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Environment, Human Reproduction, Menopause, and Andropause

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As the hypothalamic gonadotropin-releasing hormone (GnRH) pulse generator is an integrator of hormonal, metabolic, and neural signals, it is not surprising that the function of the hypothalamogonadal axis is subject to the influence of a large array of environmental factors. Before puberty, the central nervous system (CNS) restrains the GnRH pulse generator. Undernutrition, low socioeconomic status, stress, and emotional deprivation, all delay puberty. During reproductive life, among peripheral factors that effect the reproductive system, stress plays an important role. Stress, via the release of corticotropin-releasing factor (CRF), eventually triggered by interleukin 1, inhibits GnRH release, resulting in hypogonadism. Effects of CRF are probably mediated by the opioid system. Food restriction and underweight (anorexia nervosa), obesity, smoking, and alcohol all have negative effects on the GnRH pulse generator and gonadal function. Age and diet are important determinants of fertility in both men and women. The age-associated decrease in fertility in women has as a major determinant chromosomal abnormalities of the oocyte, with uterine factors playing a subsidiary role. Age at menopause, determined by ovarian oocyte depletion, is influenced by occupation, age at menarche, parity, age at last pregnancy, altitude, smoking, and use of oral contraceptives. Smoking, however, appears to be the major determinant. Premature menopause is most frequently attributable to mosaicism for Turner Syndrome, mumps ovaritis, and, above all, total hysterectomy, which has a prevalence of about 12–15% in women 50 years old. Premature ovarian failure with presence of immature follicles is most frequently caused by autoimmune diseases or is the consequence of irradiation or chemotherapy with alkylating cytostatics. Plasma estrogens have a physiological role in the prevention of osteoporosis. Obese women have osteoporosis less frequently than women who are not overweight. Early menopause, suppression of adrenal function (corticoids), and thyroid hormone treatment all increase the frequency of osteoporosis.

Aging in men is accompanied by decreased Leydig cell and Sertoli cell function, which has a predominantly primary testicular origin, although changes also occur at the hypothalamopituitary level. Plasma testosterone levels, sperm production, and sperm quality decrease, but fertility, although declining, is preserved until senescence. Stress and disease states accelerate the decline on Leydig cell function. Many occupational noxious agents have a negative effect on fertility. There is evidence for a decline of sperm quality in the general male population over the last two decades, probably a consequence of increasing pollution, irradiation, and population stress. If the evidence is confirmed, it might be mandatory to reduce drastically pollution, irradiation, and other noxious agents that may impair spermatogenesis.

Introduction

The human organism acquires its full reproductive capacity after completion of puberty, the fertile period covering about 35 years in women, whereas in men reproductive capacity, although decreasing with age, persists until a very old age.

Puberty

Puberty represents the final stage of sexual differentiation during which time the individual acquires full reproductive capacity, with not only maturation of sexual organs and formation of the oocytes and mature spermatozoa, but also development of secondary sex characteristics under the influence of sex hormones. Puberty is initiated by an increase in both frequency and amplitude of gonadotropin pulses, which activate gonadal growth and function. The increase in gonadotropin pulses is initially associated with the onset of nocturnal, non-REM (rapid eye movement) sleep (*1,2*). This pulsatile gonadotropin release by the gonadotrophs reflects the pulsatile release of gonadotropin-releasing hormone (GnRH) into the hypophyseal portal circulation by a group of specific neuroendocrine cells in the medio-basal hypothalamus called the pulse generator. The trigger of this activation of the GnRH pulse generator, and hence the initiation of puberty remains unknown. It has been suggested that the initiation of puberty might involve a decreased sensitivity of the hypothalamic pulse generator to the inhibitory effects of opiate peptides (*3*). The activation of the pulse generator is independent of the

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gonads as it occurs at the same age in agonadal individuals as in normal adolescents.

Restraint of the onset of puberty resides in the central nervous system (*1*). In industrialized countries, the age of puberty has decreased steadily over the last century in association with the improved socioeconomic status, and this suggests that nutritional status has an influence on the maturation of the pulse generator. Before the central nervous system (CNS) activates puberty, a certain level of neural maturity must be reached, and it is known that bone age is a better reflection of maturity than chronological age. A critical body mass is also required before the CNS starts to activate puberty (*4*). Underweight boys and girls and adolescents with a poor nutritional status have a delayed puberty. Chronic stress also causes maintenance of the prepubertal hypogonadotropic status, thereby delaying puberty, and such stress may be mental, as in the emotional deprivation syndrome, or organic, as in chronic disease.

