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Alkylating agents and radiation produce gonadal dysfunction in most adults. Failure of ovaries and testes occur less often in prepubertal children after comparable drug and gonadal radiation doses which produce gonadal failure in adults. Hormonal suppression of the gonads may "protect" adult gonadal

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function in patients treated with cytotoxic drugs. Sexual dysfunction and emotional problems which accompany gonadal dysfunction adversely affect the quality of life in cancer patients.

Effect Of Cytotoxic Therapy On Sexuality And Gonadal Function

By Ramona M. Chapman

CHEMICAL AGENTS have been used in the treatment of cancer for over 30 yr. As described elsewhere in this issue, these agents have produced toxicities involving multiple organ systems. Drug induced azoospermia and amenorrhea are well known, but the impact of gonadal toxicity on the quality of life needs special emphasis.[1,2] Until recently, this has received little attention.[3] Treatment of the symptoms of gonadal damage may ameliorate the emotional consequences of therapy even for those men and women for whom cytotoxic therapy offers only palliation.

PATHOPHYSIOLOGY

The pituitary gland and the gonads function in a feedback cycle. The release of follicle stimulating hormone (FSH) and luteinizing hormone (LH) is inhibited when the gonad responds with production of adequate blood levels of the appropriate hormone. Other hormones regulated by the hypothalamic pituitary system affect the pituitary gonadal axis, specifically thyroid stimulating hormone (TSH) and prolactin. Abnormalities of thyroid function are associated with irregular anovulatory menstrual cycles, menometrorrhagia, or amenorrhea in women,[4] and in men with impaired spermatogenesis, impotence, and loss of libido.[4,5] Hyperprolactinemia in women is associated with amenorrhea, abnormal pituitary release of gonadotropins and estradiol deficiency,[6] and in men with galactorrhea, gynecomastia, and impotence.[7]

In men with normal spermatogenesis, an inhibitor of FSH is produced by the testes;[8] when spermatogenesis is impaired, FSH blood levels* rise. The Leydig cells produce testosterone in a feedback cycle with LH.[9] When there is compensated Leydig–cell failure, the LH level rises and testosterone production remains adequate. But in complete Leydig–cell failure, levels of LH rise and testosterone levels fall.

In women FSH stimulates the follicular granulosa cells to divide, mature, and produce estradiol. The midcycle LH surge promotes ovulation: the rupture of one of the numerous maturing follicles. The ruptured follicle, now the corpus luteum, then produces increased progesterone levels that feedback to suppress further release of LH.[10] The remaining maturing follicles become atretic. In primary ovarian failure, greatly increased levels of FSH and LH occur with abnormally low estradiol and progesterone levels.

EFFECT ON PROGENY

Many have raised the possibility of cytotoxic induced germ cell mutations, resulting in congenital abnormalities in the progeny of those treated patients who remain fertile. To date, this hypothesis lacks firm evidence since there has been no increase in chromosomal abnormalities or congenital abnormalities in the offspring of individuals exposed to either radiation or chemotherapy; nor is the rate of spontaneous abortion any higher than that of the general population.[11-19] On the basis of the outcome of a few pregnancies occurring after men or women had been treated with both chemotherapy and radiation, Holmes and Holmes[20] have suggested that the number of spontaneous abortions or minor congenital abnormalities in this subgroup may be increased. Their data as presented, however, are statistically invalid.[21]

GONADAL DYSFUNCTION

Men

In 1948, testicular atrophy was reported at autopsy on patients who had been treated with nitrogen mustard for lymphoma.[22] Fifteen years later procarbazine was noted to affect spermatogenesis markedly,[23] a finding confirmed by later observations.[24-26] Depression of spermatogenesis in guinea pigs receiving chlorambucil and busul-

*All hormone measurements mentioned in this article refer to serum.

