ, Bardin CW, Gunsalus GL, Musto NA: Effects of lonidamine (AF 1890) and its analogues on follicle-stimulating hormone, luteinizing hormone, testosterone and rat androgen binding protein concentrations in the rat and rhesus monkey. Chemotherapy 27 (Suppl. 2):61-76, 1981.

C. Physical Methods

The suppressive effect of heat on spermatogenesis is well recognized in the temporary decreases in sperm density following an acute febrile illness or hot bath. The 2°C higher temperature of intraabdominal testes compared to intrascrotal testes is thought to account for the infertility of cryptorchidism. The thermal effect and associated changes in fertility and testicular histology 2 weeks after applications of hot water, infrared heat, microwaves, and ultrasound to rat testes are shown in Table V (67).

Table V. Effect of heat and ultrasound on rat testes (67).

Treatment	Scrotal Temperature	Duration	Impregnation of Female	Histology of Testes (14 Days)
60°C, H_2O	60°C	5 min.	3-35 days	reduction of spermatozoa
Infrared	60°C	15 min.	60-70 days	20-25% of tubules with absent spermatogenesis
Microwave[a]				
100% power	64°C	5 min.	12 months, no impregnation	absence of spermatogenesis
20% power	40°C	5 min.	65-80 days	reduction of spermatids
Ultrasound[b]				
1 w/cm^2 treated once	38°C	5 min.	150-210 days	reduction in secondary spermatocytes
1 w/cm^2 treated twice (48h apart)	38°C	5 min.	12 months, no impregnation	absence of spermatogenesis

[a] maximum output 100 W, [b] continuous output of 10^6 cycles/s

These observations indicated that electronic means of heat induction are more effective than the other methods. In addition the comparison of microwave and ultrasound suggested that ultrasound was more effective at a lower temperature, probably because of the combined effect of heat and mechanical effects of increasing membrane permeability (67).

The same group of investigators then chose ultrasound as physical means of inhibiting spermatogenesis and studied its effects in additional species (68). Cats, dogs, and monkeys all had significant suppression of spermatogenesis without any effect on Leydig cells histologically and without any lowering of plasma testosterone levels. Finally human volunteers scheduled to undergo orchiectomy for cancer of the prostate were exposed to ultrasound by immersion of testes in the cuphorn of a sonicator. Four men who had prior testis biopsies received a 10 min. treatment at 1 w/cm^2. Pain was not experienced, and scrotal temperature did not rise above 40°C. Changes in semen parameters two weeks later just before orchiectomy indicated sperm densities less than 1 mil/ml to 7 mil/ml with impaired motility and 60 to 90% dead or abnormal forms. Histology of resected testis showed absence of spermatozoa and spermatids. The authors claim that animal studies indicate that the impairment of spermatogenesis is completely reversible and that testing of progeny and chromosomal studies of spermatogonia did not disclose adverse effects (69).

67. Fahim MS, Fahim Z, Der R, Hall DG, Harman J: Heat in male contraception (hot water 60°C, infrared, microwave, and ultrasound). Contraception 11:549-562, 1975.

68. Fahim MS, Fahim Z, Harman J, Thompson I, Montie J, Hall DG: Ultrasound as a new method of male contraception. Fertil. Steril. 28:823-831, 1977.

69. Fahim MS: Male fertility regulation by means of ultrasound. In Regulation of Male Fertility. GR Cunningham, W-B Schill, ESE Hafez (eds), The Hague, Martinus Nijhoff, 1980, pp. 219-230.

D. Immunological Methods

Immunological approaches to fertility control in men can either involve induction of antibodies to hormones or induction of immunological reactions to some components of the testis, sex accessory organs or spermatozoa (70). The ideal target hormone would appear to be FSH since induction of spermatogenesis requires FSH. However, the variable ability of spermatogenesis, once established, to proceed in the absence of FSH as long as local testosterone production is normal makes interpretation of animal studies difficult (70). Thus, while neutralization of FSH with antiserum in the immature rat prevents the development of spermatogenesis, it has no effect in the adult. In contrast inhibition of FSH in three species of monkeys impairs spermatogenesis in mature animals. Most studies have used passive immunization with anti-FSH antibodies. This would not be practical long term. Active immunization with FSH has been tried in two species of monkeys with the development of azoospermia in some animals, a finding not present in passively immunized animals. Because FSH is a glycoprotein hormone sharing a common α-subunit with TSH and LH, long term active immunization would probably require the use of FSH-β subunit. The most extensive studies of this method of fertility control have been carried out in bonnet monkeys (71,72). Following passive immunization reversible infertility was achieved without a reduction in plasma LH or testosterone levels. The effect of neutralization of FSH in man is

not known. However, spermatogenesis, once established in hypogonadotropic men with FSH and LH can be maintained by injection of hCG alone (4).

Immunological approaches involving induction of an immunological reaction to some component of the testis may either involve the development of aspermatogenesis with an auto-immune orchitis or elicitation of a specific antibody response to a purified sperm antigen. Testicular homogenates injected with Freund's adjuvant result in experimental allergic orchitis in at least eight mammalian species. In the guinea pig model at least four different antigens have been identified in the testicular homogenate. Unfortunately this method requires the use of Freund's complete adjuvant and repeated subcutaneous injection. Recently Talwar has described a different approach to achieve aspermatogenesis using intratesticular injection BCG alone (74). Oligospermia was achieved within six weeks in dogs and monkeys treated with optimal doses of BCG in this manner, and testosterone levels both basally and in response to hCG remained normal (74). Reversibility of the effect in a variable period of time was noted in some animals (73). The effect appears to be local, i.e. no antisperm antibodies were detected in the serum.