Adult Reproductive Function

The reproductive function in adults is dependent on the intermittent discharge of gonadotropins under the influence of pulsatile GnRH secretion by the GnRH pulse generator, which functions as an integrator of neural, hormonal, and metabolic signals and governs gonadal function by the secretion of gonadotropins. The hypothalamo-pituitary-gonadal system is therefore extremely sensitive not only to hormonal and metabolic influences, but also to all factors affecting the central nervous system. Androgens have an inhibitory effect at the hypothalamic level and estrogens have their inhibitory effect at the pituitary level, both resulting in reduced gonadotropin secretion. Anabolic steroids, as used by some athletes and body builders, and estrogens in food ingested in large quantities also have similar inhibitory effects.

The endogenous opioid system plays a pivotal role in the modulation of the GnRH pulse generator. Opioids have a restraining effect, decreasing both leutinizing hormone (LH) pulse frequency and amplitude (*5,6*). Exogenous opioids such as morphine, methadone, and heroin have a similar inhibitory effect causing decreased LH pulse frequency and testosterone levels. Drug addicts frequently have low plasma levels of sex hormones, leading to hypogonadism, amenorrhea, and infertility.

The role of the adrenergic system in the regulation of the GnRH pulse generator in man has not been completely elucidated. It appears to stimulate the pulse generator in nonhuman primates (*7*), but no convincing effects have been detected in humans.

Among the peripheral factors affecting the reproductive system, stress plays an important role, whether mental or physical. Mild stress (chair restraint) in nonhuman primates arrests the GnRH pulse generator (*8*), an effect mediated by the corticotropin-releasing factor (CRF) (*9,10*). CRF infusion in humans causes an inhibition of pulsatile LH release (*11*). Fever is a common stressful situation and is accompanied by an increased release of CRF, which stimulates adrenal corticotropin hormone (ACTH) secretion, resulting in increased plasma cortisol levels, which inhibits pulsatile LH release. Fever-induced CRF release appears to be triggered by cytokines, especially interleukin 1, which is an important mediator of activated macrophage function. Macrophages also release vasopressin, which contributes to ACTH discharge but may also play a role in the inhibition of LH secretion. It is not surprising, therefore, that acute stress causes a rapid decline in plasma testosterone levels. Any acute infectious disease induces a decrease in LH and testosterone levels and is followed by a transient oligospermia.

Whereas the acute effects of stress on the pituitary-gonadal axis appear to be mediated by CRF itself, in chronic stress cortisol appears also to play a role in decreasing plasma LH and testosterone levels. The inhibitory effects of CRF on the GnRH pulse generator appear to be mediated by the opioid system because they are neutralized by the anti-opioid Naloxone. Emotional stress, including endogenous depression, in women may be the cause of psychologic hypothalamic amenorrhea, which appears to be secondary to impaired pulsatile GnRH release. In this condition there are low basal LH levels and decreased LH pulsatility, but a normal response to GnRH, which indicates functional integrity of the adenohypophysis and therefore a hypothalamic origin of the hypogonadotropism. There is evidence that increased hypothalamic β-endorphin plays an important role in the stress-induced inhibition of gonadotropin secretion (*12*). The emotional stress of extended school examinations may also induce a decrease in testosterone levels on boys and amenorrhea in girls (*13*).

Physical stress such as competitive sports causes a reduction in the LH pulse frequency, leading to low testosterone levels in men and amenorrhea in women (*14*). Cumming et al. (*15*) observed that running for exercise caused a reduction in LH pulse frequency without any change in pulse amplitude. Elias et al. (*16*) detected a decline in LH levels following exercise on the treadmill, reaching a nadir at 90 min, and this was associated with an increase in CRF levels, which was proposed to be the mediator of the LH changes. There does not appear to be any difference in LH level and LH pulsatility, either under basal conditions or after Naltrexone administration, after a 10–15 mile run in men trained for endurance running in comparison to sedentary controls (*17*).