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fan[27] was demonstrated in 1968, and 2–3 yr later both chlorambucil[28] and cyclophosphamide[29] were shown to have toxicity in human testes. Thereafter a spate of studies linked total dose[28,30–33] and age[33–35] to the extent of gonadal damage. The unpredictable reversibility of cyclophosphamide induced azoospermia was first suggested by Qureshi[36] and later demonstrated by others.[37,38]

In 1973, Sherins[39] confirmed that alkylating agents, such as cyclophosphamide and nitrogen mustard, used with other agents cause sterility in most adult male lymphoma patients. By 1978 Roeser[40] reported reversibility of azoospermia in four of seven men treated with cyclophosphamide, vincristine, and prednisone (CVP) but in only one of six men treated with nitrogen mustard, vinblastine, procarbazine and prednisolone (MVPP) or nitrogen mustard, vincristine, procarbazine, and prednisone (MOPP). Chapman and Sutcliffe[41] reported evidence of widespread sexual dysfunction and decreased fertility in patients with Hodgkin's disease, both during and after therapy. In a later report,[42] the same investigators described 74 men who had been treated with MVPP and showed that 27 out of 27 men had no sperm during the first 12 mo after therapy, demonstrating 100% infertility. They documented azoospermia followed by return of active spermatogenesis in only four out of 64 men (6.25%) from 15 to 51 mo after treatment was stopped. In 1981 Chapman and Sutcliffe[43] showed that only one or two cycles of MVPP therapy were required to produce azoospermia in all men, a condition persisting through the end of therapy.

Recent reports indicate that methotrexate therapy for psoriasis has little or no effect on spermatogenesis.[44–46] Although adriamycin is very toxic to primitive germ cells in mice,[47] human germ cells appear to be less susceptible, even to high total doses in the range of 400 to 700 mg/m^2.[48]

Other drugs have demonstrated variable toxicity in the testes of animal models:[47,49] cytosine arabinoside, bleomycin, hydroxyurea, the vinca alkaloids, thio-TEPA and CCNU. Results in these models suggest that hydroxyurea, 5-fluorouracil, cytosine arabinoside, and methotrexate produce reversible germ cell toxicity; this has been reported to be the case in the testes of humans treated with cytosine arabinoside and methotrexate.[44,46,50]

Women

In 1960, amenorrhea associated with busulfan therapy for chronic myelogenous leukemia was reported.[51] The same disturbance occurred in women receiving the drug as adjuvant therapy for breast cancer.[52,53] Busulfan administered to pregnant rats produces female progeny whose ovaries contain no ova, indicating a toxic effect on the developing germ cells.[54] By 1968 cyclophosphamide induced amenorrhea was noted for the first time in a group of women being treated for rheumatoid arthritis.[55] This report was quickly followed by another noting amenorrhea in four of 17 women treated with this drug for systemic lupus erythematosus.[56] Miller[57] demonstrated by ovarian biopsy that loss of ova is the cause of the cytotoxic induced functional ovarian failure. Warne confirmed this finding.[58] Kumar[59] reported that amenorrhea secondary to cyclophosphamide therapy is sometimes reversible and Uldall[60] suggested estrogen replacement in those women with postmenopausal symptoms.

In 1971, Sobrinho et al.[61] reported ovarian failure in women treated for Hodgkin's disease by multiple agents in sequence. The authors suggested that the 100% incidence of ovarian dysfunction in the 10 women described resulted from the use of multiple agents. Closer scrutiny reveals that two young women, ages 25 and 26, had unreversed ovarian dysfunction after receiving two alkylating agents, while a 28-year-old woman treated with vinblastine and cyclophosphamide had reversal of her amenorrhea and became pregnant. No women aged 30 yr or older had reversal of amenorrhea, regardless of number or type of agents used. These data suggest that the extent of ovarian damage is related to age as well as to dose.

The relationship of age to ovarian dysfunction has been reported in numerous studies of adjuvant chemotherapy for breast cancer[53,62,63] involving various alkylating agents and other drugs. In 1973 Warne[58] reported a mean age of 29.6 yr in women with ovarian failure after cyclophosphamide therapy. Further, he suggested that progressive ovarian failure was occurring, rather than an all or none phenomenon as evidenced both by his observation of

Table 1. Forty-one Women treated with MVPP Hodgkin's Disease.*

	Age (years)		Cycles of Chemotherapy†	
	< 29	≥30	6	≥7
No. of patients	(16)	(25)	(21)	(20)
Functioning (%)	5 (31%)	1 (4%)	5 (24%)	1 (5%)
Failing (%)	6 (38%)	3 (12%)	3 (14%)	6 (30%)
Failed (%)	5 (31%)	21 (84%)	13 (62%)	13 (65%)
	$0.01 < p < 0.025$		$0.05 < p < 0.10$	

*Relation of ovarian function to age and total dose of MVPP (nitrogen mustard, vinblastine, procarbazine, prednisolone). Women younger than 29 yr at therapy had a statistically significant less chance of ovarian dysfunction than older women ($0.01 < p < 0.025$). Statistical significance was not demonstrated for ovarian dysfunction in women receiving six cycles versus seven or more cycles of therapy ($0.05 < p < 0.10$).

