Surviving Adult Cancers. Part 1: Physiologic Effects

Lois J. Loescher, RN, MS; Deborah Welch-McCaffrey, RN, MSN; Susan A. Leigh, RN, BS; Barbara Hoffman, JD; and Frank L. Meyskens, Jr, MD

Purpose: To provide an overview of the physiologic long-term and late effects of adult cancers and cancer treatments by a review of the medical and nursing literature.

Data Identification: Primarily from an English-language literature search using MEDLINE (1980 to 1988) and *Index Medicus* (1980 to 1988).

Study Selection: After a consensus review by four observers, 285 articles were selected that addressed the stated purpose.

Data Extraction: Four observers assessed the literature using predetermined criteria for eliciting information about long-term and late effects.

Results and Data Synthesis: Much has been written about the acute phases of cancer and cancer treatments. In comparison, relatively few data are available that define physiologic long-term and late effects of cancer treatments in adult survivors. Review of the existing data showed that these sequelae may affect virtually any body system months or years after treatment ends. In addition, few prospective studies dealing with physiologic survivorship issues have been done.

Conclusions: Health care providers need to be aware of long-term or late complications that may affect the increasing number of adult cancer survivors. Attention to treatment regimens in the acute cancer phase and careful follow-up once the disease is eradicated may help to prevent or manage these complications. More prospective research should be done in this area.

Annals of Internal Medicine. 1989;**111**:411-432.

From Arizona Cancer Center, University of Arizona, Tucson, Arizona; and Good Samaritan Cancer Center, Phoenix, Arizona. For current author addresses, see end of text.

Five million Americans now living have had cancer at some time during their lives and three million have survived 5 years or more (1). Cancer survivors are alive largely because of improvements in early detection techniques and the use of intensive multimodal therapies using surgery, chemotherapy, radiotherapy, and hormonal therapy. These potentially curative treatments may produce long-term sequelae that occur as chronic problems after cessation of therapy, or late effects surfacing months to years later. Long-term and late effects may result in physiologic or psychosocial disability in the survivor that must be acknowledged by clinicians and researchers. The ability to identify and predict these effects of cancer treatments will facilitate the provision of appropriate comprehensive follow-up care. This two-part overview will focus on some of the physiologic long-term and late treatment effects (part I) and psychosocial sequelae (part II) experienced by survivors of adult cancers who have completed cancer therapy.

Methods

Data for this review were primarily identified using MEDLINE and the *Index Medicus.* In order to obtain the most recent information about long-term and late effects, the literature search encompassed the years 1980 to 1988. Literature of historic value describing effects related to past treatments associated with current cancer survival was secondarily identified through bibliographic reviews of textbooks, review articles, and case studies. Selection of the articles was challenging in that no MEDLINE classification delineating long-term and late effects of cancer treatments exists. Several of the articles reviewed dealt with the more acute effects of treatment. Thus, of approximately 800 articles, books, and book chapters identified via all sources, 520 that dealt with some aspect of cancer survivorship were selected by one reviewer.

To be selected, the literature had to describe a population that survived adult cancer or cancers with long-term effects that occurred as chronic problems after cessation of cancer treatment or late effects that occurred months to years after treatment. In addition, the literature selected had to focus primarily on physiologic complications. Four reviewers with a medical or nursing background agreed on 285 literature sources according to the criteria listed above. Long-term and late effects were then categorized into the body systems with which they were most often associated.

Physiologic Effects

Because survivorship of adult cancers is a relatively new phenomenon, information about the physiologic long-term and late effects of therapies is scarce. Much of the existing data have been generated from the experiences of pediatric cancer survivors. The actual

Table 1. *Potential Long-Term and Late Effects of Therapies for Adult Cancer**

System	Effects
Sex and reproductive	
Men	Germinal aplasia, testicular atrophy, azoospermia, oligospermia, increased serum FSH and LH, erectile dysfunction, ejaculatory difficulties
Women	Increased serum FSH and LH, perifollicular agenesis, ovarian fibrosis, vaginal shortening
Neurologic	Neuropathies, nerve atrophy, nerve palsies, radiation necrosis and leukoencephalopathy, radiation myelopathy, fibrosis, surgical nerve damage, neuralgia
Vascular	Strokes, arterial stenosis or occlusion, TIAs, emboli, Raynaud phenomenon, claudication
Cardiac	Cardiomyopathy, ECG changes, decreased LVEF, coronary artery obstruction, pericardial effusion, myocardial infarction, pericarditis
Pulmonary	Alveolar damage, pneumonitis, pulmonary fibrosis, pulmonary veno-occulsive disease
Urologic	Glomerular sclerosis, tubular atrophy, arteriole sclerosis, nephritis, cystitis
Gastrointestinal	
Hepatic	Transient enzyme elevation, fatty metamorphosis, portal fibrosis-cirrhosis, hepatic veno-occlusive disease
Other	Endoarteritis, infarction necrosis, esophagitis, fistulae, adhesions, obstructions

* FSH = follicle-stimulating hormone; LH = luteinizing hormone; TIAs = transient ischemic attacks; ECG = electrocardiogram; LVEF = left ventricular ejection fraction.

incidence of late effects may be underestimated, as comprehensive physical examinations, laboratory tests, radiographs, and documentation in medical records have not always been included in long-term survivor follow-up (2). In addition, most of the research in this area is retrospective, with prospective study design and measurement techniques still in early phases.

The occurrence, frequency, and severity of these sequelae depend on factors such as primary cancer type, location, size and extent of the primary tumor, intensity and type of therapy, and age and overall health of the patient (3). Long-term and late effects that will be discussed include sexual and reproductive, neurologic, vascular, cardiac, pulmonary, urologic, and gastrointestinal sequelae (Table 1). Second malignancies will also be covered. Effects on other systems are summarized in Table 2.

Sex and Reproductive Function

Chemotherapy, radiotherapy, hormonal therapy, and surgery affect gonadal and sex function. These treatments often precipitate complications with spermatogenesis, oogenesis, and vaginal, erectile, ejaculatory, and emission function.

Effects in Men

Alkylating agents have most often been implicated in gonadal impairment and may cause germinal aplasia and compromised Leydig cell dysfunction. Azoospermia or oligospermia may result, along with elevated plasma levels of follicle-stimulating hormone and luteinizing hormone (4-7). Testosterone levels may be normal (7, 8). Progressive germinal aplasia and azoospermia were noted in men treated with chlorambucil at cumulative doses of 400 mg or more with no recovery of spermatogenesis observed (9). Fairley and colleagues (10) found that 100 mg of cyclophosphamide taken daily for at least 6 months caused azoospermia in all 31 patients, with only 1 regaining spermatogenesis in less than 2 years.

Combination therapies have more profound effects on gonadal function. Sanders and associates (11) found that men treated with bone marrow transplantation and 200 mg/kg body weight of cyclophosphamide had normal luteinizing hormone levels, two thirds had normal follicle-stimulating hormone levels, and one third had spermatogenesis. Those receiving concomitant irradiation had normal luteinizing hormone levels but fewer of these patients had normal follicle-stimulating hormone levels and spermatogenesis. Other bone marrow transplantation survivors receiving cyclophosphamide and total body irradiation had elevated luteinizing hormone levels, normal testosterone levels, and normal potency with azoospermia, but needed longer follow-up to determine full recovery (12).

Shamberger and coworkers (13) found increased but reversible follicle-stimulating hormone and luteinizing hormone levels following combinations of doxorubicin, cyclophosphamide, and high-dose methotrexate in survivors of soft-tissue sarcomas. Recovery was more frequent in men under age 40 at the time of treatment. However, even in younger patients, the addition of radiotherapy to the thigh and abdomen caused persistent azoospermia, testicular atrophy, and elevated follicle-stimulating hormone levels 3 years after treatment.

Men who received MOPP therapy (mechlorethamine, vincristine, procarbazine, and prednisone) or MVPP therapy (mechlorethamine, vinblastine, procarbazine, and prednisone) with or without radiotherapy for testicular cancers, Hodgkin disease, and non-Hodgkin lymphomas had permanent germinal aplasia, testicular atrophy, azoospermia, and elevated follicle-stimulating hormone levels (4, 14-16). In most men, only one or two cycles of MVPP caused azoospermia, with minimal recovery (7, 8, 17). Increased luteinizing hormone and follicle-stimulating hormone levels after administration of MVPP and radiotherapy were evident in 80% to 95% of serum samples from survivors of Hodgkin disease 1 to 62 months after treatment (18). However, Chapman and colleagues (8) suggested that men with Hodgkin disease may have some evidence of gonadal impairment before therapy which may be related to genetic factors or metabolic disturbances from the disease itself.

Pelvic or abdominal radiotherapy also affects gonadal function. Damewood and Grochow (7) reported temporary azoospermia after 30 to 200 cGy (1 cGy = 1 rad) to the abdomen or pelvis with recovery time ranging from 1 to 38 months or more after radiation. Men who received 200 to 300 cGy recovered from azoospermia in 2 to 3 years or never recovered. Azoospermia after 400 to 600 cGy was associated with a 5-year recovery time, or lack of recovery (7, 19). Men who received mantle therapy without chemotherapy for Hodgkin disease were generally spared prolonged azoospermia (16). Some found, however, that "inverted Y" radiotherapy for Hodgkin disease caused 70% to 100% azoospermia even at low doses with testicular shielding (8, 20).

Another known complication of pelvic surgery with or without radiotherapy is erective dysfunction, which occurs when fibers of the pelvic autonomic plexus that affect the vasculogenic regulatory mechanisms of erection are damaged (21-27). Following radical prostatectomy or radical cystectomy, 85% of men were reported to have erectile dysfunction (24). Results of studies of men with Duke stage A, B, or C prostate cancer undergoing either retropubic (28-30) or perineal (29, 31-33) prostatectomy found up to 90% diminished capacity or erectile dysfunction after surgery. Younger men who have had an abdominal-perineal resection have a lower incidence of erectile problems and may have only partial impairment. However, they still are not able to attain the amount

Table 2. *Long-Term and Late Effects of Therapies for Adult Cancer Causing General Function, Extremity, Oropharyngeal, Ocular, Skeletal, Dermatologic, Endocrine, and Immunologic Problems**

Effects	Treatment	Duration, *y*	Time to Development, *y*	Reference
Decreased general functioning; decreased energy level	Chemotherapy with or without radiotherapy	1 to 21		167, 265
Upper and lower extremity problems				
Stiffness, weakness, decreased mobility	Pelvic surgery		Several	39, 63, 93
Lymphedema	Mastectomy	4		266, 267
Frozen shoulder	Mastectomy	1		90
Stump pain	Thoracotomy, amputation	≤ 1 to several		268
Oropharyngeal problems				
Swallowing disability	Glossectomy	Permanent†		92, 93
Impaired mastication	Laryngectomy			
Nasal regurgitation	Maxillectomy			
Decreased speech	Mandiblectomy			
Airway obstruction, decreased valsalva maneuver	Soft-palate resection			
Increased dental caries (alteration of saliva volume, viscosity, pH, electrolyte and immunoglobulin levels)	Laryngectomy, tracheostomy, radiotherapy to head-neck			268-270
Osteonecrosis	Radiotherapy to mandible, maxilla, or larynx		≤ 1 to several	271, 272
Ocular problems				
Cataracts	allopurinol, busulfan, steroids	≥ 1		273-275
	Single-dose TBI		1 to 12	276
Irreversible tear-duct fibrosis	5-fluorouracil		≤ 1	277, 278
Skeletal problems				
Late fractures	Radiotherapy		≤ 1 to several	21, 279
Asceptic osteonecrosis	Steroids		≤ 1 to several	89, 280
Dermatologic problems				
Persistent discomfort, induration, telangiectatic change	Radiotherapy	1 to 21		167
Pigmented excoriation, digital cutaneous ulcerations	bleomycin	≤ 1 to several		117
Dryness, lesions and plaques, abnormal pigmentation, hair, nails, mucous membranes	BMT		≥ 1	168
Monilial infection, dermatitis	Ostomy	≥ 1		93, 281
Other endocrine problems				
Increased thyroid-stimulating hormone; decreased thyroxine	Radiotherapy or BMT		≤ 6	117, 167, 282, 283
Immunologic problems				
Decreased reactivity to delayed type hypersensitivity	Radiotherapy	≤ 10		284
Depressed lymphocyte response	Radiotherapy	≤ 6		285

*TBI = total body irradiation; BMT = bone marrow transplant.
† May improve with rehabilitation measures.

or duration of rigidity necessary for successful penetration. If full recovery of erectile function occurs, it may take up to 1 year after surgery (25).

Other treatments such as bilateral orchiectomy or estrogen manipulations can result in erectile dysfunction accompanied by decreased libido, gynecomastia, and ejaculation difficulties. More than 80% of men receiving these treatments who were not fully potent before therapy completely lost potency after therapy (26). Partial penectomy for tumors of the glans, foreskin, head, or distal shaft reduces penile length which still may be sufficient for vaginal penetration (26, 34). Following total penectomy for urethral cancer, stimulation of the remaining genital tissue (including the mons pubis, perineum, and scrotum) can produce orgasm (35). Ejaculation can occur through the perineal urethrostomy accompanied by bulbocavernosus and ischiocavernosus contractions (34).

Ejaculatory difficulties commonly occur after retroperitoneal lymphadenectomy for testicular cancer staging. The sympathetic nerve fibers of the hypogastric plexus are damaged, resulting in failure of semen emission (25). The ejaculatory response still occurs, but ejaculate may be retrograde, scanty, or absent, causing infertility (25, 34). Erection, libido, and sensation of orgasm are unaffected (26). Cystectomy for bladder cancer also results in loss of semen with possible maintenance of ejaculatory contraction, although erectile capacity after this procedure is uncommon (26). Ejaculation difficulties were reported by 78% of retropubic and 100% of perineal prostatectomy survivors (28, 36). However, Walsh and colleagues (37) developed a technique (sparing the periprostatic cavernous neurovascular bundles) that preserves orgasmic and ejaculatory functions after radical retropubic prostatectomy. This procedure maintained potency in 60% of the patients, although the emission of semen was reduced because the prostate, seminal vesicles, and ampullae of the vas deferens were removed (37, 38). Simple prostatectomy results in retrograde ejaculation (39, 40).

Radiotherapy also causes erectile and ejaculatory difficulties, however, Andersen (40) indicated that the incidence of sexual complications after interstitial or external beam treatment is less than 50% of that reported after radical surgery. Others have indicated that radiotherapy caused impotence within a year after treatment in 23% to 84% of cases (21-23, 27, 41-43). This wide variation in incidence may be caused by different treatment techniques, degree of accuracy of patient reports, or the type and extent of questions asked during interviews (21). Twenty-five percent of survivors of prostatectomy with later radiotherapy were impotent (44) and although a higher rate of potency was maintained a marked reduction in frequency of sexual activity occurred (43).