The effects of physical trauma are exemplified by the decline in testosterone levels during surgery (*18*), which is proportional both in degree and in duration to the severity of the surgical procedure. Following major surgery, depressed testosterone output persists for 3 weeks. The influence of chronic physical stress, such as industrial noise or altered daily rhythms caused by night work or shiftwork, on reproduction should be considered, but there are no control data available.

Acute or chronic food restriction has an inhibitory effect on pulsatile GnRH release. Chronic undernutrition may arrest pubertal development, and it is associated with gonadal atrophy and infertility in adult men (*19*) and with irregular menstrual cycles or amenorrhea in women (*20*). Cameron et al. (*21*) showed that 1 day of fasting in rhesus

monkeys caused minimal weight loss but significant decrease in LH and testosterone pulse frequency. In men, a 48-hr fast caused a significant decrease in mean plasma LH and testosterone pulse frequency but an unchanged pulse amplitude (*22*). Komaki et al. (*23*) reported a slight increase in plasma β-endorphin levels during acute fasting but this was not maintained during prolonged fasting.

A complex interplay of fasting, malnutrition, and neuropsychiatric factors are responsible for the amenorrhea of patient with anorexia nervosa. Gonadotropin levels are low and LH pulse frequency is decreased. The responses to GnRH revert to those seen in prepubertal children. However, the normal, adult-type responses are restored by chronic treatment with pulsatile GnRH or weight gain (*24,25*).

Exogenous obesity appears to have more subtle effects on reproductive function. Male obesity is associated with a decrease in plasma levels of both total and free testosterone, the decrease in free testosterone being less important because of a concomitant decrease in sex-hormone-binding globulin (SHBG) capacity. Changes in SHBG capacity are probably caused by a direct effect of hyperinsulinism on hepatic SHBG synthesis. The mechanism for the decrease in testosterone levels is not apparent. The LH pulse frequency is normal in obese men; however, there is a reduced frequency of large amplitude pulses, and the amount of LH secreted at each pulse is less than in nonobese men.

Female obesity is frequently associated with menstrual irregularity and amenorrhea. Testosterone levels, especially free testosterone, are increased, and the binding capacity of SHBG is reduced, probably as a consequence of increased insulin and IGF-1 levels. A short-term low caloric diet of 400 kcal/day for 4 weeks will usually normalize the androgen levels with resumption of ovarian cyclical activity, although, notwithstanding weight loss, the obesity itself persists.

The effects of type of diet on the reproductive system have been examined. We could not detect any difference is plasma total or free testosterone levels between men on a normal Western diet and men consuming a macrobiotic vegetarian diet (*26*). Key and co-workers (*27*) observed that in comparison to omnivores, vegetarians had substantially higher SHBG levels, but total and free testosterone levels and estradiol (E_2) levels were similar. Belanger et al. (*28*) found higher SHBG levels in vegetarians, although testosterone levels were normal. Adlercreutz et al. (*29*) reported that women eating a Western diet had high sex hormone and low SHBG levels, resulting in a high bioavailability of the hormones compared to vegetarian women. Similar results were observed by Armstrong et al. (*30*) in postmenopausal women. There appears to be a positive correlation between dietary fiber intake and SHBG levels so that a high fiber intake would result in low levels of bioactive sex hormone (*29,31,32*), although Key et al. (*27*) could not confirm this finding (*27*). Surprisingly Meikle et al. (*33*) reported that a fatty meal reduced the levels of total and free testosterone, whereas Bennett and Ingram (*34*), on the contrary, observed an inverse correlation between fat intake and SHBG levels in postmenopausal women.

Caucasian men have higher testosterone and E_2 levels than Japanese men, but it is not certain if the differences in sex hormone levels are due to differences in diet (*35*). Similarly, Chinese men and women have much lower androstanediol glucuronide levels than their Caucasian counterparts (*36*), whereas postmenopausal American women have significantly higher estrogen levels than Japanese women (*37*). It is not clear whether dietary or genetic factors are responsible for these differences. The racial variability in sex hormone levels may be important for explaining the differences in prevalence of different types of carcinoma, or may be the reason for the different effects produced by hormonal male contraception.