†Six cycles were selected for comparison because it is the standard number given. All postpubertal patients who received 12 cycles developed failed ovarian function regardless of age.

various stages of ovarian dysfunction and failure, and by other reports of reversibility of amenorrhea.[59] Rose[52] presented evidence of progressive ovarian failure in women evaluated at 6 and 12 mo after therapy.

Chapman and Sutcliffe[64] confirmed these suggestions in 41 women treated with MVPP for Hodgkin's disease in whom progressive ovarian dysfunction, resulting in premature ovarian failure, was age and dose related (Table 1). Women treated in their twenties later developed complete ovarian failure in their early thirties. Ovarian biopsy confirmed loss of primordial follicles. A pregnancy did not prove lack of ovarian damage. One of the women treated at age 25 delivered a normal infant girl three yr after therapy and two yr later developed the failing ovary pattern. This is analogous to the situation in normal perimenopausal women who may become pregnant and later progress to normal menopause. In a recent study[64a] of women treated for Hodgkin's disease (median age of 18.5 yr at therapy), the birth rate was 64/1000 women/yr when these same women were a median age of 23 yr. This is comparable to the birth rate of women ages 30–35 yr in the general population (59/1000 women/yr).[64b] Premature ovarian aging is evident in these treated young women.[64c]

Children

Although the ovaries of prepubertal and pubertal girls are relatively insensitive to chemotherapeutic drugs,[33,35] ovarian damage and failure can occur if enough drug is given.[57,65,66] The rarity of ovarian failure in the prepubescent girl may be due to the lower level of follicular activity as compared to that of the pubescent girl or the mature woman. Similar observations obtain in prepubescent and pubescent testes.[31 36,67 69]

Irradiation

Infradiaphragmatic irradiation therapy carries a high risk of sterility in both sexes. At the time of staging laparotomy for Hodgkin's disease, the ovaries are routinely moved into position behind the uterus (oophoropexy).[70,71] The uterus is then shielded when irradiation is given.† Even with these precautions, 30%–50% of young women lose ovarian function during irradiation.[70 73] Women with other malignancies requiring infradiaphragmatic irradiation do not have the benefit of oophoropexy. Only 600–1000 rads delivered to both adult ovaries are required to produce ovarian failure in most women.[74,75] Higher doses of radiation produce the same effect in female children.[76,77] Therefore, all females who receive abdominal or pelvic irradiation are at risk for developing irreversible ovarian failure.

In men, "inverted Y" irradiation therapy for Hodgkin's disease has been reported to produce 70%–100% azoospermia despite testicular shielding.[78,79] Shalet described eight out of ten men who had received irradiation (with testicular shielding) for nephroblastoma during childhood who had oglio–or azoospermia as adults. He also studied eight prepubescent boys who had also been irradiated for abdominal malignancies and found no significant difference between their gonadotropin levels and normal prepubertal

†The usual parts of radiation include the aortic and iliac nodes, the so-called "inverted Y," to a dose of about 3600–4000 rads.

boys. Thus, the gonadal damage incurred during childhood may not be demonstrable until adulthood.[80] Less than 100 rads of scatter radiation to the adult testes can produce elevated FSH and LH levels and azoospermia; recovery may occur in 9–18 mo for doses of ≤100 rads, 2–3 yr for 200–300 rads, and 5 yr to infinity for 400–600 rads.[81]

Summary

The dose of a cytotoxic agent that produces demonstrable gonadal damage in most postpubertal adolescents and adults will affect gonadal function in some pubertal children, but in few or no prepubertal children. But if enough drug is given, individuals of all ages are affected. Radiation below the diaphragm, particularly in the pelvic area, and with or without gonadal shielding, produces irreversible gonadal failure in the majority of patients of all ages if enough rads are delivered. Therefore, the combination of radiation near the pelvis and alkylating drugs probably causes gonadal failure in the majority of persons of both sexes.