Effects in Women

Ovarian destruction (elevation of serum follicle-stimulating and luteinizing hormones, decrease in circulating estradiol) has been documented in women who received single-agent and combination chemotherapy. Cyclophosphamide has produced perifollicular agenesis, ovarian fibrosis, and destruction of ova leading to premature ovarian failure (4, 10, 45, 46). This effect may be reversible in some patients and is age-related (47). Reversal of ovarian failure in women who had cyclophosphamide and total body irradiation before bone marrow transplantation is not known with certainty; however, women under age 26 had normal menstrual cycles and gonadotropin levels a median of 6 months later. Women over age 26 developed early menopause with elevated luteinizing and follicle-stimulating hormone levels (11, 12). Use of more traditional therapies such as vinblastine or MVPP has been associated with high levels of follicle-stimulating and luteinizing hormones as well as amenorrhea which can become progressively worse and may not be reversible in women over age 30 (48, 49).

The length of treatment is also a factor. Irreversible ovarian failure was reported in women who received six cycles of MOPP for Hodgkin disease (50). A greater incidence of amenorrhea and hormonal evidence of ovarian failure occurred, however, with longer treatment courses of MVPP (46). Other long-term effects of ovarian failure include loss of libido, hot flashes, insomnia, and irritability (48, 51).

Infertility after pelvic radiotherapy is dose- and age-related. Permanent infertility occurred in 60% of women aged 15 to 40 and in 100% over age 40 after 250 to 500 cGY treatment. Permanent infertility in women aged 15 to 40 occurred 70% of the time after receiving 500 to 800 cGy. Patients who received more than 800 cGy became irreversibly infertile (52). Thirty to seventy-five percent of women lost ovarian function after radiotherapy for Hodgkin disease, despite precautions such as oophoropexy (51-54). In contrast, 20 of 26 survivors of Hodgkin disease who received total lymphoid irradiation and were actively trying to achieve pregnancy did so (52). Women at greatest risk for ovarian failure are those treated with a combination of infradiaphragmatic radiation and chemotherapy. In this group, ovarian failure is usually permanent (4, 51).

In women, cancer treatments can cause sequelae that affect sexual functioning other than ovarian destruction. The vasocongestive mechanisms of genital arousal may be damaged by pelvic or vaginal radiotherapy or by oophorectomy. The resultant loss of estrogen levels decreases vaginal lubrication during the sexual excitement phase (25, 51) and dyspareunia due to vaginal fibrosis, atrophy, or stenosis often follows (25, 55-57). Additional problems include adhesion or fistula formation after external-beam pelvic radiotherapy (55-57). Fistulas as a complication of interstitial irradiation for cervical cancer result from a combination of physical trauma to the vaginal mucosa from radium applicators, direct radiation effect on the mucosa, and estrogen deprivation from radiation castration (58). Vaginal tenderness and postcoital bleeding may also follow these forms of radiotherapy (39, 56, 58, 59).

Vaginal shortening by one half to two thirds contributes to coital discomfort after radical hysterecto-

my, radical vulvectomy, and anterior exenteration for bladder carcinoma (25, 39, 40, 56, 60, 61). Removal of the distal one-third of the vagina usually destroys the sensory perception important in sexual foreplay (62). A study of women treated with wide local incision instead of vulvectomy for microinvasive disease found that all continued to be orgasmic during sexual activity, compared with those who experienced dyspareunia and loss of orgasmic ability after radical vulvectomy (60).

Women with recurrent cervical or vulvar cancer may have pelvic exenteration, and some reports indicate that sexual dysfunction following this procedure approaches 100% (61, 62). Andersen and Hacker (63) found that women who had subsequent vaginal reconstruction either maintained satisfactory sexual relations or had disruption in the frequency of activity, dissatisfaction with arousal, or problems with the reconstructed vagina (too short, too large, chronic discharge, dyspareunia, loss of sensation). Even after total pelvic exenteration and vaginectomy, however, the labia and clitoris were still able to respond in a normal physiologic manner (25). Women with (61) or without (64) clitoral or vulvar tissue achieved orgasm. Brown and colleagues (65) also reported that 27% of women had sexual desire with digital stimulation of their colostomy or perineal scar tissue.

Neurologic Effects

Acute or chronic toxicity from chemotherapy or radiotherapy or surgical complications can lead to long-term neurologic problems in survivors. Neuropathy is common following vincristine therapy, and if several doses have been given during the course of treatment, deep tendon reflexes may be permanently lost (66, 67). A more serious problem is failure of complete resolution of foot or wrist drop which leads to troublesome motor difficulties, including a slapping gait. Severe irreversible paresthesias and ataxia have also been reported after hexamethylmelamine, cisplatin, and melphalan for ovarian cancer (68).

Chemotherapy also affects the autonomic nerves and hearing functions. Livingston and coworkers (69) reported chronic orthostatic hypotension occurring 6 years after cyclophosphamide, doxorubicin, and vincristine therapy followed by radiotherapy. High-tone hearing loss (4000-8000 Hz) after cisplatin (10 to 100 mg/m^2 body surface area) may not be reversible (70, 71).

Persons irradiated for tumors of the pituitary, ethmoid sinus, or nasal cavity developed optic atrophy and progressive visual loss presenting years after treatment (67, 72). Goepfert and associates (73) described retinal and optic damage resulting in permanent blindness 11 and 20 months after radiotherapy and intra-arterial 5-fluorouracil therapy. Retinal toxicity causing cone dysfunction was documented in a small group of patients with ovarian cancer who received high doses (200 mg/m^2) of cisplatin. Their visual acuity improved off treatment; however, abnormalities of color vision persisted as long as 16 months (74). Rare retinopathy was reported in women with breast cancer who received low-dose tamoxifen (30 mg). Retinal lesions remained unchanged when treatment was discontinued (75). Permanent palsies of the tenth, eleventh, and twelfth cranial nerves were described in individuals with oral, nasopharyngeal, and laryngeal tumors 12 to 145 months after radiotherapy (76).

Delayed radiation necrosis can occur 3 months to several years after therapy to the brain (67). Necrosis occurs after direct radiotherapy to the brain or, rarely, to an extracranial lesion (67, 77). Clinical symptoms may increase in severity, mimicking signs of a brain tumor. Recovery depends on the extent and location of the lesion and whether it can be surgically resected (67). Delayed leukoencephalopathy, a progressive degenerative process involving cerebral white matter, has been reported following brain irradiation with or without chemotherapy in long-term survivors of small cell lung cancer (78), primary brain tumors, breast cancer, acute leukemia, and central nervous system lymphoma (79). This complication has occurred as late as 4 years after treatment and may be more prevalent in older persons (78, 80). Radiotherapy doses ranged from 3000 to 5000 cGy in various fractions. Potentially neurotoxic chemotherapies used were intravenous cyclophosphamide, vincristine, cisplatin, lomustine, doxorubicin, or carmustine. In addition, methotrexate or cytarabine administered via intravenous, intracarotid, intrathecal, or intraventricular routes have also been associated with delayed leukoencephalopathy (79, 81-83). Early symptoms of apathy and abulia may occur as early as 6 months after treatment, followed by memory loss, gait ataxia, corticospinal tract signs, seizures, and eventual frank dementia (78, 83). Computed tomographic (CT) scanning or magnetic resonance imaging may detect white matter abnormalities that are present before clinical symptoms (78, 79, 84, 85). Computed tomographic scan changes in the form of mild cerebral atrophy and ventricular dilatation may precede symptoms. Seventy-five percent of survivors of small cell lung cancer who received prophylactic cranial irradiation had CT scan changes (83, 84, 86). Transient focal neurologic symptoms have occurred months to years after prophylactic cranial radiation therapy combined with chemotherapy (83, 87).

Delayed radiation myelopathy is commoner and occurs months to years after therapy to the spinal cord (88). Radiation myelopathy is characterized by sensory changes in the lower extremities that gradually involve the trunk and upper extremities in an asymmetric manner (88, 89). Muscle weakness may follow or, more seriously, para- or quadriparesis with bowel or bladder dysfunction. These complications can lead to death within 1 to 2 years (67, 88).

Fibrosis of the connective tissue surrounding the brachial plexus with secondary nerve injury can occur from 16 months to 20 years after radiotherapy. Symptoms depend on which portion of the brachial plexus is involved and may progress to complete arm disability. Lower plexus involvement may mimic ulnar neuropathy (90). Radiation fibrosis of the lumbar plexus can cause persistent motor and sensory changes in the leg

(90). Radiation-induced nonmalignant peripheral nerve tumors have been reported in lumbar, brachial, and cervical plexus sites 4 to 20 years after therapy (90, 91).

Excision of the sternocleidomastoid muscle; spinal accessory nerve; and C3, C4, and C5 plexus during radical neck dissection paralyzes the trapezius, which causes shoulder drop and scapular winging. These, in turn, lead to long-term shoulder pain; or the inability to push, lift, or carry heavy objects; or the inability to reach (89, 92, 93). Modified neck dissection spares the sternocleidomastoid and nerve structures but nerve damage may cause weakness of the trapezius which can last for as long as 18 months after surgery (92).

Post-herpetic neuralgia appears to be commoner in persons who developed the initial infection after age 50 (89). This persistent pain is often severe, disabling in nature, and difficult to treat (94).

Vascular Effects

Survivors who received radiotherapy to the head and neck regions are at risk for serious or fatal strokes long after treatment has been completed. Those affected may (95) or may not (96) have a predisposition to atherosclerosis or be in the age group commonly affected by the disease. The factors affecting development of arterial disease in cancer survivors have not been clearly identified (97-99), but total dosage, fractionation schemes, and local tissue factors have all been suggested (95, 96, 100). Radiotherapy can damage the large elastic arterial vessels causing stenosis or occlusion. The pathologic lesion may be similar to atherosclerosis (96, 101, 102), although other investigators have found medial thickening or fibroblastic changes (95, 98, 101). The arterial lesion is usually limited to the irradiated area (96, 99, 103).

These changes predispose to a neurologic event and a "delayed stroke" may occur. Patients receiving 4000 to 8200 cGy are at risk (95, 102, 104), and the neurologic event may occur up to 16 years after completion of treatment for Hodgkin disease (95, 96, 99), head and neck cancers (96, 103, 105), breast cancers (96, 103), and primary brain tumors (106). Clinical symptoms may mimic those caused by atherosclerosis not related to radiotherapy (102). Transient ischemic attacks including amaurosis fugax have been reported in patients with subsequent cerebral infarction (96, 102). Nonembolic cerebrovascular effects in the form of fatal foam-cell arteritis of the brain was reported 5 years after cervical radiotherapy for Hodgkin disease (107).

Possible transient ischemic attacks have also been reported in survivors of Hodgkin disease who received primarily MOPP therapy and mantle radiotherapy. The interval between therapy and the development of neurologic symptoms was usually greater than 1 year and patients tended to be younger than nonirradiated patients with atherosclerotic cerebrovascular disease (96, 97). Feldmann and Posner (97) also reported relatively benign transient neurologic episodes in survivors of Hodgkin disease. They felt that these events were most likely transient ischemic attacks but did not identify specific cerebrovascular lesions.

Radiation damage to the aortic arch may be a source of emboli that cause intracerebral neurologic symptoms (97, 108). Chronic fibrous obstruction of the aortic arch can cause ocular symptoms of decreased vision and cerebral symptoms of numbness and weakness (108). Radiation therapy may also produce valvular or endocardial damage that are sources of cerebral emboli (97).

Peripheral vascular disease after pelvic radiotherapy is uncommon, but iliofemoral obstruction has been seen in survivors of uterine and cervical carcinoma (99, 101, 109) and in male survivors irradiated for bone cancer (101) and head and neck cancer pelvic metastases (110). Occlusive disease was limited to the irradiated field (101, 111). Narrowing of the digital vessels after bleomycin, vinblastine, or cisplatin administration caused Raynaud phenomenon, which persisted chronically in a few cases after therapy cessation (112, 113). Subclavian artery claudication after treatment for breast cancer has also been reported as long as 36 years after radiotherapy (101, 109, 114).

Cardiac Effects

Anthracycline use has most often been associated with chronic cardiomyopathy, although this problem can be an uncommon toxic effect from other antineoplastic agents (115). Chronic cardiomyopathy after the administration of the anthracyclines doxorubicin or daunorubicin may occur as long as 2.5 to 7 years after therapy (116-118). Pathologic changes of myofibrillar and vacuolar degeneration (with subsequent mitochondrial degeneration) begin well before clinical signs and symptoms of cardiomyopathy (119, 120). Cardiomyopathy resulting from these drugs is dose-dependent, with an incidence of 3.5% after 400 mg/m^2, 7% after 550 mg/m^2, and 18% after 700 mg/m^2 of doxorubicin (119). For daunorubicin, the incidence of cardiomyopathy is 1.5% after 600 mg/m^2 and 12% after 1000 mg/m^2 (121). Cardiotoxicity appears to be less in patients who received doxorubicin weekly or via every-3-week dosing (115, 119, 122-124) and in those who received the drug by infusion rather than bolus (124, 125).

The effect of daunorubicin scheduling on cardiotoxicity development is largely unknown (115). Concomitant treatment with vincristine, bleomycin, cyclophosphamide, and dacarbazine may potentiate cardiac damage (124, 126, 127), but others did not consider doxorubicin and dacarbazine to be synergistic (128). Use of mitoxantrone in persons previously receiving anthracyclines may potentiate congestive heart failure and a decrease of ejection fraction (129, 130). Use of doxorubicin and radiotherapy may augment radiation injury to the myocardium (131), although some have found the effects to be additive but not sensitizing or enhancing (132). Most electrocardiographic changes related to doxorubicin administration appear reversible with the exception of a decrease in QRS voltage after five or more courses (115, 133). Saini and coworkers (134) recently described three cases of severe

doxorubicin-related left ventricular dysfunction that were completely reversible after treatment with digoxin, furosemide, and captropril.

The pericardium is also susceptible to radiation-induced damage with the hallmark injury expressed as myocardial fibrosis (135). Damage appears to progress for several years after cessation of radiotherapy, and effects are related to dose schedule, therapy duration, and field size. Most survivors with radiation-induced cardiac disease are asymptomatic (136). Cardiac damage may be in the form of low left ventricular ejection fraction, subclinical cardiomyopathy, coronary artery obstruction, and pericardial effusion (137-142). Pericardial effusion occurs commonly but may spontaneously resolve (136).

Late cardiac effects of radiotherapy are well-documented in survivors of Hodgkin disease and clinical effects may appear from 6 months to 30 years after radiotherapy (136). Gomez and colleagues (137) found that 55 of 96 survivors 3 to 10 years after mediastinal radiotherapy (midcardiac doses of 3500 cGy) had a decreased left ventricular ejection fraction and decrease in transverse heart diameter and cardiothoracic ratio when compared with nonirradiated controls. Annest and associates (139) reported obstruction of the proximal right coronary artery and proximal left anterior descending coronary artery in 5 of 29 long-term survivors of Hodgkin disease who had received 1500 to 3000 cGy exposure to the heart. All required coronary bypass as treatment. Myocardial infarction has also been reported in young adult survivors 5 years after radiotherapy (143-145). Aortic insufficiency has been documented after treatment with 4200 cGy for mediastinal involvement (146). Echocardiography, radionuclide angiography, fluid challenge, or cardiac catheterization has been used to detect cardiac abnormalities of diminished left ventricular cavity size, pericardial effusion, and decreased left ventricular function and functional reserve, 5 to 15 years after 4000 cGy of mediastinal radiation (138, 142, 145). Symptomatic pericarditis occurred in 50% of survivors within 6 to 34 months after receiving 3000 or more cGy (140, 142, 145).