The LDH-X isozyme is limited to the testis and spermatozoa and thus would seem to be a candidate for development of immune response for fertility control in men. Immunization with this antigen does not result in aspermatogenesis and orchitis, but instead sperm motility is impaired in rabbits in correlation with the antibody titer (75). Impaired fertility was demonstrated in rabbits and mice and shown to be reversible. The antibody to LDH-X is present in the seminal fluid and has a sperm immobilizing effect either by mechanical impairment or metabolic inhibition. There appears to be homology of LDH-X in various species providing a source of antigen. Since the generated antibody affects the mature spermatozoa, immunization of females with this antigen may also result in infertility (73).

70. Madhwa Raj HG, Sairam MR, Nieschlag E: Immunologic approach to regulation of fertility in the male. In Regulation of Male Fertility. GR Cunningham, W-B Schill and ESE Hafez (eds), The Hague, Martinus Nijhoff, 1980, pp 209-218.

71. Sheela Rani CS, Murty GSRC, Moudgal NR: Effect of chronic neutralization of endogenous FSH on testicular function in the adult male bonnet monkey - assessment using biochemical parameters. Int. J. Androl. 1:489-500, 1978.

72. Murty GSRC, Sheela Rani CS, Moudgal NR, Prasad MRN: Effect of passive immunization with specific antiserum to FSH on the spermatogenic process and fertility of adult male bonnet monkeys. J. Reprod. Fert. 26:147-163, 1979.

73. Talwar GP, Naz RK: Immunological control of male fertility. Arch. Androl. 7:177-185, 1981.

74. Talwar GP, Naz RK, Das C, Das RP: A practicable immunological approach to block spermatogenesis without loss of androgens. Proc. Natl. Acad. Sci. USA 76:5882-5885, 1979.

75. Goldberg E, Wheat TE: Induction of infertility in male rabbits by immunization with LDH-X. In Regulatory Mechanisms of Male Reproductive Physiology. CH Spilman et al. (eds), Amsterdam, Excerpta Medica, 1976, pp 133-139.

In summary in regard to attempts at fertility control by drugs and other agents that affect the testis directly: Gossypol, although used extensively in China, seems a long way from being a marketable oral contraceptive for men in this country. The significant risk of hypokalemia coupled with the uncertain reversibility suggest that either a different dosing regimen or an analogue with less toxicity will need to be developed. The indazolecarboxylic acids appear to be the only other chemicals with any promise based on animal studies, but only animal studies have been conducted so far. Ultrasound may be effective and "safe" but it is associated with an uncertain duration of effect. Most active immunization immunologic methods, in addition to the unacceptable repeated injection with Freund's adjuvant, have an indeterminate duration of effect as well. With passive immunization, the possibilities of acute allergic reactions and immune complex disease remain.

IV. DRUGS THAT AFFECT THE EPIDIDYMIS

Selective inhibition of the function of the epididymis with impairment of sperm maturation would appear to be an ideal method of fertility control in men. Theoretically the time to achieve an effect on fertility would be only one to two weeks instead of the two to three months necessary for agents affecting the pituitary or testis.

A. Antiandrogens

Since normal androgen action is necessary for epididymal function, antiandrogens were long considered as possible means to impair sperm maturation in the epididymis (76,77). Some of the studies of the antiandrogen-progestational agent, cyproterone acetate, have been mentioned in regard to pituitary inhibition. Unfortunately studies of cyproterone, the free alcohol of cyproterone acetate and a pure antiandrogen, and the nonsteroidal antiandrogen flutamide have found no success in inhibition of epididymal function. These antiandrogens inhibit the negative feedback of endogenous androgens resulting in increased LH and testosterone concentrations and the overcoming of any inhibitory effect of the antiandrogen in the epididymis (76, 77).

76. Setty BS: Regulation of epididymal function and sperm maturation -- endocrine approach to fertility control in male. Endokrinologie 74:100-117, 1979.

77. Neumann F, Schenck B: Antiandrogens: basic concepts and clinical trials. In Regulation of Male Fertility. GR Cunningham, W-B Schill, ESE Hafez (eds), The Hague, Martinus Nijhoff, 1980, pp 93-104.