SEXUAL AND EMOTIONAL PROBLEMS

We have reported the results of a questionnaire about sexual function in men before, during, and after chemotherapy for Hodgkin's disease.[42,43] Patient perceived category of libido was correlated with incidence of weekly sexual activity (Fig. 1). Even though some of the men claimed strong libido while reporting sexual activity more in line with moderate or mild libido, about half of the men perceived a decrease in libido *at the time of diagnosis* of Hodgkin's disease. This number increased to 85% during chemotherapy, and 40% of the men reported that an overall decrease in libido persisted long after stopping therapy.

Additionally, several men complained that although their libido was satisfactory, orgasm was not as strong or as satisfying as previously, and some had a dry ejaculation. Some wives, aware of the study, insisted that their husbands report that their sexual function was not right. One wife sent her husband to the clinic with his back covered with her scratches as punishment for his failure to satisfy her sexually. Another wife, more recently interviewed, said that although her husband had not perceived any problem, she had noted that he could not hold his erection longer than one or two minutes after vaginal penetration.

Because they were not informed that sexual difficulties are common during chemotherapy, some men have developed psychogenic impotence. This should be preventable with counseling. However, impotence due to Leydig-cell failure often occurs when men are treated with cytotoxic drugs and subdiaphragmatic radiation.

With the onset of illness many men experienced irritability and some became physically

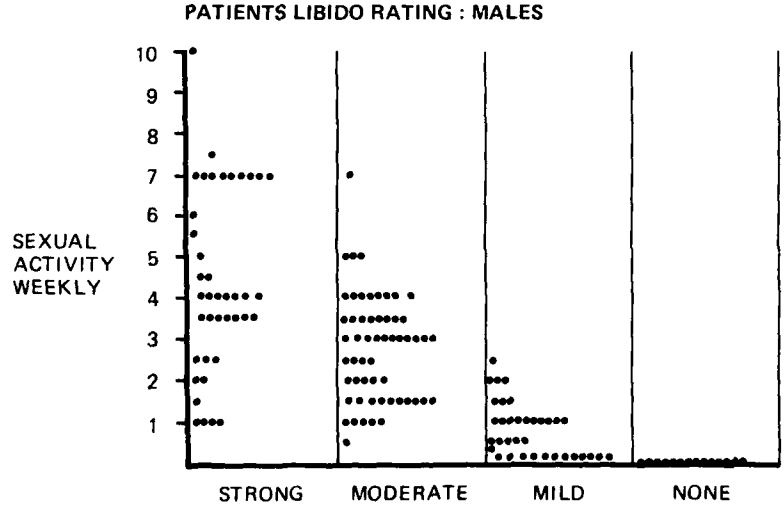

Fig. 1. Correlation of weekly sexual activity with category of libido. Patients selected their own category of libido. Most patients who claimed strong libido engaged in sexual activity ≥4 times/week, moderate 1–4 times/week, mild <1 to 1/week, none, 0/week.

violent.[43] During chemotherapy the numbers of men with these problems increased. Some men denied these problems although their spouses told us of instances of repeated wife beatings and harrassment of children by men who had not behaved in this manner prior to illness.

Similar studies on women have also shown that several claimed a stronger libido than sexual activity would substantiate,[82] and some women engaged in sexual activity to please their spouses or because they sought physical closeness. Despite this, at a median followup time of three yr after therapy, 70% of the women had mild or no libido. This number would be expected to increase as more women develop ovarian failure.

Premature menopause exacts a heavy toll on women,[82,83] especially those younger than 30. In addition to loss of libido, women with complete ovarian failure also manifest hot flushes, insomnia, and irritability. Generally women do not discuss their problems with others, but are secretly ashamed of their change in behavior. As a result many lose self-confidence and self-esteem. Loss of sexual identity is devastating to younger women who fear they will be unable to respond sexually again. Many lose their lovers or husbands and shun forming new relationships for fear of being labeled frigid. With women between the ages 25 and 30, dissolution of intimate relationships occurs four times as often as in the general population.[82] These ruptured relationships affect not only the couple, but also children, other close family members, and friends.