Pulmonary Effects

Chemotherapy or radiotherapy or both can result in long-term or late pulmonary damage, most commonly in the form of diffuse alveolar damage, pneumonitis, and interstitial pulmonary fibrosis. Bleomycin, carmustine, and cyclophosphamide toxicity has been described, but is infrequent and most often acute in nature. Symptoms may develop from 1 to 3 months after therapy, and toxicity has been reported up to 8 years after treatment (147). Pulmonary function tests indicate hypoxemia and ventilation-perfusion dysfunction (147, 148). Most patients with pneumonitis will eventually develop pulmonary fibrosis with resultant chronic pulmonary insufficiency (149). Pulmonary veno-occlusive disease, an infrequent cause of pulmonary hypertension, has been reported after treatment with bleomycin and mitomycin C, which may have a direct effect of narrowing or occluding the smaller pulmonary veins (150, 151). Most individuals with pulmonary veno-occlusive disease die within 2 years of symptom onset (151).

Fibrosis induced by bleomycin or carmustine may have associated morbidity as high as 11% (135, 152-156). The incidence of pulmonary damage is related to the cumulative dose of drug administered and increases with patient age (135, 157). Bleomycin total doses lower than 150 mg/m^2 indicated no pulmonary disease (158), whereas morbidity was increased among patients who received more than 359 mg/m^2 (159). Toxicity at lower doses, however, can occur (147, 148). Cumulative carmustine doses ranging from 580 to 2100 mg/m^2 rarely cause pulmonary fibrosis (148). Cyclophosphamide toxicity does not appear to be dose- or schedule-dependent, and has been reported after doses ranging from 150 mg to 80 g (147). Individuals who received both cyclophosphamide and bleomycin may be more prone to bleomycin pulmonary toxicity (147). Chlorambucil, mitomycin C, and teniposide have also been associated with late, and possibly fatal, pneumonopathy (135, 147).

A less common pulmonary problem related to chemotherapy is a synergistic reaction of previous mitomycin and bleomycin therapy and a high concentration of inspired oxygen during surgery. Low oxygen concentrations are recommended for anyone with a history of receiving these drugs (148, 160). Non-Hodgkin lymphoma survivors may also have increased propensity to develop severe reactions to bleomycin (147). In addition, antitumor antibiotics, particularly bleomycin and actinomycin D, are thought to enhance radiation injury to the lung when they are used simultaneously or sequentially (131, 148).

Lung irradiation results in similar long-term and late effects, some of which may be seen in survivors of Hodgkin disease, non-Hodgkin lymphoma, and carcinoma of the lung, breast, esophagus, and mediastinum (135, 161). After initial radiation injury, clinical symptoms resulting from alveolar type II cell injury may appear 1 to 3 months later. Fibrosis involving the alveolar walls and endothelial damage may not occur until 3 to 6 months after radiotherapy (135, 162, 163), and progression may be insidious over 1 to 2 years. The permanent changes of fibrosis usually remain stable after 2 years (161, 164).

Fibrosis within the lungs, pleura, and mediastinum causes secondary pleural effusion or spontaneous pneumothorax, bronchiectasis, and airway, vascular, and esophageal anatomy distortion (165). Reduction in lung volume may cause mediastinal shift toward the irradiated side along the tracheal deviation (161, 163, 165). Reduced lung compliance leads to decreased vital capacity (166).

The occurrence of radiation pneumonitis and fibrosis depends on the volume of lung involved and the dose delivered (161). Doses greater than 2000 to 3000 cGy are needed for significant fibrosis (163), which is less likely to occur after irradiation of small lung volumes and the apical regions (161, 163). Slanina and colleagues (167) reviewed 135 survivors of Hodgkin

disease who had received 3000 to 4000 cGy and found paramediastinal fibrosis which was slight in 44%, distinct in 36%, and severe in 9%. Other pulmonary complications in that group included restrictive ventilation (84%), oxygen-diffusion (18%), and obstructive ventilation (7%) disorders and increased residual volume (61%).

A significant number of survivors of allogenic or syngeneic marrow transplantation cured of their primary disease developed sinopulmonary infections and restrictive or obstructive pulmonary disease up to 4 years later (168, 169). These pulmonary complications were not a result of total body irradiation or the presence of chronic graft-versus-host disease (168).

Urologic Effects

Late nephrotoxicity from chemotherapy and or radiotherapy may be in the form of extensive glomerular sclerosis, tubular atrophy, and necrosis of the arterioles, characterized by progressive renal failure, fall in glomerular filtration rate, rising creatinine, azotemia, proteinuria, hypertension, and anemia (135, 149, 170-173).

Nitrosoureas have been associated with delayed renal failure. Onset of progressive nephrotoxicity has been reported 2 years after cessation of lomustine therapy for oat cell carcinoma (173) and months to years after semustine or carmustine administration (170-174). Nichols and Moertel (175), however, found that the incidence of renal insufficiency was low after low doses of semustine.

Cisplatin affects the kidney's ability to reabsorb magnesium, causing hypomagnesemia (170). Without adequate hydration during treatment, this defect may persist for years after discontinuation of therapy (176). With more vigorous hydration, cisplatin can be safely administered at doses of 50 mg/m^2 or more, virtually eliminating nephrotoxicity (74, 177). A moderate and permanent reduction in glomerular filtration rate with no signs of long-term tubular defects occurred in testicular cancer survivors treated with cisplatin (178). Groth and associates (179) studied the effects of cisplatin in patients with testicular cancer and found that glomerular filtration rate did not decrease until after 2 months of treatment, with significant progressive decrease during the first year after initiation of treatment. A significant increase in serum creatinine was not observed until 6 months later. Use of mitomycin-C with 5-fluorouracil rarely may lead to renal failure with microangiopathic hemolytic anemia up to a year after treatment (117, 170, 180-183).

Radiation affects the kidneys in the form of delayed radiation nephritis which may be acute or chronic in nature (135, 170). The acute form may occur within 6 to 13 months after therapy whereas chronic radiation nephritis may develop 18 months to several years later. Use of actinomycin D and vincristine, and vinblastine and bleomycin concomitantly with radiotherapy may hasten development of radiation nephritis (131, 184).

A bladder complication of hemorrhagic cystitis after cyclophosphamide administration is caused by the acrolein by-product of the drug along with inadequate hydration during treatment (149). This effect may be so severe that a cystectomy is necessary (170); however, concomitant administration of ifosfamide may prevent the occurrence of cystitis (149). Cyclophosphamide administered with radiotherapy may augment injury to the bladder (131).

Chronic cystitis and urinary diversion complications have also been reported infrequently after radical prostatectomy alone (33, 185, 186) or 5% to 27% of the time after radical perineal prostatectomy and radiotherapy (23, 187). Long-term bladder symptoms have been reported 5 to 11 years after radiotherapy alone for cervical cancer. Urgency and stress incontinence occurred in 45% of patients and significant frequency and nocturia in 35% (188).

Gastrointestinal Effects

Hepatotoxicity from cancer treatments ranges from transient enzyme elevations to permanent cirrhosis (189). Long-lasting or permanent liver injury caused by chemotherapy is uncommon and most often acute. Nitrosourea chemotherapies may produce severe and fatal damage (135). Carmustine administration caused increased serum transaminase or alkaline phosphatase levels which were delayed up to 127 days, and slowly returned to normal (190, 191). Other chemotherapies such as L-asparaginase or methotrexate caused persistent fatty metamorphosis up to 261 days after treatment (191-193) or delayed portal fibrosis or cirrhosis (117, 190, 191, 194). Azathioprine, cytarabine, and 6-mercaptopurine caused hepatic occlusive disease and necrosis or precipitated late biliary stasis which eventually resolved (149, 190, 191). Initial administration of dacarbazine may sensitize the liver and rechallenge can cause massive necrosis and hepatic veno-occlusive disease (193).

Radiation causes hepatic central vein thrombosis, leading to liver veno-occlusive disease and secondarily damaging hepatocytes (135). Acute changes may lead to progressive fibrosis and cirrhosis (195). Fibrosis of intrahepatic and extrahepatic biliary ducts may also cause obstruction which is difficult to distinguish from recurrent tumor. This fibrosis has been reported 5.5 to 30 months after therapy (196).

Progressive endoarteritis is the hallmark late lesion occurring in the gastrointestinal tract after radiotherapy and leading to bowel fibrosis, stricture, and ulcerations. Operative repair of adhesions years after radiotherapy can interfere with blood supply and lead to infarction necrosis (135, 197).

Other gastrointestinal problems may occur with combination therapies. Following radical perineal prostatectomy and radiotherapy, long-term complications of chronic proctitis, fistula formation, and rectal incontinence were reported 5% to 27% of the time, compared with a 6% occurrence of only fistula formation after surgery alone (187). Late intestinal fistulization and necrosis was reported in 29% of survivors of colorectal cancer 6 months to 2 years after radiothera-

py and 5-fluorouracil and semustine (198).

Delayed enteritis may develop after radiotherapy and actinomycin D or cisplatin, or treatment with 5-fluorouracil, hydroxyurea, methotrexate, and procarbazine (135). Severe, chronic esophagitis after radiotherapy and doxorubicin or cyclophosphamide may occur months to years later (117, 135). Chronic aspiration may be a late effect of bone marrow transplantation, particularly when the affected survivor has chronic graft-versus-host disease associated with esophageal disease (169).

Persons who have received intraperitoneal therapy with cis-platinum for ovarian, colon, and endometrial cancers, and mesothelioma, developed late intestinal obstruction due to extensive adhesion formation (199). Delayed bowel obstruction and intestinal adhesions have also been reported after radiotherapy and hexamethylmelamine, melphalan, and cisplatin therapy for ovarian cancer (68).

Oncogenesis

Survivors may be at risk for second malignancies resulting from primary cancer therapy. The potential development of second malignancies does not contraindicate the use of cancer therapy because the overall risk of neoplastic complications is low. Few deaths related to second malignancies are reported yearly, whereas over 462 000 deaths occur annually from cancer (3, 200-202). However, the potential for second cancers can be worrisome because the latency period of development may be as long as 50 years (203). Second malignancies are a serious sequelae of some cancer therapies, particularly those involving alkylating agents with or without radiotherapy.

Alkylating agents implicated include melphalan, cyclophosphamide, procarbazine, chlorambucil, and azathioprine (204). Radiation carcinogenesis is more likely to occur after high doses, inducing cancers at sites of exposure several years after therapy (200, 205). The mechanism of oncogenesis after radiation and cytotoxic drugs remains unclear, and could relate to interactions between immunosuppressive factors, direct cellular damage produced by fibrotic tissue changes, or cocarcinogenic effects with other environmental carcinogens (200, 203, 206).

Leukemias

Second malignancies occurring in large series of cancer survivors are summarized in Table 3. Acute leukemias as second malignancies are most commonly reported in Hodgkin disease, with cited odds-expected ratios and relative risks for all treatment ranging from 57 to 136. However, survivors of ovarian (3, 223-226), lung (227-229), and breast (230-232) cancers are also at risk. Prevention of leukemias via therapy changes or manipulations may be the best treatment because leukemias tend to progress rapidly, exhibit a large proportion of chromosomal aberrations, and respond poorly to standard therapy (117, 203).

Acute nonlymphocytic leukemia, with cited risks of 6% to 12% (actuarial risk), 5% to 13% (cumulative risk), and 96 to 130 (relative risk), is most often reported in survivors of Hodgkin disease who received MOPP or MVPP (208, 221, 222, 234). Survivors of Hodgkin disease who received radiotherapy in addition to MOPP had an even greater risk of leukemia development (6% to 75% actuarial risk; 58 to 253 relative risk) (207-209, 212-214, 216, 217, 219, 221, 234). Comparatively, use of ABVD (doxorubicin, bleomycin, vinblastine, dacarbazine) or PAVe (procarbazine, melphalan, vinblastine), with or without concomitant radiotherapy, was associated with a decreased risk of acute nonlymphocytic leukemia (219, 233, 234). Survivors of Hodgkin disease who received only intensive radiotherapy as primary treatment have also developed acute leukemias, but appear to be at much lower risk (odds-expected ratio, 2 to 11) than those who received adjuvant chemotherapy or chemotherapy alone (207, 210, 215, 217, 219, 234). Recent studies indicated that the peak incidence of acute leukemias occurs 6 years after therapy, with few cases reported after 10 years (221, 222).

Acute leukemias have also been reported in women treated with dihydroxybusulfan, cyclophosphamide, nitrogen mustard, chlorambucil, thio-TEPA, or melphalan for ovarian cancer (223-226). Greene and coworkers (226) found a 93-fold increase in acute nonlymphocytic leukemia in women treated with alkylating agents; those treated with melphalan were 2 to 3 times more likely to develop leukemia than those who received cyclophosphamide.

In survivors of small cell lung cancer, acute myelogenous leukemia has been shown after radiotherapy of 550 cGy and cyclophosphamide, lomustine, and methotrexate (227). Acute nonlymphocytic leukemia was also reported after radiotherapy and cyclophosphamide, doxorubicin, etopside, carmustine, vincristine, and procarbazine 2 or more years later (229). Leukemias in survivors of small cell lung cancer may be preceded by preleukemic sideroblastic anemia and pancytopenia (228, 229).

The rate of leukemia after common treatments for breast cancers such as FAC (5-fluorouracil, doxorubicin, cyclophosphamide) and radiotherapy and CMF (cyclophosphamide, methotrexate, 5-fluorouracil) is lower than that reported after other primary malignancies (231, 232, 235). Women treated with intracavitary radium or external beam radiotherapy for cervical cancer also have not had significant excess leukemias (236-238). Isolated cases of acute nonlymphocytic leukemia after bladder instillations of thio-TEPA have also been described with a latency period of 4 to 27 years (239, 240).