B. α-Chlorohydrin

α-Chlorohydrin is a simple monochloro derivative of glycerol (3-chloro-1,2-propanediol). The commercially available compound is a racemic mixture of S(+) and R(-) forms. The S(+)-α-chloro-hydrin form is active in inducing infertility and has less toxicity than the mixture (78). The R(-) isomer is ineffective in fertility control. These observations suggest that the antifertility effect is probably caused by a specific metabolic lesion and not by the random attack of an alkylating agent. The compound induces temporary infertility in rats, guinea pigs and monkeys. At the minimally effective dose of 5-7 mg/kg (orally or subcutaneously) in rats fertility was lost in less than a week of daily doses and was regained within a week posttreatment. Sterility was induced without loss of libido and without alterations

in the ejaculatory process or the gross morphology of ejaculated spermatozoa. At higher doses epididymal blockade and spermatoceles were found. The biochemical studies indicate that α-chlorohydrin may inhibit oxidative phosphorylation, glycolysis, and glycerol metabolism. The site of inhibition of glycolysis appears to be at glyceraldehyde-3-phosphate dehydrogenase reaction (79). The compound apparently induces transient changes resembling those of castration in the anterior pituitary, i.e. increased gonadotropins. However, testosterone levels were unchanged. The toxicity of α-chlorohydrin appears to be the limiting factor in extending studies to man. Trials of the compound in monkeys were associated with bone marrow depression at a dose of 30 mg/kg. α-Chlorohydrin has also been associated with hepatotoxicity in some species and nephrotoxicity at high doses in the rat (80). A better understanding of the specific mechanism of action of the drug in inducing infertility might lead to the development of other less toxic compounds.

78. Lobl TJ: α-Chlorohydrin: review of a model posttesticular antifertility agent. In Regulation of Male Fertility. GR Cunningham, W-B Schill, ESE Hafez (eds), The Hague, Martinus Nijhoff, 1980, pp 109-122.

79. Ford WCL, Harrison A: Effect of α-chlorohydrin on gluclose metabolism by spermatozoa from the cauda epididymidis of the rhesus monkey (Macaca mulatta). J. Reprod. Fert. 60:59-64, 1980.

80. Morris ID, Williams LM: Some preliminary observations of the nephrotoxicity of the male antifertility drug (±)α-chlorohydrin. J. Pharm. Pharmacol. 32:35-38, 1980.

C. Chlorinated Sugars

The realization in the studies of α-chlorohydrin that the glycolytic pathway in spermatozoa was a potential target for selective attack led to the investigation of 6-chloro-6-deoxysugars (81). Like α-chlorohydrin these compounds produce infertility in male rats after oral administration for five days, and the effect is reversible. The acute toxicity of 6-chloro-6-deoxyglucose is low in rats and mice, so these compounds seemed attractive for further development. Attempts at demonstrating a direct effect of 6-chloro-6-deoxyglucose on spermatozoa have been unsuccessful. Thus it is probable that this compound and other 6-chloro-6-deoxysugars are metabolized to an active product in the body. Rats made infertile with 6-chloro-6-deoxyglucose (24 mg/kg/d) continue to produce normal numbers of spermatozoa and to mate with females as frequently as controls. Spermatozoa from these animals are unable to oxidize glucose at an appreciable rate, and they quickly become immotile after removal from the epididymis and incubation with glucose as an energy source. As with α-chlorohydrin there appears to be a block at the glyceraldehyde-3-phosphate dehydrogenase reaction. Unfortunately neurotoxicity of 6-chloro-6-deoxyglucose has been detected in the marmoset and mouse given high doses (82).

81. Ford WCL: The contraceptive effect of 6-chloro-6-deoxysugars in the male. In Regulation of Male Fertility. GR Cunningham, W-B Schill, ESE Hafez (eds), The Hague, Martinus Nijhoff, 1980, pp 123-126.

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In summary in regard to drugs that affect the epididymis: Antiandrogens are ineffective. α-Chlorohydrin and chlorinated sugars are effective in animals but have significant toxicity.

V. MECHANICAL INTERRUPTION OF SPERM TRANSPORT IN THE VAS DEFERENS

Occlusion or obstruction of the vas deferens might be considered to be quite different than partial vasectomy since the former implies a greater likelihood of reversibility. However, the studies of vas obstruction are relatively few and will only be considered as one of the different methods of accomplishing the same end.

A. History of Vasectomy and Current Use of this Method of Contraception

Vasectomy in the late nineteenth and early twentieth centuries was a much abused surgical procedure. Two early reports in the J.A.M.A. stress the desirability of the operation for sterilization of habitual criminals (83,84). One of these authors in addition suggests that "the same treatment could reasonably be suggested for chronic inebriates, imbeciles, perverts and paupers" (83). From 1910 to 1920 Steinach, on the basis of experiments in rats, proposed that vasectomy could produce sexual rejuvenation in elderly men (reviewed in 85). He maintained that degeneration of germinal epithelium was associated with hypertrophy of Leydig cells. Despite conflicting experimental evidence thousands of operations were performed. And we are all aware of the sterilization for supposed race improvement by Nazi Germany. What is hard to believe is that by 1933, 23 states had laws permitting involuntary vasectomy for institutionalized persons for a variety of purposes from hereditary disease to "feeble-mindedness" (86). Just as scientific awareness brought an end to rejuvenation operations, political, social, and moral consciousness restricted eugenic sterilization.

Voluntary sterilization became increasingly popular in the late 1950's and 1960's. Data from the 1970 US National Fertility Study indicated that about 25% of couples practicing contraception with the wife 30 to 44 years of age had been sterilized (87). There was about an even split between vasectomy and tubal ligation in these couples. The 1975 National Fertility Study found that sterilization is now the method of choice for contraception among couples married a decade or more as well as among couples who have all the children they want (88). Again, about half of the couples chose vasectomy. Expressed another way 47% of couples married 10 or more years have had surgical sterilization of one partner (88). The annual rate of vasectomy in the United States has apparently stabilized in recent years at about 1 million per year (89). A study of almost a thousand men undergoing vasectomy in Montreal noted the change in the profile of vasectomy subjects over the past decade (Table VI) (90). Average age, length of marriage, and number of living children prior to vasectomy were greater in 1968 - 1971 group than in the 1974 - 1978 group.