ACCELERATED AGING IN SUCCESSFULLY TREATED PATIENTS

In 1972, Campos[84] described what he called "continuous positive aging" in populations in remission from Hodgkin's disease. He felt that death was delayed by treatment but "at an apparent homeostatic cost that makes death more likely with the passage of time." This process could not be demonstrated in patients with this disease prior to the development of intensive chemotherapy and radiation. On the other hand, women who were successfully treated locally for carcinoma of the cervix did not demonstrate this phenomenon.

The changes in the endocrine system may be an example of this process. Chapman and Sutcliffe found evidence of multiple endocrine abnormalities in the majority of people in remission from Hodgkin's disease:[42,43,64] unexplained high prolactin levels, elevated levels of FSH, LH, estradiol, TSH, low to low-normal testosterone and progesterone levels, and severe estrogen deficiency. Other investigators have noted varying degrees of hypothalamic-pituitary-end-organ damage.[65,85] It is not known if shifts in hormonal ratios lead to increased risk of cardiovascular disease in young men and women, but certainly young women living many years in a menopausal state that occurred 20 yr ahead of schedule are at increased risk for osteoporosis. Young women treated for gynecologic malignancies, breast cancer, and lymphomas constitute a sizeable population at risk. Whether men with a testosterone:estrogen imbalance share this risk is unknown, nor do we understand the possible future effects of delayed onset of puberty[31,65] or of gonadal damage occurring in prepubertal and pubertal children who receive intensive cytotoxic therapy. Toxicities in other organ systems may also significantly accelerate aging in aggressively treated people.

The implications of cytotoxic induced gonadal dysfunction go far beyond the observation of azoospermia, amenorrhea, or altered hormone levels. The real importance of such findings lies in the impact of these and associated changes in sexuality on the quality of life for the patient. The days of disregarding sexual and gonadal dysfunction in cancer patients are past. Ignoring complaints relevant to hormonal deficiency is as inappropriate as failing to respond to a breast cancer patient who complains of back pain.

DIAGNOSIS

A questionnaire often can identify those people needing further evaluation and treatment. Patients should be interviewed alone. If the spouse or lover is present the truth may be distorted to protect the other's feelings. The interview should begin with reassurance that the majority of patients receiving intensive therapy experience some degree of sexual dysfunction. If patients realize that their problems are not unique, they may be relieved of shame, thus setting the stage for honest answers. Routine counseling prior to therapy also alerts patients to the possible symptoms of gonadal dysfunction.

Informed patients are likely to report these undesirable sequelae of intensive therapy and request help.

A sexual questionnaire should not be filed in the patient's record and the patient should be aware of this to maximize openness. The paper on which the questions are written serves as neutral ground. The eyes of examiner and patient can be focused on the paper, reducing the perception of threat.

When problems referring to sexual or gonadal dysfunction arise, a thorough evaluation is appropriate. When a young man asks about his prospects as a father, a sperm count is in order. If he has azoospermia, a semen analysis every six months can keep him informed. If a man complains of decreased potency, consider whether he has had any subdiaphragmatic radiation. Also inquire about the events surrounding the onset of impotence. Did an uninformed man experience sexual dysfunction during therapy, and could associated events have started the cycle of psychogenic impotence? Blood levels of testosterone, estradiol, prolactin, T_3, T_4, and TSH may provide evidence for treatable physiologic damage to the hypothalamic–pituitary–testicular axis.

When a woman inquires about her fertility, it is appropriate to take a detailed menstrual history. If she is asymptomatic and has regular menses, then she has intact ovarian function and can be reassured. If she has irregular menses, then a measurement of FSH and estradiol during a prolonged period of amenorrhea or during the first five days of a menstrual flow should give a good indication of ovarian function. If the FSH level is elevated or the estradiol level is either depressed or greatly elevated, there is evidence of abnormal ovarian response to gonadotropin stimulation; this woman is in a perimenopausal state and is still potentially fertile, although she may progress to premature menopause within months.[64]

If the patient has amenorrhea, she should be questioned about changes of libido and presence or absence of hot flushes, insomnia, irritability or dyspareunia. A FSH level will further define her menopausal status.[86] If she is asymptomatic, she may experience reversal of her amenorrhea. Prolactin, T_3, T_4, and TSH levels are helpful in identifying treatable causes of ovarian dysfunction.

A similar approach may be taken in response to complaints of sexual dysfunction. Knowledge of menstrual history and presence or absence of menopausal symptoms coupled with appropriate hormone levels will answer most questions. More complicated problems can be referred to an endocrinologist.