Male smokers have higher levels of total and free testosterone than nonsmokers (*26*). Some reports (*38,39*) indicate that smoking does not have a significant effect on spermatogenesis or sperm quality. However, Spira et al. (*40*), studying the sperm characteristics of 409 men being investigated for infertility and 311 men requesting vasectomy, observed that sperm density, motility, and morphology were lower among fertile smokers than fertile nonsmokers, and the semen of infertile smokers contained lower numbers of spermatozoa with normal morphology. The alterations of sperm characteristics were unrelated to the quantity of tobacco smoked or inhaled.

Smoking has been reported to be accompanied by slightly increased E_2 and progesterone levels during the follicular phase of premenopausal women and in postmenopausal women, and this was attributed to stimulation of the adrenal cortex (*41*). Estradiol metabolism in smokers is shifted toward the inactive 2-hydroxylated catechol metabolites instead of toward 16-hydroxylated metabolites (*42*). The newborn babies of women who smoke heavily have a significantly lower weight than those of nonsmokers.

Acute alcohol intoxication following 1.5 g alcohol/kg body weight decreases plasma testosterone levels in men by about 25% between 10–16 hr after the start of drinking, although SHBG levels are unchanged, and LH pulsatility and biological activity are unaffected. This suggests a direct effect on the testis (*43,44*), but the absence of enhanced LH secretion in response to low testosterone suggests an inappropriate pituitary response in addition (*45*).

Chronic alcoholics have reduced plasma testosterone levels but usually still within the normal range (*46,48*), and the reduction is directly correlated with the severity and duration of the alcoholism and the eventual hepatic injury (*47*). Testicular atrophy often accompanies alcoholic liver cirrhosis (*49*). A multicenter World Health Organization study of infertile couples that examined sperm characteristics found that men with excessive alcohol consumption had a higher prevalence of azoospermia (9.6% versus 7.2%) and seminal abnormalities (52% versus 36%), but the differences were not significant (*50*). Similar results were found by Spira et al. (*40*).

Infections may have a direct effect on fertility, including mumps, which causes orchitis and oophoritis in a large proportion of cases when occurring after puberty, and this may produce infertility as a consequence. The

human immunodeficiency virus (HIV) may also cause infertility.

Age and Fertility

Age appears to affect fecundity in both men and women. It has recently been shown that women whose husbands had azoospermia and who had received artificial insemination with donor semen (AID) had a significant decline in fecundity after the age of 35 years (*51–53*). The rate of spontaneous abortion also increases with maternal age (*53*), probably due to an increased frequency of chromosomal abnormalities (*54,55*). The percentage of fetuses with chromosomal anomalies is double in women over 40 in comparison to women under 20. Prolonged follicular phase or delayed fertilization in relation to reduced coital frequency in older couples may play a role in the reduction of fecundity (*56,57*). It therefore appears that the decline in fertility with age may be due mainly to a diminishing number of oocytes that are capable of forming normal embryos (*58*).

Uterine factors may also have an effect on the declining fertility with age. However, the age-associated increase in trisomy is detected earlier than the age-associated effects on uterine function, and it can therefore be concluded that the effects of aging on the quality of the ova appear at a younger age than the effects of age on uterine function. Decreasing fertility with age is also associated with an increased frequency of endometriosis, fibroids, or tubal pathology as a result of pelvic infections.

Male fertility has an almost linear decline after the age of 40, according to Anderson et al. (*59*). However, Mineau and Trussel (*60*) claim a decline in fertility from the age of 25. The increasing prevalence of epididymitis, ductal obstruction, and chronic prostatitis may contribute to the decline in male fertility with age.

Factors Altering the Age of Menopause

Menopause signifies the irreversible end of reproductive life in women and is a consequence of the progressive depletion of ovarian follicles. The primary origin of the menopause in the ovary in women is in clear distinction to the situation in some laboratory animals such as the rat in which the cessation of estrous cycles has a hypothalamic origin. Transplantation of ovaries from old rats into young rats may result in a resurrection of cyclical activity.