Table VI. Characteristics of two groups of vasectomy patients in Montreal (90).

Group	Age <35 yrs.	No. of children 1 or 2	Married ≤ 10 yrs.
1968 - 1971	26%	31%	23%
1974 - 1978	55%	58%	61%
p	<0.01	<0.01	<0.01

Voluntary sterilization is now the most widely used contraceptive method in the world, with about 80 million couples estimated to be using it in 1977. The change from 1970 and the number of couples using other methods is shown in Table VII (91).

Table VII. Estimated number of couples using birth control, worldwide, by method in 1970 and 1977 (91).

	1970 (millions)	1977 (millions)
Voluntary sterilization	20	80
Oral contraceptives	30	55
Condom	25	35
IUD	12	15
Other methods*	60	65
Total	147	250

*Diaphragm, spermicides, rhythm, withdrawal.

Although in a number of countries sterilization of men is less popular than sterilization of woman, India is an example of a country in which vasectomy as a method of fertility control has been extensively adopted. By 1973 it was estimated that more than 8 million men in India had undergone vasectomy. And in 1976 alone of the more than 8 million new adopters of sterilization in India, over 75% of them or more than 6 million were men receiving vasectomies (91). This represented about 10 times the number of vasectomies being performed in the United States during the same period. However the percentage of the married women of reproductive age protected from pregnancy by sterilization during this period was still somewhat less in India (20.6%) than that in the U.S. (29.0%) (91).

China is another large country for which information on population and birth control was recently summarized (92). Sterilization is second (after the IUD) as the most widely used contraceptive method in China, relied on by 30% of all contraceptive users. According to Chinese data, a total of 20.3 million tubal ligations and 13.8 million vasectomies were performed between 1971 and 1978 (92).

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84. Sharp HC: Vasectomy as a means of preventing procreation in defectives. JAMA 53:1897-1902, 1909.

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86. Hackett RE, Waterhouse K: Vasectomy -- reviewed. Am. J. Obstet. Gynecol. 116:438-455, 1973.

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91. Population Reports, Series M, No. 2. Voluntary sterilization: world's leading contraceptive method. Washington, D.C., George Washington University Medical Center, Population Information Program, March 1978, pp. 37-70.

92. Population Reports, Series J, No. 25. Population and birth planning in the People's Republic of China. Washington, D.C., George Washington University Medical Center, Population Information Program, Jan-Feb 1982, pp. 577-618.

B. Methods, Success Rate, and Acute Complications

In the adult man the vas deferens is about 35 cm in length and extends from the tail of the epididymis to the prostate, where with the duct of the seminal vesicle it forms the ejaculatory duct (Fig. 11). Histologically, the vas is composed of adventitial, muscular, and mucosal layers which surround a lumen of approximately 0.05 cm (86). The adventitial layer is rich in blood vessels and small nerve branches. The muscular layer consists of a middle circular layer between inner and outer longitudinal layers. The mucosa in the scrotal portion of the vas is pseudostratified and contains a basal layer of cuboidal cells and a luminal layer of columnar cells. Microvilli extend from the columnar cells into the lumen. A variable portion of the testicular end of the vas is lined by ciliated columnar epithelium.

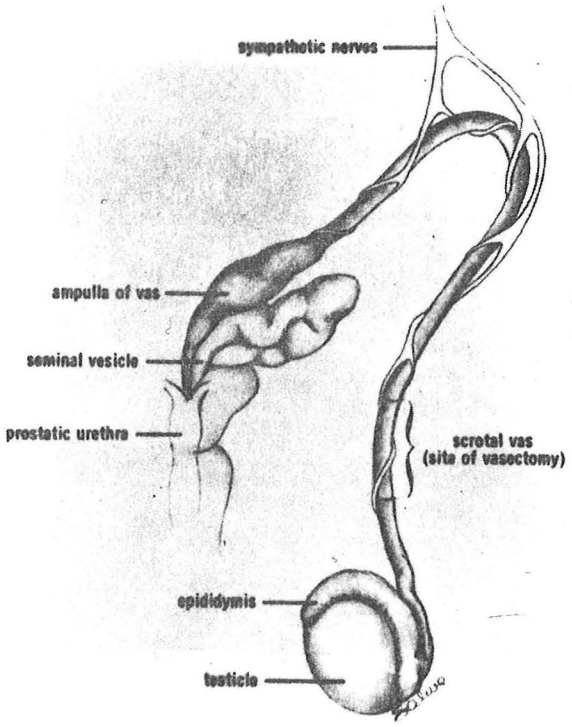

Fig. 11

The abdominal (distal) part of the human vas contains more adrenergic nerve fibers and has a higher norepinephrine content than the testicular (proximal) portion. In vitro contractions of human vasa stimulated by norepinephrine are blocked by phentolamine. Although some cholinergic nerves have been described in the vas, it appears that the primary neural control of the vas is the sympathetic nervous system acting through alpha-adrenergic receptors (reviewed in 89). The importance of the sympathetic nerve supply of the vas for normal sperm transport has been inferred from the study of infertility following retroperitoneal lymph node dissection in patients with testicular cancer. Lack of emission due to interruptions of nerve supply to the vas rather than retrograde ejaculation has been implicated as the presumed cause of the infertility by the absence of sperm and fructose in post-masturbation bladder washings.