Other Second Malignancies

Second malignancies other than leukemia have also been documented. Multiple myeloma has been diagnosed in women 6 years after surgery and radiotherapy for breast cancer (241). Non-Hodgkin lymphoma has occurred in survivors of Hodgkin disease (217-234, 242, 244). List and associates (243) suggested

Table 3. *Second Malignant Neoplasms Related to Cancer Treatments Cited in Large Series Reported since 1980 Comprising More than 150 Patients* [a]

Primary Cancer	Reference	Treatment	Patients, *n*	
			Total	With Second Malignant Neoplasms
Hodgkin disease	217	All treatments	1222	59
		Radiotherapy	501	27
		Radiotherapy and chemotherapy	677	30
		Chemotherapy	44	2
Hodgkin disease	208	All treatments	659	32
		Radiotherapy	95	1
		MOPP	102	5
		MOPP and radiotherapy	283	16
		Salvage chemotherapy	179	10
Hodgkin disease	218	All treatments	798	27
		chlorambucil and mechlorethamine		
		chlorambucil		
		Chemotherapy and radiotherapy		
Hodgkin disease	244	All treatments	334	21
		Radiotherapy with or without vinblastine	176	7
		Radiotherapy with or without vinblastine [j]	104	4
		Radiotherapy with or without MOPP or MAC [j]	54	10
Hodgkin disease	215	All treatments	2591	74
		No intensive therapy	1394	41
		Intensive radiotherapy, no intensive chemotherapy	696	15
		Intensive chemotherapy, no intensive radiotherapy	360	13

Table 3. *(Continued)*

Type and Number of Second Malignancies	Years after Diagnosis of First Malignancy		Risk Rate
	Median	Range	
All types		0.7 to 12.4	9.9% (AR)[b], 5.41 (OE)
Solid tumors (32)	5.6	0.7 to 11.3	5.9% (AR)[b], 3.13 (OE)
Acute leukemias (23)	4.5	1.3 to 8.7	3.5% (AR)[b], 69.6 (OE)
Non-Hodgkin lymphoma (4)		3.5 to 12.4	0.5% (AR)[b]
			5.12 (OE)[c]
Solid tumors (20)	5.4	0.7 to 9.7	4.04 (OE)[d]
Non-Hodgkin lymphoma (2)	Not given		0.9% (AR)[b]
Acute leukemias (5)	5		Not given
	Not given		6.17 (OE)[c]
Solid tumors (12)	5.7	1.1 to 11.3	2.63 (OE)[e]
Acute leukemias (16)	5		Not given
Non-Hodgkin lymphoma (2)	Not given		0.7% (AR)[b]
Acute leukemias (2)			15.6% (AR)[b]
		1.6 to 7.5	Not given
Acute leukemias (21)			
Solid tumors (11)			
Solid tumor	Not given		0% (AR)[f]
			Not given
Acute leukemias (3)			6.2% (AR)[f]
Solid tumors (2)			
	Not given		Not given
Acute leukemias (11)			6.4% (AR)[f]
Solid tumors (5)			
	Not given		Not given
Acute leukemias (7)			7.7% (AR)[f]
Solid tumors (3)			
Acute leukemias (10)	6		133 (RR)[g], 5.6% (LE)[g]
Solid tumors (17)	7.5		2.2 (RR), 9.4% (LE)
Acute leukemias (5)	Not given		691 (RR), 26.2% (LE)
Acute leukemias (3)	Not given		234 (RR), 9% (LE)
Other (11)	Not given		3.3 (RR)[h]
All types	10	2 to 16	4.55 (OE)[b,g], 13.2% (AR)[i]
	10	2 to 16	2.16 (OE), 5.5% (AR)[i]
Breast (2)			
Esophagus (1)			
Basal cell (1)			
Non-Hodgkin lymphoma (1)			
Testicular (1)			
Acute leukemia (1)			14 (OE)
		4 to 11	3.60 (OE), 11.6% (AR)[i]
Basal cell (1)			
Esophagus (1)			
Parotid (1)			
Bronchus (1)			
		0 to 15	32 (OE)[g], 38.3% (AR)[i]
Acute leukemias (3)			
Non-Hodgkin lymphoma (2)			
Bladder (1)			
Basal cell (1)			
Bronchus (1)			
Melanoma (1)			
Multiple (1)			300 (OE)[g]
All types		1 to 38	
Acute leukemias (21)			136 (RR)
Solid tumors (53)			
		1 to 38	
Solid tumors (34)			1.8 (OE)[l], 19.5 (RR)
Acute leukemias (7)			2.0 (OE)
		1 to 38	
Solid tumors (12)			2.1 (OE)[l], 25.0 (OE)[m]
Acute leukemias (3)			7.0 (OE)
		1 to 38	
Solid tumors (5)			1.8 (OE)[l]
Acute leukemias (8)			140 (RR)

(Footnotes defined on page 426)

(Continued)

Table 3. *(Continued)*

Primary Cancer	Reference	Treatment	Patients	
			Total	With Second Malignant Neoplasms
		Intensive radiotherapy and intensive chemotherapy	141	5
Hodgkin disease	255	Radiotherapy and MOP or ABVD	1405	6
Hodgkin disease	220	All treatments	529	27
		Radiotherapy	146	6
		MVPP	192	6
		MVPP and radiotherapy	49	1
		Other	194	14
Hodgkin disease	246	All treatments	320	23
		Radiotherapy	129	10
		Radiotherapy and MAC	135	9
		MOPP	69	5
		Non-MOPP	66	4
		Radiotherapy and SAC	32	2
		SAC or MAC	0	0
Hodgkin disease	221	MOPP with or without radiotherapy	192	29
Hodgkin disease	222	Alkylators (MOPP, MOPP-like) with or without radiotherapy	391	34
		Alkylators alone	320	Not given
Hodgkin disease	234	All treatments	1507	83
		Radiotherapy	535	23
		Radiotherapy and ABVD or MOPP or PAVe or VBM	648	38
		Radiotherapy and MOPP	179	6
		Radiotherapy and MOPP and gold	Included in radiotherapy and MOPP	8

Table 3. *(Continued)*

Type and Number of Second Malignancies	Years after Diagnosis of First Malignancy		Risk Rate
	Median	Range	
		1 to 38	
Solid tumors (2)			3.3 (OE)[l]
Acute leukemias (3)			125 (RR)
Melanoma	4.5	1 to 13	8.0 (RR)[n], 3.3% (CR)[o]
All types		1 to 15	3.5 (OE)[g]
Solid tumors (18)	Not given		2.5 (OE)[g]
Acute leukemias (5)	5		57 (OE)[g]
Non-Hodgkin lymphoma (4)			32 (OE)[g]
All types [p]	8	1 to 15	2.6 (OE), 4% (AR)[b]
Bladder (1)			5.2 (OE)[q]
All types [p]	6	2 to 10	0.9 (OE), 6% (AR)[b]
Penis (1)			100 (OE)[r]
Unknown primary	7		1.7 (OE), 12% (AR)[b]
All types [p]	7	1.4 to 13	7.4 (OE)[c], 20% (AR)[i]
Acute leukemias (5)	5		57 (OE)[c]
Bladder (1)			5.2 (OE)[q]
Thyroid (1)			25 (OE)[s]
Osteosarcoma (1)			50 (OE)[t]
Kaposi sarcoma (1)			31 (OE)[u]
All types	7	1.3 to 16.1	4.76 (OE)[s]
Solid tumors (21)			
Acute leukemias (2)			
Not given		1 to 11	3.73 (OE)[s], 2.5% (AR)[b]
Not given		1 to 15+	7.10 (OE)[s]
Not given		5 to 15+	13.89 (OE)[s], >75% (AR)[v]
Not given		1 to 15+	4.41 (OE), 22% (AR)[o]
Not given		1 to 15+	8.33 (OE)
0	0		0
All types		1 to 13	
Leukemias (12)	6	2 to 11.6	10% (CR)[b], 96 (RR)
Solid tumors (17)	Not given		Not given
Acute leukemias (20)			
Lung (4)		1.3 to 10.4[w]	5.2% (CR)[b]
Gastrointestinal (3)			
Gynecologic (2)			
Renal (1)			
Sarcoma (1)			
Breast (1)			
Larynx (1)			
Skin (1)			
Acute leukemias (above)		2 to 10	13% (CR)
All types			5.2 (OE), 17.6 (AR), 72.6 (AbR)[i]
Acute leukemias (28)			3.3% (AR), 29.9 (AbR), 66 (OE)
Non-Hodgkin lymphoma (27)			1.6% (AR), 9.2 (AbR), 18 (OE)
Solid tumors (46)			13.2% (AR), 34.1 (AbR), 3.2 (OE)
		0.4 to 14.3	Not given
Solid tumors (16)			2.8 (OE), 7.0% (AR)[i]
Non-Hodgkin lymphoma (5)			21 (OE), 3.5% (AR)[i]
Acute leukemias (2)			11 (OE), 0.6% (AR)[i]
		0.4 to 14.3	Not given
Acute leukemias (18)			117 (OE), 4.9% (AR)
Solid tumors (16)			4.4 (OE), 11.7% (AR)
Non-Hodgkin lymphoma (4)			22 (OE), 0.9% (AR)
		0.4 to 14.3	Not given
Solid tumors (4)			3.7 (OE), 16.5% (AR)
Acute leukemias (2)			58 (OE), 1.8% (AR)
		0.4 to 14.3	Not given
Solid tumors (5)			22 (OE), 35% (AR)
Acute leukemias (3)			253 (OE), 12.3% (AR)

(Footnotes defined on page 426)

(Continued)

Table 3. *(Continued)*

Primary Cancer	Reference	Treatment	Patients	
			Total	With Second Malignant Neoplasms
		Radiotherapy and gold	65	4
		MOPP	80	4
Breast	231	All treatments	8483	43
		Radical, total or segmental mastectomy	2068	3
		Total or segmental mastectomy and radiotherapy	1116	6
		Surgery and L-PAM and 5-FU with or without methotrexate with or without tamoxifen with or without cyclophosphamide	5299	34
Breast	232	All treatments	983	19
		Surgery and radiotherapy	186	9
		Surgery and FAC or FAC with or without radiotherapy	797	10
Breast	264	Simple excision and radiotherapy	300	1
Uterine cervix	236	Radiotherapy	497	108
Uterine cervix	253	All types	763	44
		Radiotherapy ($\leq$ 3000 cGy and radium)	350	21
		Radiotherapy ($>$ 3000 cGy and radium)	375	20
Uterine cervix	238	All treatments	7127	528
		Radiotherapy	5997	449
		Surgery with or without chemotherapy with or without hormones	1130	79

Table 3. *(Continued)*

Type and Number of Second Malignancies	Years after Diagnosis of First Malignancy		Risk Rate
	Median	Range	
Solid tumors (4)			7.0 (OE), 21.9% (AR)
		0.4 to 14.3	
Acute leukemias (3)			130 (OE), 11.5 (AR)
Solid tumor (1)			1.1 (OE), 5.5% (AR)
	Not given		Not given
Acute leukemias (32)			
Myelodysplastic syndrome (7)		4 to 4.8	
Chronic myelogenous leukemias (4)			
Acute leukemias	4.2	3.8 to 5	0.06% (CR)[b], 1.5 (RR)
Acute leukemias (4)	6.6		1.37% (CR)[b]
Chronic myelogenous leukemias (2)			6.1 (RR)[s]
	4.2		
Acute leukemias (26)			1.11% (CR)[b]
Myelodysplastic syndrome (7)			11.0 (RR)[r]
Chronic myelogenous leukemia (1)			
		0 to 5.2	Not given
Gynecologic (3)	1.1	0 to 5.2[w]	5% (AR)[n,w]
Acute leukemias (2)			
Gastrointestinal (2)			
Thyroid (1)			
Melanoma (1)			
Head, neck (4)	1.5	0 to 5[w]	1.9% (AR)[n,w]
Gastrointestinal (2)			
Leukemia (2)			
Melanoma (1)			
Gynecologic (1)			
Sarcoma	10.5		Not given
All types [p]		5 to 35	1.7 (OE)[r]
Rectum (15)			4.1 (OE)[r]
Ovary (8)			2.4 (OE)[s]
Lung (7)			3.2 (OE)[s]
Vulval, vaginal (6)			10.0 (OE)[s]
Small intestine (3)			15.0 (OE)[s]
Oropharynx (2)			20.0 (OE)[s]
Central nervous system (2)			10.0 (OE)[s]
All types [p,x]		0.5 to 20	1.23 (OE)
Lung (11)			5.71 (OE)[s]
Vulval, vaginal (5)			14.71 (OE)[r]
Breast (4)			0.379 (OE)[s]
Larynx (2)			13.07 (OE)[s]
Bone (1)			16.393 (OE)[r]
All types		0.2 to 38	28.5% (AR), 1.44 (RR)[s,y]
All types [p]	> 15	0.2 to 38	1.44 (RR), (OE)[s]
Lung (64)			5.1 (OE)[s]
Breast (58)			0.7 (OE)[s]
Uterine (39)			1.4 (OE)[s]
Rectum (30)			1.6 (OE)[s]
Bladder (26)			3.4 (OE)[s]
Ovaries (25)			1.6 (OE)[s]
Unknown primary (24)			2.1 (OE)[s]
Other genital (19)			1.8 (OE)[s]
Kidneys (14)			2.8 (OE)[s]
Buccal cavity (13)			2.3 (OE)[s]
Sarcoma (12)			2.6 (OE)[s]
Esophagus (6)			3.0 (OE)[s]
Connective tissue (5)			3.3 (OE)[s]
Larynx (4)			4.0 (OE)[s]
All types [p]			1.3 (OE)[s]
Breast (27)			1.4 (OE)[s]
Other genital (8)			4.4 (OE)[s]
Unknown primary (7)			3.3 (OE)[s]
Buccal (4)			3.3 (OE)[s]
Larynx (3)			15.0 (OE)[s]

(Footnotes defined on page 426)

(Continued)

Table 3. *(Continued)*

Primary Cancer	Reference	Treatment	Patients	
			Total	With Second Malignant Neoplasms
Ovarian	226	All treatments	3363	35
		Surgery	595	0
		Radiotherapy	955	2
		Alkylators with or without radiotherapy	1794	33
		melphalan	605	21
		cyclophosphamide	333	3
Testicular	251	Radiotherapy	517	57
Prostate	250	All treatments	3675	220
		Surgery	2543	Not given
		Radiotherapy	817	14
		Hormones	829	9
		Chemotherapy	33	Not given

[a] ABVD = doxorubicin, bleomycin, vinblastine, dacarbazine; FAC = 5-fluorouracil, doxorubicin, cyclophosphamide; 5-FU = 5 fluorouracil; L-PAM = phenylalanine mustard; MAC = multiagent chemotherapy; MOP = mechlorethamine, vincristine, procarbazine; MOPP = mechlorethamine, vincristine, prednisone, procarbazine; MVPP = mechlorethamine, vinblastine, procarbazine, prednisone; PAVe = procarbazine, melphalan, vinblastine; SAC = single agent chemotherapy; VBM = vinblastine, bleomycin, methotrexate; Abr = absolute risk; AR = actuarial risk; CR = cumulative risk; LE = life-table estimate; OE = odds-expected ratio; RR = relative risk.
[b] At 10 years.
[c] $P < 0.0001$.
[d] $P < 0.003$.
[e] $P < 0.002$.
[f] At 7 years.
[g] $P < 0.001$.
[h] $P = 0.0008$.
[i] At 15 years.
[j] For relapse.
[k] $P < 0.0003$.
[l] 1 to 38 years.
[m] 10 to 38 years.
[n] At 5 years.
[o] At 14 years.
[p] Only statistically significant listed.
[q] $P = 0.06$.
[r] $P < 0.01$.
[s] $P < 0.05$.
[t] $P < 0.03$.
[u] $P < 0.04$.
[v] At 4 years.
[w] For all.
[x] Not listed by treatment.
[y] > 15 years.

that Epstein-Barr virus may influence B-cell non-Hodgkin lymphoma development, which was reported up to 12 years after radiotherapy. Survivors of Hodgkin disease also have an increased risk (odds-expected ratio, 2 to 3; relative risk, 20; cumulative risk, 5.2%; actuarial risk, 13%; absolute risk, 34.1) for solid tumor second malignancies. These malignancies may arise after a longer latency period (10 to 15 years) than that reported for leukemia occurrence (217, 234, 245, 246).