The premenopausal period has a variable duration of 1–10 years and is characterized by a progressive lengthening of the menstrual cycle in contrast to the tendency of progressive shortening with age prior to this period. The progressive depletion of follicles makes the ovary relatively resistant to gonadotropins, which is reflected in the relatively high follicle-stimulating hormone (FSH) levels in the presence of relatively low E_2 levels. There is frequent anovulator,v dysfunctional uterine bleeding. Estradiol levels only occasionally and at irregular intervals reach the threshold capable of inducing an ovulatory LH peak, and this is followed by a luteal phase, which is often short or inadequate. At birth, about 3,000,000 oocytes are present, but this falls to just over 300,000 at puberty and very few are present at the menopause.

Menopause in Western countries generally occurs between the ages of 46 and 58 (mean: 51.5 years), and there is a small secular trend toward an older age at menopause. Environmental factors that may affect the age at menopause have been examined in a few studies. Van Keep et al. (*61*) suggest that *a*) housewives and agricultural workers have their menopause approximately 1 year later than manual workers or other occupational categories. *b*) Single women have an earlier menopause than married women. *c*) Smoking advances the age of menopause by a mean of 1.5 years, confirming previous data (*62–64*). *d*) Parity and age at last pregnancy is positively correlated with a later menopause. *e*) Weight adjusted for height (body mass index) does not influence the age at menopause, although other authors have reported a later menopause in obese women (*65*) or menstrual irregularities occurring 4–5 years earlier in the premenstrual period in obese women. *f*) Undernutrition may induce an early menopause. Data from sub-Saharan Africa or the Punjab suggest a mean age at menopause in the early 40s, but other authors (*67*) cast doubt on the effect of nutritional status on the rate at which the ovary is depleted of oocytes. However, nutritional status may determine when the last menstrual period occurs (nutritional amenorrhea and premature ovarian failure). *g*) Early menarche appears to be associated with late menopause and vice versa. *h*) Altitude-associated hypoxia may cause early menopause as indicated by data from the altiplano of Peru, where the age of menopause is advanced by just over 3 years (*68*).

Recently, the role of some of these factors as codeterminants of age at menopause was challenged by Brambilla and McKinlay (*66*) who concluded from multivariate analyses that married status, parity, weight, education, income, and use of oral contraception did not influence the age at menopause, and the only relevant factor was smoking, which was associated with a significantly earlier menopause. It should be stressed that the influence of all of the above factors is limited, and each one produces at the most a difference of 1–2 years in mean age at menopause.

Subjects with mosaic forms of Turner's syndrome or women with short-arm deletion of one X-chromosome may be fertile, but usually have a premature menopause. Mumps oophoritis may also cause premature menopause (*69*). However, the most frequent cause of premature menopause is total hysterectomy and oophorectomy. In Western Europe, 10–15% of women aged 50 have undergone a hysterectomy (*70*), whereas in Pittsburgh, Pennsylvania, 24% whites and 47% of blacks aged 40–50 have had this operation (*71*). Unfortunately, no data are available on the frequency of concomitant oophorectomy.

Premature menopause implies depletion of ovarian follicles as a consequence of accelerated atresia or decreased germ cell number and is therefore irreversible. On the other hand, premature ovarian failure in its strictest sense is characterized by a resistant ovary with the continued presence of immature follicles in association with elevated peripheral gonadotropin levels. This may be an idiopathic disorder of unknown etiology or may be associated with

autoimmune disorders, among which the most frequent are thyroiditis and autoimmune Addison's disease. Circulating antibodies to ovarian tissue are frequently detected, and antibodies to FSH receptors may also be found occasionally. Autoimmune premature ovarian failure may also be part of a polyglandular failure including hypoparathyroidism, hypoadrenocorticalism, and mucocutaneous conditions.

Irradiation and chemotherapy, especially with alkylating agents, frequently cause premature ovarian failure. Autoimmune, postirradiation, and postchemotherapy ovarian failure all may be reversible, thus proving that the ovary was not completely depleted of follicles. These conditions, therefore, must be differentiated from true menopause.

The age at menopause may be related to longevity. In an epidemiological study, 5287 white Adventists aged 55–100 years who had reached menopause naturally were investigated (*72*), and the age-adjusted death rate over a 6-year period calculated. The ratio of the death rate for women who reached a natural menopause before the age of 40 compared to the death rate for women reporting a natural menopause at age 50–54 years was 1.95 (95% confidence limits 1.24–3.07).