TREATMENT

Counseling

Every opportunity should be taken to counsel patients. When possible, counseling of patient and sexual partner is recommended so that the patient and the intimate partner can work together to overcome the emotional realities of infertility and sexual dysfunction. In addition, the partner may identify symptoms of dysfunction before the patient does, thus making early therapeutic intervention possible.

Men should be told that it is the rule for men to develop decreased libido and even impotence during therapy.[42,43] They should be informed that these problems usually resolve once therapy is discontinued. If sexual dysfunction does not improve, they should be encouraged to tell their physician so that proper investigation and therapy can be initiated. They should be told that the quality of the sexual encounter may be changed. When men or their partners complain of premature ejaculation, either the oncologist or a good sex counselor can explain alternatives to vaginal intercourse whereby a man can satisfy a woman sexually, and vice versa.

They should be informed that prolonged therapy with alkylating agents produces azoospermia in all men and that reversibility is variable, though unlikely if two or more gonadotoxic agents are employed. They should be reassured that azoospermia and infertility do not affect their manhood or "masculinity."

Women should be told about the possibility of ovarian failure, and warned of the symptoms associated with premature menopause as well as of infertility and possible future osteoporosis. They should be reassured that decreased libido and irritability are typical responses to ovarian failure and that these symptoms can be reversed with hormonal replacement.

Infertile couples may wish to investigate adoption, although adoption agencies are loathe to

place an infant with a couple when one of them has the label of "cancer." However, older children may be available for adoption. When the man is infertile, the couple has the option of artificial insemination by donor (AID), where the donor of the semen is selected to match the husband's physical characteristics as closely as possible. For this couple AID may be better than adoption since half the genes would be from the wife, and both spouses can share the experience of the pregnancy together. For the sake of the child, we strongly urge that if either husband or wife has *any* reservations about AID, they should not consider it.

A man with a treatable malignancy that carries a good prognosis should have semen analysis performed before initiation of therapy. If he has a sperm concentration of ≥40 million per ml and a motility of at least 60%, he can be given the option of sperm banking if he wishes to father a child in the future. By these criteria many men may not have adequate semen.[43,87,88]

Hormone Replacement

If a man has complete testicular failure as defined by azoospermia, impotence and a testosterone level below normal, he can benefit from reassurance and testosterone replacement. Testosterone enanthate 200 mg IM for 2–3 weeks will suffice in most cases. A man with psychogenic impotence may need only reassurance plus one or two injections of testosterone as a psychologic boost.

If TSH is greatly elevated, thyroid hormone replacement titrated to suppress TSH into the normal range may provide a concomitant decrease in prolactin levels. It may also correct any subtle or unrecognized sequelae associated with compensated thyroid failure. If the serum prolactin level is persistently elevated on serial testing, tomograms of the sella turcica should be done to rule out a pituitary microadenoma. When this diagnosis is made, appropriate therapy may correct the sexual dysfunction. The relationship between elevated prolactin levels and depression of spermatogenesis is not clear.

Hormonal replacement and counseling for women with cytotoxic induced premature menopause has many benefits.[64,89] The symptoms of depressed libido, dyspareunia, hot flushes, and irritability are reversed. I have successfully employed progesterone and estrogen in sequence, mimicking the normal hormonal cycle. Estrogen replacement in women younger than 45 yr is instituted in gradually increasing doses to avoid nausea. The regimen is as follows:

> For the first mo 20 mcg of ethinyl estradiol is prescribed on the even numbered days from day 8 to the end of the month. This is increased to 40 mcg on even days, 20 mcg on odd days, from day 8 to the end of the month thereafter. Once they have adjusted to full replacement doses, some women may prefer to take the full 40 mcg from day 8 to the end of the month. Medroxyprogesterone acetate 5.0 mg daily (one half tablet) is prescribed for days 1 through 7 of every calendar month.

Withdrawal bleeding usually begins between days 8 and 11. Spotting may occur during the first two cycles due to the low estrogen doses. Advanced warning and reassurance is generally all that is necessary. The first true withdrawal bleed may be associated with cramping. After that menstrual flows will be similar to those the woman had before onset of amenorrheaa.