An increased risk of second cancers of the bladder (242-251), kidney (250, 252), ureters (252), and urethra (250, 251) has been associated with cyclophosphamide use with or without radiotherapy; these cancers occurred 3 to 15 years later (247, 248, 252). Kleinerman and colleagues (238) and Kapp and coworkers (253) also reported excessive solid tumors occurring 15 or more years after radiotherapy for cervical cancer.

A higher incidence of skin cancers also following cyclophosphamide therapy was thought to be related to increased cutaneous photosensitivity during treatment (119, 254). Melanoma occurring after Hodgkin disease may be increased in survivors with dysplastic nevus syndrome (relative risk, 8.0; cumulative risk, 3.3%) (255). An excess of melanomas on the head and neck region, upper extremities, and trunk were noted in prostate cancer survivors (250).

Radiotherapy for breast carcinoma was reported to cause osteosarcoma in rib, scapula, clavicle, humerus, and sternum 3 to 24 years after treatment with 1800 to 11 000 cGy (256-259). Osteosarcomas occurring in rib, humerus, sternum, scapula, ilium, pubis, and clavicle occurred years after radiotherapy for lung cancer, non-Hodgkin lymphoma (257, 260), Hodgkin disease, and ovarian (257), uterine (260), and thyroid (261) cancers. Osteosarcomas were also reported up to 29 years after external beam or intracavitary radium for cervical cancer (257, 259, 260).

Henson and Urich (67) reviewed reports of fibrosarcomas that developed several years after radiotherapy for astrocytoma, glioblastoma, and pituitary adenoma. No excessive second malignancies have been reported after adjuvant thio-TEPA therapy for breast and colon cancer (203, 262); however, Ferguson and associates (263) found a 3% incidence of second cancer after 6000 to 7400 cGy for breast cancer. Kurtz and associates (264) reported one sarcoma after sim-

Table 3. *(Continued)*

Type and Number of Second Malignancies	Years after Diagnosis of First Malignancy		Risk Rate
	Median	Range	
	6	1 to 11	8.5% (CR)[b]
Acute leukemias (28)			23.5 (OE)
Myelodysplastic syndrome (7)			
0	0		0
Acute leukemias			0.1% (CR)[b]
	6	1 to 11	8.4% (CR)[b]
Acute leukemias (26)			93 (RR)
Myelodysplastic syndrome (7)			
			11.2% (CR)[b]
			5.4%(CR)[b]
All types [p]	15.4	2 to 29	1.87 (OE)[g]
Testicular (7)	5		23.10 (OE)[g,n]
Genitourinary (9)		15 to 19	2.37 (OE)[s]
Skin (8)			2.58 (OE)[s]
Unknown primary (3)			8.36 (OE)[s]
All types [p,x]			1.2 (OE)[r]
Bladder (30)			2.2 (OE)[r]
Kidney (17)			3.3 (OE)[r]
Urethra (6)			12.0 (OE)[s]
Melanoma (7)			2.5 (OE)[r]

ple excision and radiotherapy for breast cancer. The incidence of second malignancies after irradiation for head and neck tumors is not greater than that occurring after surgery alone (203). Malignant peripheral nerve tumors occurred after radiotherapy for breast and cervical carcinoma and reticulum cell sarcoma (91).

Recommendations and Conclusions

The physiologic long-term and late problems that may result from adult cancer therapies may range from those minimally affecting daily living to major complications that impair organ systems and may cause death. As the population of cancer survivors continues to increase, additional effects not yet documented will surface. For the survivor, the existence of, or potential for these sequelae may be more devastating than the disease and treatment itself. With the advent of cancer survivorship, therefore, the primary goals of cancer treatment include not only eradication of disease but also minimization of the potential deleterious physiologic long-term and late effects of therapies. The ultimate goal of treatment is to return the survivor to as healthy a lifestyle as possible.

Health care practitioners can integrate the information presented here into the care of patients with active disease. Drugs with equal anticancer benefit, but with fewer associated long-term or late effects can be substituted for alkylating agents and anthracyclines known to cause these complications. Careful review of use of combination radiotherapy and chemotherapy may indicate that either agent alone may have similar anticancer benefit, but fewer long-term or late sequelae.

Health care practitioners also have an obligation to participate in the development and implementation of interventions which maximize rehabilitation after treatment. One method to approaching rehabilitation is the formation of a comprehensive interdisciplinary follow-up program for cancer survivors. This program may be structured in the form of a survivor clinic or consist of referrals to appropriate specialists. Either approach should incorporate interventions based not only on potential or existing physiologic long-term and late effects, but on psychological and socioeconomic sequelae as well. As will be discussed in Part 2, all of these types of effects may interrelate in ways that will affect survivor rehabilitation.

The physiologic component of long-term cancer survivor follow-up should include a yearly comprehensive physical examination to detect cancer recurrence, second malignancies, and other noncancerous sequelae. Appropriate radiographs, scans, and laboratory testing should also be done as needed. Many of the long-term and late problems that occur are system specific and may need to be assessed by a specialist in that area. Ideally, specialists should be sensitive to the cancer survivor's previous disease and therapy. In addition to addressing overt physiologic problems, follow-up should include interventions aimed at general disease prevention and the development of healthful lifestyle behaviors. Thus, another physiologic component of a survivor program could incorporate nutritional counseling, exercise testing, or teaching of screening techniques for later cancers. The ideal comprehensive survivor program monitors and treats existing sequelae while maintaining a wellness orientation. This approach focuses on preventing and controlling long-term and late effects of therapies and enabling the survivor to adapt to them.

Secondary physiologic effects of cancer and cancer therapy warrant further research. Those who develop new drugs, radiotherapy techniques, combination

therapies, and dosage schedules should bear in mind the existing or potential long-term or late effects of the treatments. Prospective studies examining variables such as incidence, type, and severity of potential effects should begin at the initiation of cancer therapies.

Acknowledgments: The authors thank William M. Feinberg, MD, for review of the neurologic section, Mary Lippman for research of tabular data, and Patricia Conrad and Rayna Goldman for preparation of the manuscript.

Grant Support: Supported in part by the National Institutes of Health grant CA-23074 and Arizona Disease Control Research Commission grant 3364-0000000-1-1-AP-6621.

Requests for Reprints: Lois J. Loescher, RN, MS, Arizona Cancer Center, 1515 North Campbell Avenue, Tucson, AZ 85724.

Current Author Addresses: Ms. Loescher and Ms. Leigh: Arizona Cancer Center, 1515 North Campbell Avenue, Tucson, AZ 85724.
Ms. Welch-McCaffrey: Good Samaritan Cancer Center, 1111 East McDowell Road, Phoenix, AZ 85006.
Ms. Hoffman: 9 Madison Road, Cranbury, NJ 08512.
Dr. Meyskens: UCI Cancer Center, 101 The City Drive, Building 44, Route 81, Orange, CA 92668.

References

1. **Cancer Facts and Figures.** American Cancer Society; 1988.
2. **Meadows AT, D'Angio GJ.** Late effects of cancer treatment: methods and techniques for detection. *Semin Oncol.* 1974;**1:**87-90.
3. **Li FP.** Second cancers. In: DeVita VT, Rosenberg SA, Hellman S, eds. *Cancer: Principles and Practice of Oncology,* v 2. Philadephia: J.B. Lippincott; 1985:2040-9.
4. **Chapman RM.** Effect of cytotoxic therapy on sexuality and gonadal function. In: Perry MC, Yarbro JW, eds. *Toxicity of Chemotherapy.* Orlando, Florida: Grune & Stratton; 1984:343-63.
5. **Sherins RJ, DeVita VT Jr.** Effects of drug treatment for lymphoma on male reproductive capacity. *Ann Intern Med.* 1973;**79:**216-20.
6. **Clarke SJ, Resnick MI.** Infertility following radiation and chemotherapy. *Urol Clin North Am.* 1978;**5:**531-5.
7. **Damewood MD, Grochow LB.** Prospects for fertility after chemotherapy or radiation for neoplastic disease. *Fertil Steril.* 1986;**45:**443-59.
8. **Chapman RM, Sutcliffe SB, Malpas JS.** Male gonadal dysfunction in Hodgkin's disease. A prospective study. *JAMA.* 1981;**245:**1323-8.
9. **Richter P, Calamera JC, Morgenfeld MC, Kierszenbaum AL, Lavieri JC, Mancini RE.** Effect of chlorambucil on spermatogenesis in the human with malignant lymphoma. *Cancer.* 1970;**25:**1026-30.
10. **Fairley KF, Barrie JU, Johnson W.** Sterility and testicular atrophy related to cyclophosphamide therapy. *Lancet.* 1972;**1:**568-9.
11. **Sanders JE, Buckner CD, Leonard JM, et al.** Late effects on gonadal function of cyclophosphamide, total-body irradiation, and marrow transplantation. *Transplantation.* 1983;**36:**252-5.
12. **Barrett A, Nicholls J, Gibson B.** Late effects of total body irradiation. *Radiother Oncol.* 1987;**9:**131-5.
13. **Shamberger RC, Sherins RJ, Rosenberg SA.** The effects of postoperative adjuvant chemotherapy and radiotherapy on testicular function in men undergoing treatment for soft tissue sarcoma. *Cancer.* 1981;**470:**2368-74.
14. **Asbjornsen G, Molne K, Klepp O, Aakvaag A.** Testicular function after combination chemotherapy for Hodgkin's disease. *Scand J Haematol.* 1976;**16:**66-9.
15. **Roeser HP, Stocks AE, Smith AJ.** Testicular damage due to cytotoxic drugs and recovery after cessation of therapy. *Aust NZ J Med.* 1978;**8:**250-4.
16. **Redman JR, Bajorunas DR, Goldstein MC, et al.** Semen cryopreservation and artificial insemination for Hodgkin's disease. *J Clin Oncol.* 1987;**5:**233-8.
17. **Whitehead E, Shalet SM, Blackledge G, Todd I, Crowther D, Beardwell CG.** The effects of Hodgkin's disease and combination chemotherapy on gonadal function in the adult male. *Cancer.* 1982;**49:**418-22.
18. **Chapman RM, Sutcliffe SB, Rees LH, Edwards CR, Malpas JS.** Cyclical combination chemotherapy and gonadal function. Retrospective study in males. *Lancet.* 1979;**1:**285-9.
19. **Rowley MJ, Leach DR, Warner GA, Heller CG.** Effect of graded doses of ionizing radiation on the human testis. *Radiat Res.* 1974;**59:**665-78.
20. **Speiser B, Rubin P, Casarett G.** Aspermia following lower truncal irradiation in Hodgkin's disease. *Cancer.* 1973;**32:**692-8.
21. **Ray GR, Cassady JR, Bagshaw MA.** Definitive radiation therapy of carcinoma of the prostate. *Radiology.* 1973;**106:**407-18.
22. **Mollenkamp JS, Cooper JF, Kagan AR.** Clinical experience with supervoltage radiotherapy in carcinoma of the prostate: a preliminary report. *J Urol.* 1975;**113:**374-7.
23. **Ray GR, Bagshaw MA.** The role of radiation therapy in the definitive treatment of adenocarcinoma of the prostate. In: Creger W, Coggins CH, Hancock EW, eds. *Annual Review of Medicine.* Palo Alto: Annual Reviews, Inc.; 1975:567-88.
24. **Swanson DA.** Cancer of the bladder and prostate: the impact of therapy on sexual function. In: Von Eschenbach AC, Rodriguez DB, eds. *Sexual Rehabilitation of the Urologic Cancer Patient.* Boston: G.K. Hall; 1981:88-107.
25. **Von Eschenbach AC, Schover LR.** Sexual rehabilitation of cancer patients. In: Gunn AE, ed. *Cancer Rehabilitation.* New York: Raven Press; 1984:155-73.
26. **Stoudemire A, Techman T, Graham SD Jr.** Sexual assessment of the urologic oncology patient. *Psychosomatics,* 1985;**26:**405-8, 410.
27. **Goldstein I, Feldman MI, Deckers PJ, Babayan RK, Krane RJ.** Radiation-associated impotence. *JAMA.* 1984;**251:**903-10.
28. **Kopecky AA, Laskowski TZ, Scott R Jr.** Radical retropubic prostatectomy in the treatment of prostate carcinoma. *J Urol.* 1970;**103:**641-4.
29. **Jewett HJ.** The present status of radical prostatectomy for stages A and B prostatic cancer. *Urol Clin North Am.* 1975;**2:**105-24.
30. **Walsh PC, Donker PJ.** Impotence following radical prostatectomy: insight into etiology and prevention. *J Urol.* 1982;**128:**492-7.
31. **Jewett AL, Bridge RW, Gray GF Jr, Shelley WM.** The palpable nodule of prostate cancer. *JAMA.* 1968;**203:**403-6.
32. **Finkle JE, Finkle PS, Finkle AL.** Encouraging preservation of sexual function after prostatectomy. *Urology.* 1975;**6:**697-702.
33. **Correa RJ, Gibbons RP, Cummings KB, Mason JT.** Total prostatectomy for stage B carcinoma of the prostate. *J Urol.* 1977;**117:**328-9.
34. **Bracken RB, Johnson DE.** Sexual function and fecundity after treatment for testicular tumors. *Urology.* 1976;**7:**35-8.
35. **Witkin MH, Kaplan HS.** Sex therapy and penectomy. *J Sex Marital Ther.* 1982;**8:**209-21.
36. **Ormond JK.** Radical prostatectomy for carcinoma. *J Urol.* 1947;**58:**61-7.
37. **Walsh PC, Lepor H, Eggleston JC.** Radical prostatectomy with preservation of sexual function: anatomical and pathological considerations. *Prostate.* 1983;**4:**473-85.
38. **Finkle AL, Williams RD.** Sexual potency before and after radical prostatectomy. *West J Med.* 1985;**143:**474-5.
39. **Lamb MA, Woods NF.** Sexuality and the cancer patient. *Cancer Nurs.* 1981;**4:**137-44.
40. **Andersen BL.** Sexual functioning morbidity among cancer survivors. *Cancer.* 1985;**55:**1835-42.
41. **Loh ES, Brown HE, Beiler DD.** Radiotherapy of carcinoma of the prostate: preliminary report. *J Urol.* 1971;**106:**906-9.
42. **Rhamy RK, Wilson SK, Caldwell WL.** Biopsy-proved tumor following definitive irradiation for resectable carcinoma of the prostate. *J Urol.* 1972;**107:**627-30.
43. **Bergman B, Damber JE, Littbrand B, Sjögren K, Tomic R.** Sexual function in prostate cancer patients treated with radiotherapy, orchiectomy or oestrogens. *Br J Urol.* 1984;**56:**64-9.
44. **Forman JD, Wharam MD, Lee DJ, Zinreich ES, Order SE.** Definitive radiotherapy following prostatectomy: results and complications. *Int J Radiat Oncol Biol Phys.* 1986;**12:**185-9.
45. **Miller JJ 3d, Williams GF, Leissring JC.** Multiple late complications of therapy with cyclophosphamide, including ovarian destruction. *Am J Med.* 1971;**50:**530-5.
46. **Maguire LC.** Fertility and cancer therapy. *Postgrad Med.* 1979;**65:**293-5, 298-9.
47. **Kumar R, Biggart JD, McEvoy J, McGeown MG.** Cyclophosphamide and reproductive function. *Lancet.* 1972;**1:**1212-4.
48. **Chapman RM, Sutcliffe SB, Malpas JS.** Cytotoxic-induced ovarian failure in women with Hodgkin's disease. I. Hormone function. *JAMA.* 1979;**242:**1877-81.
49. **Sobrinho LG, Levine RA, DeConti RC.** Amenorrhea in patients with Hodgkin's disease treated with antineoplastic agents. *Am J Obstet Gynecol.* 1971;**109:**135-9.
50. **Schilsky RL, Sherins RJ, Hubbard SM, Wesley MN, Young RC, DeVita VT.** Long-term follow up of ovarian function in women treated with MOPP chemotherapy for Hodgkin's disease. *Am J Med.* 1981;**71:**552-6.
51. **Cooley ME, Cobb SC.** Sexual and reproductive issues for women with Hodgkin's disease: overview of issues. *Cancer Nurs.* 1986;**9:**188-93.
52. **Horning SJ, Hoppe RT, Kaplan HS, Rosenberg SA.** Female reproductive potential after treatment for Hodgkin's disease. *N Engl J Med.* 1981;**304:**1376-81.
53. **Ray GR, Trueblood HW, Enright LP, Kaplan HS, Nelsen TS.** Oophoropexy: a means of preserving ovarian function following pelvic megavoltage radiotherapy for Hodgkin's disease. *Radiology.* 1970;**96:**175-80.