The Postmenopausal Era

The postmenopausal years are characterized by extremely low levels of estrogens. In the first 3 years after the menopause the ovary still contributes to the estrogen levels which are, however, lower than in the early follicular phase before the menopause. In later menopause, more than 4 years after cessation of menses, the estrogens are synthesized almost exclusively in peripheral tissue, especially fat and muscle, from androgens secreted by the adrenals (*73*). A rare exception is thecal hyperplasia in which the ovary produces an excess of estrogen. Adrenal androgen secretion decreases progressively with age, the levels of dehydroepiandrosterone at the age of 75 years being only one-fifth the levels at 20 years.

The estrogens produced by peripheral conversion of androgens, although present at a low level, do have a physiological role in that they reduce pathological postmenopausal osteoporosis.

Cigarette smokers have significantly higher levels of androstenedione than nonsmokers (*42*), also during early menopause (*75*). Smoking causes a shift of estrogen metabolism toward inactive metabolites and a consequent reduction in estrogen levels which increases the risk of osteoporosis and pathological fractures (*76*). Estrone and estradiol levels tend to decline with increasing alcohol consumption.

Physically active women have lower estrogen levels than physically inactive women, but surprisingly there is a positive correlation between muscle strength and estrogen level (*74*). Obese women have higher estrogen levels as a result of increased conversion of androgens into estrogens in fat tissue and consequently have a lower frequency of osteoporosis. Osteoporosis is much more frequent in thinner women and in women receiving glucocorticoids, which not only have a catabolic effect but also depress the secretion of adrenal precursors of estrogens. Chronic stress and depressive states in postmenopausal women are accompanied by low androstenedione and estrogen levels and excretion (*77*).

Andropause

Middle age in males, in contrast to females, is not characterized by a sudden discontinuity in fertility although fertility declines progressively from the age of 25–40 onwards (*53,59,60*). It is now generally accepted that Leydig cell function declines in elderly men. Almost all authors report a significant age-associated decrease in free testosterone levels, although in exceptional cases healthy elderly men maintain unchanged levels of total testosterone. Primary testicular factors undoubtedly play a major role in the age-dependent decline in plasma testosterone levels and this is associated with a decreased number of Leydig cells (*78*), impaired testicular perfusion (*79*), impaired steroid synthesis (*80*), and decreased testosterone output in response to hCG stimulation (*81,82*). A similar diminished response to increased biologically active LH levels occur after clomiphene administration (*83*). The moderate but significant increase of LH levels with age is consistent with primary testicular deficiency in the elderly.

In addition to primary testicular failure in elderly men, there are also alterations of the hypothalamo-pituitary pole of the hypothalamo-gonadal axis as evidenced by *a*) failure to maintain normal free testosterone levels in spite of adequate secretory reserve of both gonadotrophs and Leydig cells, *b*) disappearance of nychthemeral variations in testosterone levels (*84*), *c*) decreased frequency of large amplitude LH pulses (*85*), *d*) decreased or absent response of LH levels to antiopioids or anti-estrogens (*86,87*), and *e*) increased sensitivity of the gonadotrophs to sex hormone feedback (*85,88*).

The aging process has less of an influence on spermatogenesis. Alterations in sperm quality in old age are minimal and characterized essentially by a decrease in motility and number of spermatozoa with normal morphology (*72,73*). However, there is a significant decrease in daily sperm production in elderly men (*90*). Plasma FSH levels increase with age, probably in relation to a decreased inhibin secretion, which is a consequence of the age-associated impairment of Sertoli cell function in addition to the decrease in the number of Sertoli cells in men 50–80 years old (*91*). Although there is clear evidence for a decrease in fertility in elderly men (*59,60,92*) the zona-free hamster egg fertilizing ability of spermatozoa from healthy elderly men appears to be similar to that of young men (*89,92*).

Leydig cell function is more resistant to environmental factors than Sertoli cells, and there is no clinical hallmark of Sertoli cell function in elderly men, who are generally no longer interested in fertility. It is not surprising, therefore, that few data are available on factors that accelerate the decline in testicular function with age. However, this decline is dramatically accelerated by acute or chronic

disease as a consequence of transient hypogonadotropism, although direct effects at the testicular level may also play a role (*93*). Plasma testosterone levels decrease much more rapidly with age in subjects who have even a minor chronic affliction than in perfectly healthy men.