Bilateral partial vasectomy is a relatively uncomplicated operative procedure that produces sterility by interrupting the vas deferens, thereby preventing sperm from being ejaculated with other components of the semen. The procedure is usually performed with local anesthesia. The different incision sites and some of the techniques for vasectomy are shown in Fig. 12 (89). The dorsal lithotomy position allows the weight of the testes to elongate and stretch the vasa, facilitating entrapment of each vas between the thumb and forefinger of the surgeon to allow infiltration of local anesthetic both in the skin and around the isolated vas. The skin above the vas is incised, the vas separated from its surrounding sheath, and a minimum of 1 cm excised. Whatever technique is used for permanent closure of the remaining vasal stumps (Fig. 12), the possibility of spontaneous recanalization, though rare, is always present (see below). The skin edges are usually only loosely approximated, and an ice pack is recommended for 12 hours with scrotal support for 72 hours.

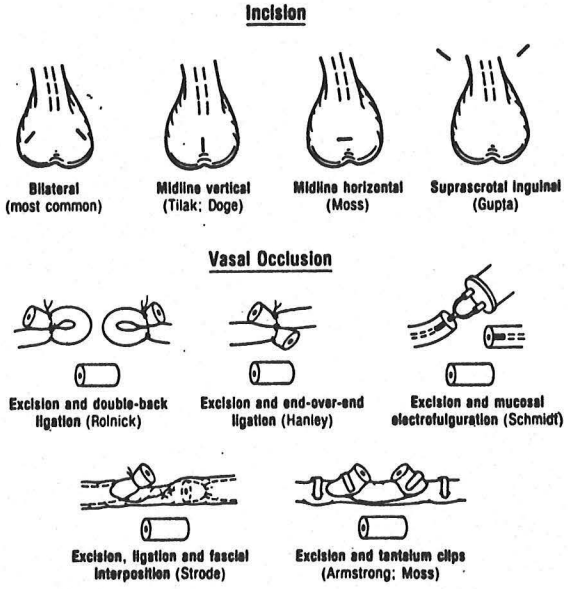

Fig. 12

The Chinese have reported a more rapid (less than 10 minutes) "nonsurgical" method of male sterilization by spermatic duct injection (93). More than 50,000 men reportedly received this treatment since 1972 in which 0.02 ml of a phenol mixture mixture is injected into the vas to block the duct for 1.5 cm. The method is claimed to be 91% successful and to be less complicated than vasectomy with less risk of hematoma and infection.

The early studies of intravasal devices aimed at producing a "reversible" vasectomy are reviewed in ref. 89. Recent animal studies include injectable non-occlusive chemical contraception using a polymer in the rat (94), insertion of 1.5 cm of non-occlusive copper wire in the rat (95), and long term observations (2-3 years) on a flexible prosthetic valve device for reversible obstruction in the dog (96). All of these methods have been found to be relatively effective by their individual supporters. It is not clear that any of the techniques will receive widespread use and adaptation to man.

The most common causes of vasectomy failure are division or ligation of some cord structure other than the vas (thus the need for pathological examination of the resected tissue) and spontaneous postsurgical recanalization. In two different series of more than 2000 patients each the failure rate due to recanalization varied from 0.3% (97) to 1.2% (98). The greater the length of the vas resected, the less likely was recanalization (98).

Generally the vasectomy is considered to be successful when there is failure to demonstrate sperm in a direct wet mount of the semen from two consecutive specimens. The median time for azoospermia following vasectomy is 24 ejaculations. Thus most patients are evaluated at three months. One clinician has suggested that time of postvasectomy testing can be performed sooner since most residual sperm are immotile within two weeks. He recommends initial exam at one month with search only for motile sperm (99). These cannot be ignored since conception six weeks following a technically successful vasectomy has been reported due to residual sperm (100). Even reported examination of ejaculate with azoospermia at three months will not prevent the return of fertility due to recanalization which occurs at a median time of six months (97).

The postoperative acute complications of vasectomy range from minor swelling to significant hematoma and inflammation to recanalization. The frequency of complications in three large series are shown in Table VIII (97, 101-102). In Leader's series of 2,711 vasectomies the rate of major complications dropped from 3.3% to 2.7% by using hemoclips instead of ligatures (97). Vasitis, funiculitis, and epididymitis appear not to be infection-mediated, but rather are secondary to extravasation of sperm into the interstitum (101).

Table VIII. Postoperative complications of vasectomy in three large series

Complication	Series* Total	A (2711)	B (1000)	C (843)
Epididymitis		1.0%	1.8%	1.8%
Abscess formation		0.7		1.5
Vasitis and funiculitis		0.4	3.2	
Hematoma		0.5	0.3	0.5
Hydrocele		0.1		0.4
Sperm granuloma		< 0.1	1.2	
Vas cutaneous adhesion		0.7		
Vas cutaneous fistula		0.5		
Cellulitis and other		1.2		1.1
Recanalization		0.3	0.8	0.2
		5.4	7.3	5.5

* A (ref. 97), B (101), C (102).