54. **Thomas PR, Winstanly D, Peckham MJ, Austin DE, Murray MA, Jacobs HS.** Reproductive and endocrine function in patients with Hodgkin's disease: effects of oophoropexy and irradiation. *Br J Cancer.* 1976;**33:**226-31.
55. **Jusenius K.** Sexuality and gynecologic cancer. *Cancer Nurs.* 1981;**4:**479-84.
56. **Abitol MM, Davenport JH.** Sexual dysfunction after therapy for cervical carcinoma. *Am J Obstet Gynecol.* 1974;**119:**181-9.
57. **Vasika A, Popovich NR, Brausch CC.** Postradiation course of patients with cervical carcinoma. *Obstet Gynecol.* 1958;**11:**403-14.
58. **Pitkin RM, Van Voorhis LW.** Post irradiation vaginitis: an evaluation of prophylaxis with topical estrogen. *Ther Radiol.* 1971;**99:**417-21.
59. **Kaufman RH, Topek NH, Wall JA.** Late irradiation changes in vaginal cytology. *Am J Obstet Gynecol.* 1961;**81:**859-63.
60. **DiSaia PJ, Creasman WT, Rich WM.** An alternate approach to early cancer of the vulva. *Am J Obstet Gynecol.* 1979;**133:**825-32.
61. **Seibel MM, Freeman MG, Graves WL.** Carcinoma of the cervix and sexual function. *Obstet Gynecol.* 1980;**55:**484-7.
62. **Donohue VC, Knapp RC.** Sexual rehabilitation of gynecologic cancer patients. *Obstet Gynecol.* 1977;**49:**118-21.
63. **Andersen BL, Hacker NF.** Psychosexual adjustment following pelvic exenteration. *Obstet Gynecol.* 1983;**61:**331-8.
64. **Morley GW, Lindenauer SM, Youngs D.** Vaginal reconstruction following pelvic exenteration: surgical and psychological considerations. *Am J Obstet Gynecol.* 1973;**116:**996-1002.
65. **Brown RS, Haddox V, Posada A, Rubio A.** Social and psychological adjustment following pelvic exenteration. *Am J Obstet Gynecol.* 1972;**114:**162-71.
66. **Rosenthal S, Kaufman S.** Vincristine neurotoxicity. *Ann Intern Med.* 1974;**80:**733-7.
67. **Henson RA, Urich H.** *Cancer and the Nervous System.* Boston: Blackwell Scientific Publications; 1982:573-621.
68. **Goldhirsch A, Greiner R, Davis B.** Chemotherapy followed by whole abdominal radiation therapy for ovarian cancer. In: Alberts DS, Surwit EA, eds. *Ovarian Cancer.* Boston: Martinus Nijhoff; 1985:213-26.
69. **Livingston RB, Stephens RL, Bonnet JD, Grozea PN, Lehane DE.** Long-term survival and toxicity in small cell lung cancer. *Am J Med.* 1984;**77:**415-7.
70. **Piel IJ, Meyer D, Perlia CP, Wolfe VI.** Effects of cis-diamminedichloroplatinum (NSC-119875) on hearing function in man. *Cancer Chemother Rep.* 1974;**58:**871-5.
71. **Von Hoff DD, Schilsky R, Reichert CM, et al.** Toxic effects of cis-dichlorodiammineplatinum(II) in man. *Cancer Treat Rep.* 1979;**63:**1527-31.
72. **Shutovsky LJ, Fletcher GH.** Retinal and optic nerve complications in a high dose irradiation technique of ethmoid sinus and nasal cavity. *Radiology.* 1972;**104:**629-34.
73. **Goepfert H, Jesse RH, Lindberg RD.** Arterial infusion and radiation therapy in the treatment of advanced cancer of the nasal cavity and paranasal sinuses. *Am J. Surg.* 1973;**126:**464-8.
74. **Wilding G, Caruso R, Lawrence TS, et al.** Retinal toxicity after high-dose cisplatin therapy. *J Clin Oncol.* 1985;**3:**1683-9.
75. **Vinding T, Nielsen NV.** Retinopathy caused by treatment with tamoxifen in low dosage. *Acta Opthalmol (Copenh).* 1983;**61:**45-50.
76. **Berger PS, Bataini J.** Radiation-induced cranial nerve palsy. *Cancer.* 1977;**40:**152-5.
77. **Pennybacker J, Russell DS.** Necrosis of the brain due to radiation therapy. *J Neurol Neurosurg Psychiatry.* 1948;**11:**183-98.
78. **So NK, O'Neill BP, Frytak S, Eagan RT, Earnest F 4th, Lee RE.** Delayed leukoencephalopathy in survivors with small cell lung cancer. *Neurology.* 1987;**37:**1198-201.
79. **Lee YY, Nauert C, Glass JP.** Treatment-related white matter changes in cancer patients. *Cancer.* 1986;**57:**1473-82.
80. **Tsuruda JS, Kortman KE, Bradley WG, Wheeler DC, Van Dalsem W, Bradley TP.** Radiation effects on cerebral white matter: MR evaluation. *AJR.* 1987;**149:**165-71.
81. **Bleyer WA.** Current status of intrathecal chemotherapy for human meningeal neoplasms. In: Bailar JC, Weisburger EK, Aoki T, et al. eds. *Modern Concepts in Brain Tumor Therapy: Laboratory and Clinical Investigations.* Bethesda: U.S. Department of Health, Education, and Welfare; 1977:171-8. DHEW publication no. (NIH) 77-12367.
82. **Nelson RW, Frank JT.** Intrathecal methotrexate-induced neurotoxicities. *Am J Hosp Pharm.* 1981;**38:**65-8.
83. **Johnson BE, Becker B, Goff WB 2d, et al.** Neurologic, neuropsychologic, and computed cranial tomography scan abnormalities in 2- to 10-year survivors of small-cell lung cancer. *J Clin Oncol.* 1985;**3:**1659-67.
84. **Craig JB, Jackson DV, Moody D, et al.** Prospective evaluation of changes in computed cranial tomography in patients with small cell lung carcinoma treated with chemotherapy and prophylactic cranial irradiation. *J Clin Oncol.* 1984;**2:**1151-6.
85. **Frytak S, Earnest F 4th, O'Neill BP, Lee RE, Creagan ET, Trautmann JC.** Magnetic resonance imaging for neurotoxicity in long-term survivors of carcinoma. *Mayo Clin Proc.* 1985;**60:**803-12.
86. **Catane R, Schwade JG, Yarr I, et al.** Follow-up neurological evaluation in patients with small cell lung carcinoma treated with prophylactic cranial irradiation and chemotherapy. *Int J Radiat Oncol Biol Phys.* 1981;**7:**105-9.
87. **Licciardello J, Bromer D, Karp S, Hoffer D, Paquette D, Hong W.** Delayed neurotoxicity after prophylactic cranial irradiation or mediastinal irradiation with chemotherapy for patients with small cell lung cancer. In: *Proceedings of the Nineteenth Annual Meeting of the American Society of Clinical Oncology.* San Diego: American Society of Clinical Oncology; 1983:189. Available from the American Society of Clinical Oncology.
88. **Obbens EA, Posner JB.** Systemic cancer involving the spinal cord. In: Davidoff RA, ed. *Handbook of the Spinal Cord.* v 4, 5. New York: Marcel Dekker; 1987:451-89.
89. **Foley KM.** Pain syndromes in patients with cancer. In: Bonica JJ, Albe-Fessard DG, eds. *Advances in Pain Research and Therapy.* v 2. New York: Raven Press; 1979:59-75.
90. **Foley KM.** Pain syndromes in patients with cancer. *Med Clin North Am.* 1987;**71:**169-84.
91. **Foley KM, Woodruff JM, Ellis FT, Posner JB.** Radiation-induced malignant and atypical peripheral nerve sheath tumors. *Ann Neurol.* 1980;**7:**311-8.
92. **Medina JE, Aussenberg L, Gunn AE.** Rehabilitation problems in patients with cancer of the head and neck. In: Gunn AE, ed. *Cancer Rehabilitation.* New York: Raven Press; 1984:41-5.
93. **DeLisa JA, Miller RM, Melnick RR, Mikulic MA, Gerber.** Rehabilitation of the cancer patient. In: Devita VT, Hellman S, Rosenberg SA, eds. *Cancer: Principles and Practice of Oncology.* v 2. Philadelphia: J.B. Lippincott; 1985:2155-88.
94. **Portenoy RK, Duma C, Foley KM.** Acute herpetic and postherpetic neuralgia: clinical review and current management. *Ann Neurol.* 1986;**20:**651-64.
95. **Conomy JP, Kellermeyer RW.** Delayed cerebrovascular consequences of therapeutic radiation. *Cancer.* 1975;**36:**1702-8.
96. **Silverberg GD, Britt KH, Goffinet DR.** Radiation-induced carotid artery disease. *Cancer.* 1978;**41:**130-7.
97. **Feldmann E, Posner JB.** Episodic neurologic dysfunction in patients with Hodgkin's disease. *Arch Neurol.* 1986;**43:**1227-33.
98. **Levinson SA, Close MB, Ehrenfeld WK, Stoney RJ.** Carotid artery occlusive disease following external cervical irradiation. *Arch Surg.* 1973;**107:**395-7.
99. **McCready RA, Hyde GL, Bivins BA, Mattingly SS, Griffen WO Jr.** Radiation-induced arterial injuries. *Surgery.* 1983;**93:**306-12.
100. **Lamberts HB, DeBoer WG.** X-ray-induced atheromatous lesions in the arterial wall of hypercholesterolaemic rabbits. *Int J Radiat Biol.* 1963;**6:**343-50.
101. **Benson EP.** Radiation injury to large arteries. *Radiology.* 1973;**106:**195-7.
102. **Graus F, Rogers LR, Posner JB.** Cerebrovascular complications in patients with cancer. *Medicine (Baltimore).* 1985;**64:**16-35.
103. **Kearsley JH, Tattersall MH.** Cerebral embolism in cancer patients. *Q J Med.* 1982;**51:**279-91.
104. **Elerding SC, Fernandez RN, Grotta JC, Lindberg RD, Causay LC, McMurtrey MJ.** Carotid artery disease following external cervical irradiation. *Ann Surg.* 1981;**194:**609-15.
105. **Glick B.** Bilateral carotid occlusive disease following irradiation for carcinoma of the vocal cords. *Arch Pathol.* 1972;**93:**352-5.
106. **Mori K, Takeuchi J, Ishikawa M, Handa H, Toyama M, Yamaki T.** Occlusive arteriography and brain tumor. *J Neurosurg.* 1978;**49:**22-35.
107. **Kagan AR, Bruce DW, Di Chiro G.** Fatal foam cell arteritis of the brain after irradiation for Hodgkin's disease: angiography and pathology. *Stroke.* 1971;**2:**232-8.
108. **Whitaker WW, Brewer D, Fitzgerald M, Heath D.** Clinical pathologic conference. *Am Heart J.* 1964;**68:**549-55.
109. **Peters WR, Schlicke CP, Schmutz DD.** Peripheral vascular disease following radiation therapy. *Am Surg.* 1979;**45:**700-2.
110. **Gross L, Manfredi OL, Frederick WC.** Radiation-induced major vascular occlusion in a patient cured of widespread metastases of nasopharyngeal origin. *Radiology.* 1969;**93:**664-6.
111. **Savlov ED, Nahhas WA, May AG.** Iliac and femoral arteriosclerosis following pelvic irradiation for carcinoma of the ovary. *Obstet Gynecol.* 1969;**34:**345-51.
112. **Soble AR.** Chronic bleomycin-associated Raynaud's phenomenon [Letter]. *Cancer Treat Rep.* 1978;**62:**570.
113. **Scheulen ME, Schmidt CG.** Raynaud's phenomenon and cancer chemotherapy [Letter]. *Ann Intern Med.* 1982;**96:**256-7.
114. **Budin JA, Casarella WJ, Harisiadis L.** Subclavian artery occlusion following radiotherapy for carcinoma of the breast. *Radiology.* 1976;**118:**169-73.
115. **Tokaz LK, Von Hoff DD.** The cardiotoxicity of anticancer agents. In: Perry MC, Yarbro JW, eds. *Toxicity of Chemotherapy.* Orlando, Florida: Grune & Stratton; 1984:199-226.