Depression is associated with a decrease in both LH and testosterone levels, probably mediated by CRF, the levels of which are increased in many cases. Systemic diseases such as granulomatous leprosy may damage the testes directly, whereas hemosiderosis has an indirect effect, acting by way of impairment of hypothalamo-pituitary function. Other diseases may alter hormone release or metabolism at multiple sites in the hypothalmo-pituitary gonadal axis as occurs in renal failure, which is associated with increased prolactin levels, decreased pituitary response to GnRH, and decreased testicular response to hCG. In chronic pulmonary fibrosis, there is significant correlation between plasma testosterone levels and arterial oxygen tension (PaO_2). Testosterone levels become subnormal when PaO_2 drops below 55 mm Hg because hypoxia suppresses the hypothalamo-pituitary axis (*94*). Uncorrected varicocele causes a more rapid decline in Leydig and Sertoli cell function with age in comparison to normal controls (*96*).

There is clear evidence that aging is associated with a decreased ability to maintain homeostatic functions and associated with a decreased responsiveness to stress. It must be asked, therefore, if chronic stress accelerates the neurodegenerative aspects of aging. Considerable experimental evidence in animals suggests that chronic stress accelerates hippocampal neuronal death due to excessive exposure to glucocorticoid (*95*). However, only very little information is available in men, and this is hardly surprising considering the absence of a universally accepted definition of stress. Several papers have suggested that there has been a decline in sperm quality and fertility in the general population over the last few decades, which may be due to the combined effects of increasing population, exposure to radiation, and population stress (*91,97–101*).

Toxic Effects of Drugs or Chemicals on Gonadal Function

There is a large list of various substances that have been reported to have an adverse effect on gonadal function, and it will not be possible to discuss each one at length. Only some of the most important substances will be mentioned, and drugs affecting potency, such as anti-dopaminergics, will not be discussed.

Centrally Acting Drugs. The effects of morphine and its analogues on the pulse generator have already been discussed. All heroin addicts, and 45% of methadone addicts, have decreased spermatozoa motility, and 25% also have teratospermia (*102*).

Some cocaine abusers have higher than normal prolactin levels, but no significant differences in either LH or testosterone pulse frequency (*103*). Cannabinoids are reported to depress Leydig cell function (*104*).

Heavy Metals. Lead intoxication sufficient to cause clinical poisoning (blood lead levels of 66–139 μg/dL) appears to induce oligo- and azoospermia in a substantial proportion of exposed individuals (*105*). Cadmium is known to damage testicular blood vessels, causing ischemia and tubular necrosis. Chronic exposure to thallium is less toxic because it is taken up by metallothionein, which is formed in the testis (*106*).

Nitrogen, Sulfur, or Phosphorus-Containing Compounds. Nitrofurans inhibit spermatogenesis (*107*). Chronic exposure to carbon disulfide, used in the viscose industry, causes an increase in gonadotropin levels among workers exposed for an average of 15 years to an atmospheric level of 120–240 mg/m^3 (*108*). Organophosphates (parathione) cause infertility in farm animals, inhibit testosterone metabolism in rodents, but have no apparent effects on Leydig cell function in man (*109*).

Hormones. Aminoglutethimide, spironolactone, ketoconazol, metyrapone, *ortho-para*-DDD, and cimetidine all have a direct effect on sex hormone activity.

Anabolic steroids, abused by body builders, block pituitary gonadotropin release leading to a hypogonadotropic state and low intratesticular androgen concentrations. It is not surprising, therefore, that oligozoospermia is a frequent finding in body builders abusing anabolic steroids. However, this inhibition of spermatogenesis is reversible even after prolonged use of very large doses (*110*).

Progestational drugs such as megestrolacetate, medroxyprogesterone acetate, and cyproterone acetate block gonadotropin secretion and therefore block Leydig cell function and spermatogenesis. They also have some anti-androgenic activity.

Pure antiandrogens such as flutamide or anandron activate the secretion of gonadotropin and sex hormones. The effects at the cellular levels of sex hormones are blocked by the competitive binding of antiandrogens to the androgen receptors.