Thus the complication rate is about 6%. Interestingly, the third series above (C) was performed by a family practice clinic (102).

Sperm granuloma, once thought to occur rarely, is now considered to be the most common serious postoperative complication of vasectomy (89). It is apparently less common with a double back ligature technique and electrofulguration than with simple vasal excision and ligation (101). Immediately following the surgical procedure there is induration and swelling of the stumps. This probably results from the compromise in the blood supply to the stumps by the ligature. In most cases a normal scar forms and the ends of the vas are sealed off. If the circulation of the stump is too severely compromised, necrosis of the ligated stump may follow resulting in a leak and formation of a sperm granuloma. Sperm granulomas are painful and may cause a vasectomy to fail by initiating a spontaneous reanastomosis. Islands of mucosal cells can be found in the inflammatory tissue after a leak which may eventually proliferate to irregular narrow canals finally connecting the two ends.

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C. Effects on Testis Histology and Hormonal Status

The changes that occur in the testis following occlusion of the vas have been most extensively studied in animals. Our own Dr. Neaves has published an extensive review of the biological effects of vasectomy (103). The changes in the

testes vary from species to species and depend on the site and type of operative vasal occlusion. In general there is agreement that occlusion of the vas deferens is compatible with continued spermatogenesis in the primate testis (103). The sperm may be resorbed or stored in distended ducts and cysts. In a prospective study in man testicular volume did not change after vasectomy (104). The transient degeneration of the germinal epithelium detected in the immediate postoperative period were not demonstrable 2 to 3 1/2 years following vasectomy. Studies in man demonstrate that in contrast to the transient changes in the testes there may be persistent changes in the epididymis with rupture and fibrosis (105). This author suggests that faulty sperm transport and maturation in the epididymis may be a cause of failure of fertility following vasovasostomy. However, recent studies in an animal model report an intact blood epididymal barrier in vasectomized hamsters (106).

Vasectomy was initially claimed as being beneficial in the treatment of benign prostatic hyperplasia (BPH). This was subsequently disproven. However, one might wonder whether men undergoing vasectomy in their 30's and 40's might have a decreased incidence of BPH twenty to thirty years later. If one postulates that vas deferens luminal transport is a more important source of androgen to the prostate than that derived from the blood, then perhaps dihydrotestosterone content of the prostate in vasectomized men would be slightly less for a sufficiently long period of time to decrease the incidence of BPH. I could not find evidence for such observations in the literature. It is interesting in this regard that in a study of 78 men 24-45 years old vasectomized 1-8 years previously almost all components of the seminal plasma of prostatic origin were significantly decreased compared to an appropriate control group (107).

There appears to be no controversy regarding the long term endocrine effects of vasectomy. Five representative studies could not demonstrate an adverse effect of vasectomy on Leydig cell function of the testis as assessed by plasma testosterone and LH levels (108-112). Nor was a change in plasma FSH detected. These studies include prospective trials (109, 110, and 112) and followup for as long as five years (109, 112). In addition, Leydig cell reserve as assessed by response to hCG was found to be normal in six men in one study four years after vasectomy (112).

103. Neaves WB: Biological aspects of vasectomy. In Handbook of Physiology, Section 7. RO Greep, EB Astwood (eds). American Physiological Society, Washington, D.C., Vol. V, Male Reproductive System, 1975, Ch. 18, pp. 383-404.

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D. Antibodies and Atherosclerosis

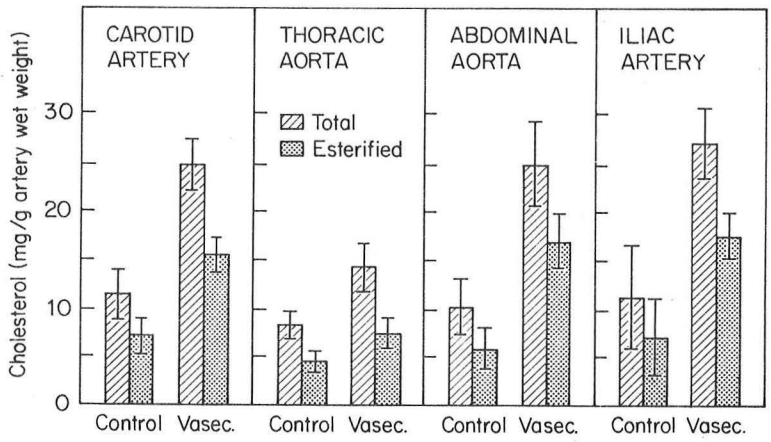
Sperm-agglutinating antibodies in the sera of vasectomized men were first reported in 1959 (113). Later, an increased level of complement-dependent sperm-immobilizing antibodies were also reported following vasectomy (114). Sperm antibodies increase beginning 7 to 11 days after the operative procedure (115). Approximately 2% of prevasectomy patients have sperm agglutinating titers while no immobilizing antibody could be detected in the fertile, prevasectomy population (115). Although reports vary, in general about 40% of men one year post-vasectomy have significant agglutinating antibody titers compared to 20% with sperm immobilizing antibodies (89, 115, 116). Comparing the sperm-agglutinating and sperm-immobilizing antibodies, Alexander and her colleagues demonstrated that the sperm immobilization test was a sensitive assay of complement fixation and was specific for complement fixing antibodies to sperm (117). All sera with agglutinating titers >1:80 had associated sperm-immobilizing antibodies, and sperm-immobilizing titers were not present in sera lacking agglutinating antibodies (117). However, it does not appear that these two antibody tests measure identical antigens since there is a greater increase in sperm-immobilizing titers after suture ligation for vasectomy than there is with the fulguration technique, while sperm agglutinating titers are not significantly different with the two procedures (116). In this last report both types of antibodies were shown to be present in men as long as 11 years after vasectomy. Quinlivan and coworkers demonstrated that the IgG fraction of postvasectomy sera could produce both the sperm agglutinating and sperm-immobilizing reactions (118).