116. **Gottlieb SL, Edmiston WA Jr, Haywood LJ.** Late, late doxorubicin cardiotoxicity. *Chest.* 1980;**78:**880-2.
117. **Sunnenberg TD, Kramer B.** Long-term effects of cancer chemotherapy. *Compr Ther.* 1985;**11:**58-67.
118. **Freter CE, Lee TC, Billingham ME, Chak L, Bristow MR.** Doxorubicin cardiac toxicity manifesting seven years after treatment. *Am J Med.* 1986;**80:**483-5.
119. **Von Hoff DD, Layard MW, Basa P, et al.** Risk factors for doxorubicin-induced congestive heart failure. *Ann Intern Med.* 1979;**91:**710-7.
120. **Saltiel E, McGuire W.** Doxorubicin (adriamycin) cardiomyopathy. *West J Med.* 1983;**139:**332-41.
121. **Von Hoff DD, Rozencweig M, Layard M, et al.** Daunomycin-induced cardiotoxicity in children and adults. A review of 110 cases. *Am J Med.* 1977;**62:**200-8.
122. **Chlebowski RT, Paroly WS, Pugh RP, et al.** Adriamycin given as a weekly schedule without a loading dose: clinically effective with reduced incidence of cardiotoxicity. *Cancer Treat Rep.* 1980;**64:**47-51.
123. **Torti FM, Bristow MR, Howes AE, et al.** Reduced cardiotoxicity of doxorubicin delivered on a weekly schedule. *Ann Intern Med.* 1983;**99:**745-9.
124. **Praga C, Beretta G, Vigo PL, et al.** Adriamycin cardiotoxicity: a survey of 1273 patients. *Cancer Treat Rep.* 1979;**63:**827-34.
125. **Legha SS, Benjamin RS, MacKay B, et al.** Reduction of doxorubicin cardiotoxicity by prolonged continuous intravenous infusion. *Ann Intern Med.* 1982;**96:**133-9.
126. **Minow RA, Benjamin RS, Gottlieb JA.** Adriamycin cardiomyopathy: an overview with determination of risk factors. *Cancer Chemother Rep.* 1975;**6:**195-201.
127. **Minow RA, Benjamin RS, Lee ET, Gottlieb JA.** Adriamycin cardiomyopathy–risk factors. *Cancer.* 1977;**39:**1397-402.
128. **Beretta G, Villani F.** Cardiomyopathy in adults after combination adriamycin and DTIC [Letter]. *Cancer Treat Rep.* 1980;**64:**353.
129. **Crossley RJ.** Clinical safety and tolerance of mitoxantrone. *Semin Oncol.* 1984;**11:**54-8.
130. **Unverferth DV, Unverferth BJ, Balcerzak SP, Bashore TA, Neidhart JA.** Cardiac evaluation of mitoxantrone. *Cancer Treat Rep.* 1983;**67:**343-50.
131. **Phillips TL, Fu KK.** Quantification of combined radiation therapy and chemotherapy effects on critical normal tissues. *Cancer.* 1976;**37:**1186-200.
132. **Eltringham JR.** Cardiac response to combined modality therapy. *Front Radiat Ther Oncol.* 1979;**13:**161-74.
133. **Cortes EP, Lutman G, Wanka J, Pickren J, Holland JF.** Adriamycin toxicity in adults with cancer. *Clin Res.* 1973;**21:**412.
134. **Saini J, Rich MW, Lyss AP.** Reversibility of severe left ventricular dysfunction due to doxorubicin cardiotoxicity. *Ann Intern Med.* 1987;**106:**814-6.
135. **Rubin P.** The Franz Buschke lecture: late effects of chemotherapy and radiation therapy: a new hypothesis. *Int J Radiat Oncol Biol Phys.* 1984;**10:**5-34.
136. **Niemtzow RC, Reynolds RD.** Radiation therapy and the heart. In: Kapoor AS, ed. *Cancer and the Heart.* New York: Springer-Verlag; 1986:232-45.
137. **Gomez GA, Park JJ, Panahon KL, et al.** Heart size and function after radiation therapy to the mediastinum in patients with Hodgkin's disease. *Cancer Treat Rep.* 1983;**67:**1099-103.
138. **Gottdiener JS, Katin MJ, Borer JS, Bacharach SL, Green MV.** Late cardiac effects of therapeutic mediastinal irradiation. *New Engl J Med.* 1983;**308:**569-72.
139. **Annest LS, Anderson RP, Li W, Hafermann MD.** Coronary artery disease following mediastinal radiation therapy. *J Thorac Cardiovasc Surg.* 1983;**85:**257-63.
140. **Mill WB, Baglan RJ, Kurichety P, Prasad S, Lee JY, Moller R.** Symptomatic radiation-induced pericarditis in Hodgkin's disease. *Int J Radiat Oncol Biol Phys.* 1984;**10:**2061-5.
141. **Svahn-Tappar G, Baldethorp L, Landberg T.** Mantle treatment of Hodgkin's disease. Results and side effects. *Acta Radiol Ther Phys Biol.* 1976;**15:**369-86.
142. **Applefeld MM, Wiernik PH.** Cardiac disease after radiation therapy for Hodgkin's disease: analysis of 48 patients. *Am J Cardiol.* 1983;**51:**1679-81.
143. **Simon EB, Ling J, Mendizabal RC, Midwall J.** Radiation-induced coronary artery disease. *Am Heart J.* 1984;**108:**1032-4.
144. **Ali MK, Khalil KG, Fuller LM, et al.** Radiation-related myocardial injury. Management of two cases. *Cancer.* 1976;**38:**1941-6.
145. **Pohjola-Sintonen S, Totterman KJ, Salmo M, Siltanen P.** Late cardiac effects of mediastinal radiotherapy in patients with Hodgkin's disease. *Cancer.* 1987;**60:**31-7.
146. **Shashaty GG.** Aortic insufficiency following mediastinal radiation for Hodgkin's disease. *Am J Med Sci.* 1984;**287:**46-7.
147. **Ginsberg SJ, Comis RL.** The pulmonary toxicity of antineoplastic agents. In: Perry MC, Yarbro JW, eds. *Toxicity of Chemotherapy.* Orlando, Florida: Grune & Stratton; 1984:227-68.
148. **Weiss RB, Muggia FM.** Cytotoxic drug-induced pulmonary disease: update 1980. *Am J Med.* 1980;**68:**259-66.
149. **Cullen MH.** Acceptable damage to normal tissues. In: Stoll BA, ed. *Cancer Treatment: End Point Evaluation.* New York: John Wiley & Sons; 1983:139-71.
150. **Knight BK, Rose AG.** Pulmonary veno-occlusive disease after chemotherapy. *Thorax.* 1985;**40:**874-5.
151. **Joselson R, Warnock M.** Pulmonary veno-occlusive disease after chemotherapy. *Hum Pathol.* 1983;**14:**88-91.
152. **Yagoda A, Mukherji B, Young C, et al.** Bleomycin, an antitumor antibiotic. Clinical experience in 274 patients. *Ann Intern Med.* 1970;**77:**861-70.
153. **Mathe G.** Study of the clinical efficacy of bleomycin in human cancer. *Br Med J.* 1970;**2:**643-5.
154. **Halman KE, Bleehan NM, Brewin TB, et al.** Early clinical experience with bleomycin in the United Kingdom in a series of 105 patients. *Br Med J.* 1972;**4:**635-8.
155. **Crooke ST, Bradner WT.** Bleomycin, a review. *J Med.* 1976;**7:**333-428.
156. **Ichikawa T.** Studies of bleomycin: discovery of its clinical effect, combination treatment with bleomycin and radiotherapy side effects and long-term survival. *Jpn J Cancer Res.* 1976;**19:**99-115.
157. **Blum RH, Carter SK, Agre K.** A clinical review of bleomycin–a new antineoplastic agent. *Cancer.* 1973;**31:**903-14.
158. **Sostman HD, Matthay RA, Putman CE.** Cytotoxic drug-induced lung disease. *Am J Med.* 1977;**62:**608-15.
159. **Schein PS, Winokur SH.** Immunosuppressive and cytotoxic chemotherapy: long-term complications. *Ann Intern Med.* 1975;**82:**84-95.
160. **Goldiner PL, Carlon GC, Critkovic E, Schweizer O, Howland WS.** Factors influencing postoperative morbidity and mortality in patients treated with bleomycin. *Br Med J.* 1978;**1:**1664-7.
161. **Phillips TL, Wyatt JR.** Radiation fibrosis. In: Fishman AP, ed. *Pulmonary Diseases and Disorders.* v I. New York: McGraw-Hill; 1980:658-75.
162. **Travis EL, Harley RA, Fenn JO, Klobukowski CJ, Hargrove HB.** Pathologic changes in the lung following single and multi-fraction irradiation. *Int J Radiat Oncol Biol Phys.* 1977;**2:**475-90.
163. **Coggle JE, Lambert BE, Moores SR.** Radiation effects in the lung. *Environ Health Perspect.* 1986;**70:**261-91.
164. **Gross NJ.** Pulmonary effects of radiation therapy. *Ann Intern Med.* 1977;**86:**81-92.
165. **Pagani JJ, Libshitz HI.** CT manifestations of radiation-induced change in chest tissue. *J Comput Assist Tomogr.* 1982;**6:**243-8.
166. **Deeley TJ.** The effects of radiation on the lungs in the treatment of carcinoma of the bronchus. *Clin Radiol.* 1960;**11:**33-9.
167. **Slanina J, Mushoff K, Rahner T, Stiasny R.** Long-term side effects in irradiated patients with Hodgkin's disease. *Int J Radiat Oncol Biol Phys.* 1977;**2:**1-19.
168. **Deeg HJ, Storb R, Thomas ED.** Bone marrow transplantation: a review of delayed complications. *Br J Haematol.* 1984;**57:**185-208.
169. **Krowka MJ, Rosenow EC 3d, Hoagland HC.** Pulmonary complications of bone marrow transplantation. *Chest.* 1985;**87:**237-46.
170. **Schilsky RL.** Renal and metabolic toxicities of cancer treatment. In: Perry MC, Yarbro JW, eds. *Toxicity of Chemotherapy.* Orlando, Florida: Grune & Stratton: 1984:317-42.
171. **VanSlyck EJ, Bermudez GA.** Radiation nephritis. *Yale J Biol Med.* 1968;**41:**243-56.
172. **Madrazo A, Schwarz G, Churg J.** Radiation nephritis: a review. *J Urol.* 1975;**124:**822-7.
173. **Silver HK, Morton DL.** CCNU nephrotoxicity following sustained remission in oat cell carcinoma. *Cancer Treat Rep.* 1979;**63:**226-7.
174. **Schacht RG, Feiner HD, Gallo GR, Lieberman A, Baldwin DS.** Nephrotoxicity of nitrosoureas. *Cancer.* 1981;**48:**1328-34.
175. **Nichols WC, Moertel CG.** Nephrotoxicity of methyl CCNU [Letter]. *N Engl J Med.* 1979;**301:**1181.
176. **Schilsky RL, Barlock A, Ozols RF.** Persistent hypomagnesemia following cisplatin chemotherapy for testicular cancer. *Cancer Treat Rep.* 1982;**66:**1767-9.
177. **Vogl SE, Zaravinos T, Kaplan BH, Wollner D.** Safe and effective two-hour outpatient regimen of hydration and diuresis for the administration of cis-diamminedichloroplatinum (II). *Eur J Cancer.* 1981;**17:**345-50.
178. **Fjeldborg P, Sorensen J, Helkjaer PE.** The long-term effect of cisplatin on renal function. *Cancer.* 1986;**58:**2214-7.
179. **Groth S, Nielsen H, Sorensen JB, Christensen AB, Pedersen AG, Rorth M.** Acute and long-term nephrotoxicity of cis-platinum in man. *Cancer Chemother Pharmacol.* 1986;**17:**191-6.
180. **Gulati SC, Sordillo P, Kempin S, et al.** Microangiopathic anemia observed after treatment of epidermoid carcinoma with mitomycin C and 5-fluorouracil. *Cancer.* 1980;**45:**2252-7.
181. **Liu K, Mittelman A, Sproul EE, Elias EG.** Renal toxicity in man treated with mitomycin C. *Cancer.* 1971;**28:**1314-20.
182. **Hanna WT, Krauss S, Regester RF, Murphy WM.** Renal disease after mitomycin C therapy. *Cancer.* 1981;**48:**2583-8.