Anti-estrogens such as chlomiphene or tamoxifen also activate gonadotropin secretion and may be used to induce ovulation or induce spermatogenesis. Oral contraceptives prevent conception by blocking ovulation and/or by causing changes in cervical mucus characteristics that retard sperm penetration and by hindering implantation of the zygote.

Pesticides. Several reports have mentioned infertility associated with oligo- and azoospermia amongst workers exposed to kepone pesticides such as dibromochloropropane (DBCP) (*111*). DBCP (a nematocide) and 2,3-dibromopropanol induce oligo- or even azoospermia in factory employees (*112*), which appears to be partially reversible when exposure ceases if FSH levels have remained normal. Polychlorinated biphenyls (PCB), polychlorinated dibenzdioxins (PCDD), and dibenzfurans (DBF) have similar effects.

Cytostatics and Antimetabolites. ALKYLATING AGENTS. Chlorambucil (Leukeran), Melphalan (Alkeran), cyclophosphamide, Ifosfamide and nitrosourea derivates (BCNU, CCNU), and imidazo carboxamides (dacarbazine) are known to induce germinal aplasia in men, whereas

Leydig cell function is generally preserved or only slightly impaired. The onset of the testicular toxic effect is dose dependent, and a partial recovery of spermatogenesis may be expected on cessation of therapy with even the possibility of paternity. These alkylating agents in women have a toxic effect on the primary follicles and oocytes and induce amenorrhea. The age at treatment is an important determinant: younger women resume ovulatory activity more frequently than women over 40 years of age. As a rule, ovaries are more resistant to chemotherapy-induced damage than testes. Treatment with alkylating drugs before puberty or in adolescence does not affect fertility in women, whereas only a small proportion of men who survive appear to retain fertility. Nevertheless, the testes of prepubertal boys are relatively more resistant to alkylating agents than adult testes.

ANTIMETABOLITES. The antimetabolites such as folic acid antagonists (methotrexate), purine analogues (mercaptopurine, azothioprine) and pyrimidine analogues (fluorouracil, cytarabine) cause less severe effects on spermatogenesis, and only when used at higher doses.

CYTOSTATIC ACTIVE ANTIBIOTICS. Actinomycin, daunorubicin, doxorubicin, epirubicin, bleomycin vinca alkaloids (vincristine, vinblastine) and etoposide have less toxic effects on the gonads. Combination chemotherapy using cytostatic regimes that include alkylating agents or procarbazine frequently produce irreversible azoospermia, whereas combinations not containing these drugs produce germ cell aplasia less frequently and the depressive effects are generally transient (*113*). Attempts to prevent the toxic effects on the testis by using GnRH analogues in order to inhibit spermatogenesis have proved ineffective.

RADIATION. The effects of radiation on spermatogenesis (transient or permanent azoospermia) depend on the total dose received and on whether the dose is fractionated (*114*). The ovary is less sensitive to irradiation than the testis. The younger the woman, the less the chance of permanent sterility. This age difference is related to the number of oocytes remaining in the ovary. Children of parents exposed to either radiation or chemotherapy do not appear to have an increased incidence of chromosomal abnormalities or congenital anomalies.

Conclusion

The hypothalamo-pituitary-gonadal axis is regulated by a complex interplay of neural, hormonal, and metabolic signals, and not surprisingly, therefore, may be affected by many environmental factors. Stress of any form, acute or chronic disease, nutrition, obesity, alcohol, smoking, and drugs of addiction all affect reproductive function, Moreover, a large number of pharmaceutical agents, alkylating agents, industrial toxins, and pesticides, in addition to irradiation, induce infertility, which is not infrequently irreversible.

Fertility decreases significantly with age in both men and women, and chromosomal abnormalities play an important part in this decline. Age at menopause is largely determined by genetic factors, and environmental factors play a minor role. Premature ovarian failure with persistent immature follicles is a secondary phenomenon generally related to autoimmune diseases.

Of great concern is the suggestive evidence of decline in sperm quality over the last decades. If this is confirmed, preservation of the human race may necessitate strict measures to reduce pollution drastically and to control irradiation and other noxious agents which impair spermatogenesis.

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