An association of the development of antisperm antibodies (specifically head agglutinating antibodies) and the HLA antigen A28 has been claimed (119). Further suggestion of the possibility of genetic influences on the sperm antibody response comes from a study of guinea pigs (120). Studies of different strains of guinea pigs indicated a certain strain was a high responder in antibody production while another was a nonresponder. Matings of the two strains with back crosses of the F_1 suggest that the autoimmune antibody response to sperm surface antigens in vasectomized guinea pigs is controlled by a single dominant autosomal or X-linked gene (120).

The findings of autoimmunity to sperm antigens raised the question as to whether there might be an increased generalized autoimmune reaction

postvasectomy. Two studies involving more than a thousand men who had prior vasectomy could not demonstrate any increased incidence of antibodies directed to antigens other than sperm compared to controls (121, 122). And no autoimmune disease was detected in the vasectomized men (122).

The autoantibodies detected in men following vasectomy remained primarily a curiosity until 1978 when Alexander and Clarkson reported that vasectomy increased the severity of diet-induced atherosclerosis in cynomolgus monkeys (123). It had been recognized that diet-induced atherosclerosis in rabbits could be enhanced by experimentally inducing serum sickness (an immune complex disease) (124). In the studies of cynomolgus monkeys two groups of five animals each were fed a diet containing sufficient cholesterol to raise the plasma concentration to the 500 to 600 mg/dl range for 6 months prior to vasectomy or sham vasectomy. The animals then continued the diet for an additional 10 months before necropsy. Both pathological assessment of the extent of atherosclerosis as well as chemical measurement of the cholesterol content of the vessels (Fig. 13) was greater in the vasectomized compared to the control group (123). The pathological changes were most pronounced in the abdominal aorta, carotid arteries, and intracranial cerebral arteries. Antibodies to sperm developed in all vasectomized monkeys, and complement and immunoglobulins were associated with the atherosclerotic plaques in some of the vasectomized animals.



(Alexander and Clarkson, 1978)

Fig. 13

The same investigators next reported on the effects of long-term vasectomy on the occurrence and extent of atherosclerosis in rhesus monkeys fed monkey chow (devoid of cholesterol and low in fat) (125). The monkeys had been vasectomized 9-14 years previously and were compared with an age-matched control group at necropsy. Although both sets of animals had atherosclerosis, the lesions were more extensive in the vasectomized group. Histologically, the lesions of vasectomized monkeys did not appear different from those of control animals. The distribution of the lesions in the vasectomized animals was different from that in the controls and that of lesions induced by atherogenic diets, i.e. the lesions were distributed randomly within the artery rather than around bifurcations. The extent of atherosclerosis in the 10 vasectomized animals was greater in the 6 animals with persistently negative tests for free antisperm antibodies (Table IX). Almost all vasectomized rhesus monkeys develop antisperm antibodies shortly after vasectomy, but by 4-6 months only about half of the animals retain demonstrable free antisperm antibodies. The authors suggest that the animals without detectable free antisperm antibodies are in sperm antigen excess and thus likely to form immune complexes.

Table IX. Relationship of the presence or absence of free antisperm antibody to the extent of atherosclerosis in vasectomized rhesus monkeys (125).

Free Antibody States	No. of Monkeys	Mean percentage of intimal surface with plaques		
		thoracic aorta	abdominal aorta	iliac arteries
Positive	4	2.5	0.5	5.0
Negative	6	14.2	40.0	17.5

The possibility that these results might be somehow unique to monkeys is suggested by the finding that immune complex-associated orchitis develops in nonvasectomized as well as vasectomized rhesus monkeys (126).

The concern about possible immune complex-associated atherosclerosis in vasectomized animals led to a search for immune complexes in vasectomized men. A recent paper reviews the prior report of largely unsuccessful attempts to demonstrate circulating immune complexes in vasectomized men and presents a prospective study using more sensitive enzyme linked immunosorbent assays (ELISA) (127). Sera from 35 men were collected before and at timed intervals subsequent to vasectomy. Fewer than 10% of the men examined were ever positive for antisperm antibodies. However, sperm-related antigens were elevated in the sera of 26% of the men at 4 months post-vasectomy. The increases in patient circulating immune complex levels after vasectomy are shown in Fig. 14 (127). Using the Raji cell assay 19 to 25% of the patients had higher circulating immune complex concentrations at the various intervals postvasectomy compared to their prevasectomy level. Similar results were obtained with the bull sperm assay while fewer patients had increased circulating immune complex levels postvasectomy by the Anti C1q assay than by the other assays. All subject differences were statistically significant at $p<0.01$. The components of the immune complexes from nine patients were assayed, and six contained antigen reactive with antisperm IgG and four contained complement components C3 and/or C1q. Thus circulating immune complexes are present in increased quantity in the sera of men following vasectomy.