Estrogens have been shown to be efficacious in treating osteoporosis in postmenopausal women.[90] It is reasonable to assume that estrogen replacement at the onset of estrogen deficiency may prevent this complication in women with premature menopause.

In women in whom estrogen therapy is thought to be contraindicated, a centrally acting alpha–adrenergic agent, such as oral clonidine, 25 to 75 mcg twice daily, is useful for reducing the number and severity of hot flushes.[91] Benadryl 50 mg at bedtime may help control hot flushes and promote sleep. Progesterone or androgens in modest doses may improve libido. Investigation and treatment of thyroid dysfunction or hyperprolactinemia in women is important in maintaining a normal hypothalamic–pituitary–ovarian axis.

Combined estrogen and progesterone oral contraceptives given during cytotoxic therapy prevent the symptoms of ovarian failure in all premenopausal women and provides adequate birth control, thus forestalling a decision about abortion of a cytotoxic exposed fetus. These combined hormonal drugs put the ovary at rest by suppressing the release of pituitary gonadotropins.[10] Chapman and Sutcliffe[92] have noted preservation of ova in biopsied ovaries of three women and normal ovarian function at two years in five

women treated with contraceptive drugs during intensive cytotoxic therapy. Theoretically, this maneuver should be of benefit during irradiation therapy as well since the fetal ovaries are greatly resistant to radiation damage.[34,35] Returning the adult testes to a prepubertal like state may confer similar resistance to cytotoxic germ cell damage. A recent paper, depending on the survival of two treated mice, reported protection of spermatogenesis during cyclophosphamide therapy by means of hormonal suppression with gonadotropin releasing hormone.[93]

For over 30 yr we have administered radiation and cytotoxic chemicals. Because we now know what these toxicities mean in human terms, we have an obligation to identify, evaluate, and treat each patient affected while we search for methods of prevention. An obstinate oncologist criticized this aspect of medical practice, saying, "My patients never have any of these problems." I suggest that he never asked his patients the right questions, in a sympathetic manner, in a private setting.

At the beginning of our study of sexuality in Hodgkin's disease, my associate, Dr. Simon Sutcliffe, questioned a 45-yr-old man with non-Hodgkin's lymphoma about his sexual adequacy. This man had been ill for several years, had relapsed three times, and had been treated with extensive chemotherapy and irradiation to the groin. He had been cared for, at one time or another, by more than a dozen physicians, none of whom had learned of his devastating personal problems. Now he told his story to a physician for the first time. Since diagnosis and therapy he had experienced decreased libido and had become impotent. He could not understand why, after 23 yr of stable married life, he could not find his wife in any way attractive and he wondered whether the impotence was his fault or hers. He sought out a prostitute and he failed sexually. Later, he told his wife of this experience. She was hurt. They considered separation. Finally they decided to continue living together, but the previous peace and trust of their relationship was gone. He also told Dr. Sutcliffe that during one of his hospitalizations a fellow patient, who also had received extensive therapy, asked if he had quarreled with his family after beginning treatment. The patient then realized that he had become quite quarrelsome and touchy and that his disposition had alienated his grown children.

This vignette demonstrates that these serious side effects were common knowledge within families and that the information was exchanged among patients while oncologists remained ignorant. The disease, not the patient, has been our province.

SUMMARY

Many chemotherapeutic agents have been shown to cause variable degrees of gonadal dysfunction in both sexes and in all age groups. The severity of the dysfunction depends on the total drug dose and the age at time of therapy. In general, cytotoxic agents produce gonadal dysfunction in men while they produce premature gonadal failure in women. Men develop azoospermia and compensated Leydig-cell function; women sustain ovarian damage causing impaired fertility in the short term and early ovarian failure later.

This dysfunction is associated with sexual and emotional difficulties in many patients. In order to discover these problems the physician must sympathetically ask patients and families about their sexual and emotional health. Endocrine and psychologic evaluation help the physician identify the problem. Appropriate counseling and hormone replacement therapy may ameliorate most symptoms and help the patient emotionally adjust to illness and infertility. Prevention of gonadal damage during cytotoxic therapy may be possible in the future.

For those young people who retain fertility after cytotoxic therapy, prognosis should be taken into account when counseling about parenthood is given. There is no evidence of genetic abnormalities in the offspring of people previously treated with chemotherapy or irradiation.

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