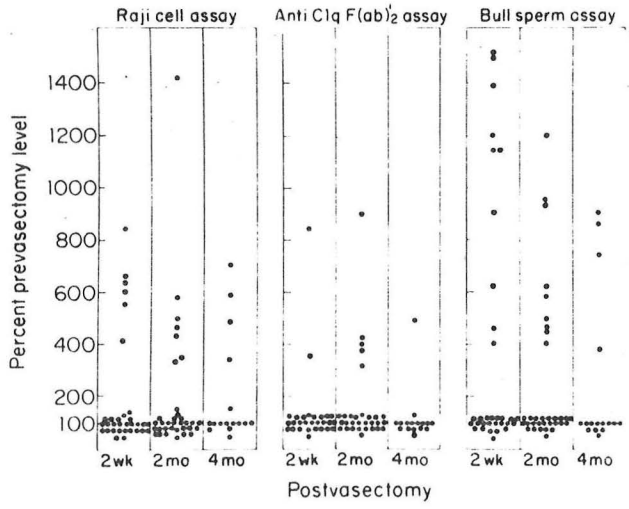


FIGURE 14 Circulating immune complexes in the sera of vasectomized men. Pre- and postvasectomy sera were assayed for CIC by the Raji cell ELISA, anti-Clq $F(ab')_2$ ELISA and bull sperm ELISA. The values for each individual are plotted as described in Fig. 1.

The significance of the immune complexes in vasectomized men has yet to be demonstrated. In the mean time five reports of studies have appeared examining vasectomized men compared to appropriate controls for the incidence of nonfatal myocardial infarction (128), coronary artery disease (129), hospitalization rates for a variety of conditions (130), a variety of physiologic measures (131), and symptoms of illness and/or history of diseases (132). In all cases no increased prevalence of atherosclerotic cardiovascular disease or its symptoms could be found in the vasectomized group. Several of the studies involved four to six thousand vasectomized men (128, 130-132). In at least two of the studies (128, 130) a sizable number of men had undergone the vasectomy greater than 10 years previously. Epidemiological studies are always somehow suspect since the lack of randomization and prospective followup leaves open the possibility that some unknown confounding factor has not been considered and is responsible for the negative findings. Negative studies might result from studying the wrong population, studying too few subjects, failing to control for the right variables, or failing to ask the right questions. In spite of these drawbacks, the lack of an association of vasectomy with atherosclerosis is reassuring.

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E. Psychosexual Effects

A number of studies have indicated that almost all men who have undergone vasectomy are satisfied with the procedure and would, in retrospect, undergo the operation again (133-135). Increased sexual enjoyment and frequency of intercourse are also often reported, probably related to decreased anxiety about an unwanted pregnancy. In general, vasectomy has no deleterious effect on potency or sexual performance. In addition, almost all couples report that marital harmony in general either improves or remains unchanged following vasectomy.

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F. Vasectomy Reversal

Vasectomy should only be recommended to patients who desire a permanent means of sterilization. However, the large number of vasectomies performed each year results in some patients desiring vasectomy reversal by vasovasostomy. Reasons for desiring this reversal procedure include remarriage after divorce or

death of wife, death of one or more children, and improved economic situation. The merits of the two surgical techniques (singlelayer closure and double-layer microscopic closure) are controversial, and neither has clearly proven to be superior (reviewed in 136). In either case the usual success rate for return of sperm in the ejaculate is about 80 to 90%. However, the associated pregnancy rate is only 30 to 40%. Three relatively recent series from the literature have not improved on these numbers (137-139). Although a number of technical considerations are associated with anatomical success, most investigators feel that the functional success is related to the presence of antisperm antibodies (Table X) (140-143). The men who were able to father a child after vasovasostomy were less likely to have antisperm antibodies than those who were unable to do so. One study did not find such a relationship (144). In any case the relationship was not absolute, and in one report the data were only given for men with high titers (>1:256) compared with those with lower titers (143). Presumably the antisperm antibodies interfere with sperm function similar to the experimental anti-LDH antibodies induced in animals described above. Isolated IgG and Fab antibodies from vasectomized guinea pigs inhibit fertilization in vitro (145).

Table X. Percent of vasovasostomy subjects with positive antisperm antibody in relationship to achieving pregnancy.

Series*	A	B	C	D
No. of couples	45	51	20	51
Pregnancy	48	18	8	15
No Pregnancy	94	69	75	71

* (ref 140), B (141), C (142), D (143).

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In summary in regard to fertility control in men by vasectomy: Vasectomy is a relatively simple procedure that is over 99% effective in resulting in permanent infertility. The postoperative complications are minor. No adverse effects on the testis or hormonal status have been detected. Although vasectomized monkeys may develop immune-complex associated acceleration of atherosclerosis, no evidence is available to date to support a similar phenomenon in man. Functional vasectomy reversal with fertility may be possible in 30 to 40% of vasectomized men.