183. **Kressel BR, Ryan KP, Duong AT, Berenberg J, Schein PS.** Microangiopathic hemolytic anemia, thrombocytopenia, and renal failure in patients treated for adenocarcinoma. *Cancer.* 1981;**48:**1738-45.
184. **Churchill DN, Hong K, Gault MH.** Radiation nephritis following combined abdominal radiation and chemotherapy (bleomycin-vinblastine). *Cancer.* 1978;**41:**2162-4.
185. **Veenema RJ, Gursel EO, Lattimer J.** Radical retropubic prostatectomy for cancer: a 20-year experience. *J Urol.* 1977;**117:**330-1.
186. **Middleton AW Jr.** Pelvic lymphadenectomy with modified radical retropubic prostatectomy as a single operation: technique used and results in 50 consecutive cases. *J Urol.* 1981;**125:**353-6.
187. **Gibbons RP, Cole BS, Richardson RG, et al.** Adjuvant radiotherapy following radical prostatectomy: results and complications. *J Urol.* 1986;**135:**65-8.
188. **Parkin DE, Davis JA, Symonds RP.** Long-term bladder symptomatology following radiotherapy for cervical carcinoma. *Radiother Oncol.* 1987;**9:**195-9.
189. **Perry MC.** Hepatotoxicity of chemotherapeutic agents. In: Perry MC, Yarbro JW, eds. *Toxicity of Chemotherapy.* Orlando, Florida: Grune & Stratton; 1984;297-315.
190. **Menard DB, Gisselbrecht C, Marty M, Reyes F, Dhumeaux D.** Antineoplastic agents and the liver. *Gastroenterology.* 1980;**78:**142-64.
191. **Perry MC.** Hepatotoxicity of chemotherapeutic agents. *Semin Oncol.* 1982;**9:**65-74.
192. **Pratt CB, Johnson WW.** Duration and severity of fatty metamorphosis of the liver following L-asparaginase therapy. *Cancer.* 1971;**28:**361-4.
193. **Woolley PV 3d.** Hepatic and pancreatic damage produced by cytotoxic drugs. *Cancer Treat Rev.* 1983;**10:**117-37.
194. **Thigpen JT.** Single agent chemotherapy in carcinoma of the cervix. In: Surwit EA, Alberts DS, eds. *Cervix Cancer.* Boston: Martinus Nijhoff; 1987:119-36.
195. **Ingold JA, Reed GB, Kaplan HS, Bagshaw MA.** Radiation hepatitis. *Am J Roentgenol.* 1965;**93:**200-8.
196. **Martenson JA Jr, Gunderson LL, Buskirk SJ, et al.** Hepatic duct stricture after radical radiation therapy for biliary cancer: recurrence or fibrosis? *Mayo Clin Proc.* 1986;**61:**530-6.
197. **Hacker NF, Berek JS.** Surgical staging of cervical cancer. In: Surwit EA, Alberts DS, eds. *Cervix Cancer.* Boston: Martinus Nijhoff; 1987:43-57.
198. **Danjoux CE, Catton GE.** Delayed complications in colo-rectal carcinoma treated by combination radiotherapy and 5-fluorouracil–Eastern Cooperative Oncology Group (E.C.O.G.) pilot study. *Int J Radiat Oncol Biol Phys.* 1979;**5:**311-5.
199. **Markman M, Cleary S, Howell SB, Lucas WE.** Complications of extensive adhesion formation after intraperitoneal chemotherapy. *Surg Gynecol Obstet.* 1986;**162:**445-8.
200. **Kohn HI, Fry RJ.** Radiation carcinogenesis. *N Engl J Med.* 1984;**310:**504-11.
201. **Kyle RA.** Second malignancies associated with chemotherapy. In: Perry MC, Yarbro JW, eds. *Toxicity of Chemotherapy.* Orlando, Florida: Grune & Stratton; 1984:479-506.
202. **United States General Accounting Office.** Cancer patient survival: what progress has been made? Washington, DC: Government Printing Office; 1987. Publication no. GAO/PEMD-87-13.
203. **Penn I.** Second malignancies following radiotherapy or chemotherapy for cancer. In: Serrou B, Rosenfeld C, Dubois JB, eds. *The Immunopharmacologic Effects of Radiation Therapy.* New York: Raven Press; 1981:415-37.
204. Anticancer drugs causing cancer [Editorial]. *Lancet.* 1982;**1:**234.
205. **Hutchison GB.** Late neoplastic changes following medical irradiation. *Cancer.* 1976;**37:**1102-10.
206. **Arseneau JC, Canellos GP, Johnson R, DeVita VT Jr.** Risk of new cancers in patients with Hodgkin's disease. *Cancer.* 1977;**40:**1912-6.
207. **Canellos GP, Arseneau JC, DeVita VT, Whang-Peng J, Johnson RE.** Second malignancies complicating Hodgkin's disease in remission. *Lancet.* 1975;**1:**947-9.
208. **Coltman CA Jr, Dixon DO.** Second malignancies complicating Hodgkin's disease: a Southwest Oncology Group 10-year followup. *Cancer Treat Rep.* 1982;**66:**1023-33.
209. **Coleman CN, Williams CJ, Flint A, Glatstein EJ, Rosenberg SA, Kaplan HS.** Hematologic neoplasia in patients treated for Hodgkin's disease. *N Engl J Med.* 1977;**297:**1249-52.
210. **Cadman EC, Capizzi RL, Bertino JR.** Acute nonlymphocytic leukemia: a delayed complication of Hodgkin's disease therapy: Analysis of 109 cases. *Cancer.* 1977;**40:**1280-96.
211. **Brody RS, Schottenfeld D, Reid A.** Multiple primary cancer risk after therapy for Hodgkin's disease. *Cancer.* 1977;**40:**1917-26.
212. **Toland DM, Coltman CA, Moon TE.** Second malignancies complicating Hodgkin's disease: the Southwest Oncology Group experience. *Cancer Clin Trials.* 1978;**1:**27-33.
213. **Baccarani M, Bosi A, Papa G.** Second malignancy in patients treated for Hodgkin's disease. *Cancer.* 1980;**46:**1735-40.
214. **Valagussa P, Santoro A, Kenda R, et al.** Second malignancies in Hodgkin's disease: a complication of certain forms of treatment. *Br Med J.* 1980;**280:**216-9.
215. **Boivin JF, Hutchison GB.** Leukemia and other cancers after radiotherapy and chemotherapy for Hodgkin's disease. *J Natl Cancer Inst.* 1981;**67:**751-60.
216. **Nelson DF, Cooper S, Weston MG, Rubin P.** Second malignant neoplasms in patients treated for Hodgkin's disease with radiotherapy or radiotherapy and chemotherapy. *Cancer.* 1981;**48:**2386-93.
217. **Coleman CN, Kaplan HS, Cox R, Varghese A, Butterfield P, Rosenberg SA.** Leukemias, non-Hodgkin's lymphomas and solid tumors in patients treated for Hodgkin's disease. *Cancer Surv.* 1982;**1:**734-44.
218. **Glicksman AS, Pajak TF, Gottlieb A, Nissen H, Stutzman L, Cooper MR.** Second malignant neoplasms in patients successfully treated for Hodgkin's disease: a Cancer and Leukemia Group B study. *Cancer Treat Rep.* 1982;**66:**1035-44.
219. **Valagussa P, Santoro A, Fossati Bellani F, Franchi F, Banfi A, Bonadonna G.** Absence of treatment-induced second neoplasms after ABVD in Hodgkin's disease. *Blood.* 1982;**59:**488-94.
220. **Doreen MS, Gregory WM, Wrigley PF, Stansfeld AG, Lister TA.** Second primary malignant neoplasms in patients treated for Hodgkin's disease at St. Bartholomew's Hospital. *Hematol Oncol.* 1986;**4:**149-61.
221. **Blayney DW, Longo DL, Young RC, et al.** Decreasing risk of leukemia with prolonged follow-up after chemotherapy and radiotherapy for Hodgkin's disease. *N Engl J Med.* 1987;**316:**710-4.
222. **Pedersen-Bjergaard J, Specht L, Larsen SO, et al.** Risk of therapy-related leukaemia and preleukaemia after Hodgkin's disease. Relation to age, cumulative dose of alkylating agents, and time from chemotherapy. *Lancet.* 1987;**2:**83-8.
223. **Reimer RR, Hoover R, Fraumeni JF Jr, Young RC.** Acute leukemia after alkylating-agent therapy of ovarian cancer. *N Engl J Med.* 1977;**297:**177-81.
224. **Einhorn N.** Acute leukemia after chemotherapy (melphalan). *Cancer.* 1978;**41:**444-7.
225. **Pedersen-Bjergaard J, Nissen NI, Sorensen HM, et al.** Acute nonlymphocytic leukemia in patients with ovarian carcinoma following long-term treatment with Treosulfan (= dihydroxybusulfan). *Cancer.* 1980;**45:**19-29.
226. **Greene MH, Harris EL, Gershenson DM, et al.** Melphalan may be a more potent leukemogen than cyclophosphamide. *Ann Intern Med.* 1986;**105:**360-7.
227. **Shimp W, Belzer MB.** Acute leukemia after treatment of small-cell carcinoma of the lung [Letter]. *N Engl J Med.* 1981;**304:**845-6.
228. **Bradley EC, Schechter GP, Matthews MJ, et al.** Erythroleukemia and other hematologic complications of intensive therapy in long-term survivors of small cell lung cancer. *Cancer.* 1982;**49:**221-3.
229. **Markham M, Pavy MD, Abeloff MD.** Acute leukemia following intensive therapy for small-cell carcinoma of the lung. *Cancer.* 1982;**50:**672-5.
230. **Rosner F, Grunwald HW, Zarrabi MH.** Acute leukemia as a complication of cytotoxic chemotherapy. *Int J Radiat Oncol Biol Phys.* 1979;**5:**1705-7.
231. **Fisher B, Rockette H, Fisher ER, Wickerham DL, Redmond C, Brown A.** Leukemia in breast cancer patients following adjuvant chemotherapy or postoperative radiation: the NSABP experience. *J Clin Oncol.* 1985;**3:**1640-58.
232. **Herring MK, Buzdar AU, Smith TL, Hortobagyi GN, Blumenschein GR.** Second neoplasms after adjuvant chemotherapy for operable breast cancer. *Am J Clin Oncol.* 1986;**9:**269-75.
233. **Amadori S, Papa G, Anselmo AP, Fidani P, Mandelli F, Biagini C.** Acute promyelocytic leukemia following ABVD and radiotherapy for Hodgkin's disease. *Cancer Treat Rep.* 1983;**67:**603-4.
234. **Tucker MA, Coleman CN, Cox RS, Varghese A, Rosenberg SA.** Risk of second cancers after treatment for Hodgkin's disease. *N Engl J Med.* 1988;**318:**76-81.
235. **Bonadonna G, Valagussa P, Rossi A, et al.** CMF adjuvant chemotherapy in operable breast cancer. In: Bonadonna G, Salmon SE, eds. *Adjuvant Therapies of Cancer.* New York: Grune & Stratton; 1979:227-35.
236. **Zippin C, Bailar JC 3d, Kohn HI, Lum D, Eisenberg H.** Radiation therapy for cervical cancer: late effects on life span and on leukemia incidence. *Cancer.* 1971;**28:**937-42.
237. **Boice JD, Hutchison GB.** Leukemia in women following radiotherapy for cervical cancer. *J Natl Cancer Inst.* 1980;**65:**115-29.
238. **Kleinerman RA, Curtis RE, Boice JD Jr, Flannery JT, Fraumeni JF Jr.** Second cancers following radiotherapy for cervical cancer. *J Natl Cancer Inst.* 1982;**69:**1027-33.
239. **Easton DJ, Poon MA.** Acute nonlymphocytic leukemia following bladder installations with thiotepa. *Can Med Assoc J.* 1983;**129:**578-9.
240. **Silberberg JM, Zarrabi MH.** Acute nonlymphocytic leukemia after thiotepa installation into the bladder: report of 2 cases and a

review of the literature. *J Urol.* 1987;**138:**402-3.
241. **Yeh GK, Axelrod MR.** Development of multiple myeloma in long term survivors of breast cancer. *Clin Oncol.* 1979;**5:**175-7.
242. **Krikorian JG, Burke JS, Rosenberg SA, Kaplan HS.** Occurrence of non-Hodgkin's lymphoma after therapy for Hodgkin's disease. *N Engl J Med.* 1979;**300:**452-8.
243. **List AF, Greer JP, Cousar JB, et al.** Non-Hodgkin's lymphoma after treatment of Hodgkin's disease: association with Epstein-Barr virus. *Ann Intern Med.* 1986;**105:**668-73.
244. **Henry-Amar M.** Second cancers after radiotherapy and chemotherapy for early stages of Hodgkin's disease. *J Natl Cancer Inst.* 1983;**71:**911-6.
245. **Boivin JF, Hutchison GB, Lyden M, Godbold J, Chorosh J, Schottenfeld D.** Second primary cancers following treatment of Hodgkin's disease. *J Natl Cancer Inst.* 1984;**72:**233-41.
246. **Rubin P, Zagars G, Chuang C, Thomas EM.** Hodgkin's disease. Is there a price for successful treatment? A 25-year experience. *Int J Radiat Oncol Biol Phys.* 1986;**12:**153-66.
247. **Pearson RM, Soloway MS.** Does cyclophosphamide induce bladder cancer? *Urology.* 1978;**11:**437-47.
248. **Wall RL, Clausen KP.** Carcinoma of the urinary bladder in patients receiving cyclophosphamide. *N Engl J Med.* 1975;**293:**271-3.
249. **Sekine I, Kawase Y, Ooi J, Matsumoto K.** Development of malignant tumors following irradiation for preexisting tumors. Study based on autopsy cases of double cancer. *J Radiat Res.* 1986;**27:**151-62.
250. **Greenberg RS, Rustin ED, Clark WS.** Risk of genitourinary malignancies after cancer of the prostate. *Cancer.* 1988;**61:**396-401.
251. **Hay JH, Duncan W, Kerr GR.** Subsequent malignancies in patients irradiated for testicular tumors. *Br J Radiol.* 1984;**57:**597-602.
252. **Brenner DW, Schellhammer PF.** Upper tract urothelial malignancy after cyclophosphamide therapy: a case report and literature review. *J Urol.* 1987;**137:**1226-7.
253. **Kapp DS, Fischer D, Grady KJ, Schwartz PE.** Subsequent malignancies associated with carcinoma of the uterine cervix: including an analysis of the effect of patient and treatment parameters on incidence and sites of metachronous malignancies. *Int J Radiat Oncol Biol Phys.* 1982;**8:**197-205.
254. **Marshall V.** Premalignant and malignant skin tumours in immunosuppressed patients. *Transplantation.* 1974;**17:**272-5.
255. **Tucker MA, Misfeldt D, Coleman CN, Clark WH Jr.** Cutaneous malignant melanoma after Hodgkin's disease. *Ann Intern Med.* 1985;**102:**37-41.
256. **Tobin HE, Miles PA.** Radiation induced osteosarcoma of the clavicle: a case report and literature review. *Milit Med.* 1987;**152:**89-92.
257. **Smith J.** Radiation-induced sarcoma of bone: clinical and radiographic findings in 43 patients irradiated for soft tissue neoplasms. *Clin Radiol.* 1982;**33:**205-21.
258. **Young JW, Liebscher LA.** Postirradiation osteogenic sarcoma with unilateral metastatic spread within the field of irradiation. *Skeletal Radiol.* 1982;**8:**279-83.
259. **Dahlin DC, Coventry MB.** Osteogenic sarcoma. *J Bone Joint Surg [Am].* 1967;**49:**101-10.
260. **Mindell ER, Shah NK, Webster JH.** Postradiation sarcoma of bone and soft tissues. *Orthop Clin North Am.* 1977;**8:**821-34.
261. **Wasylewski AH, Lohmann J, Fischer M, Muller RP, Edel G.** The rare occurrence of a radiation-induced osteosarcoma in the clavicle after treatment of thyroid cancer. *Path Res Pract.* 1984;**178:**441-5.
262. **Boice JD, Greene MH, Keehn RJ, Higgins GA, Fraumeni JF Jr.** Late effects of low-dose adjuvant chemotherapy in colorectal cancer. *J Natl Cancer Inst.* 1980;**64:**501-11.
263. **Ferguson DJ, Sutton HG Jr, Dawson PJ.** Late effects of adjuvant radiotherapy for breast cancer. *Cancer.* 1984;**54:**2319-23.
264. **Kurtz JM, Amalric R, Delouche G, Pierquin B, Roth J, Spitalier JM.** The second ten years: long-term risks of breast conservation in early breast cancer. *Int J Radiat Oncol Biol Phys.* 1987;**13:**1327-32.
265. **Fobair P, Hoppe RT, Bloom J, Cox R, Varghese A, Speigel D.** Psychosocial problems among survivors of Hodgkin's disease. *J Clin Oncol.* 1986;**4:**805-14.
266. **Woods NF, Earp GL.** Women with cured breast cancer: a study of mastectomy patients in North Carolina. *Nurs Res.* 1978;**27:**279-85.
267. **Springer M.** Radical vulvectomy: physical, psychological, social and sexual implications. *Oncol Nurs Forum.* 1982;**9:**19-21.
268. **Sherman RA, Sherman CJ, Parker L.** Chronic phantom and stump pain among American veterans: results of a survey. *Pain.* 1984;**18:**83-95.
269. **Rothwell BR.** Prevention and treatment of the orofacial complications of radiotherapy. *J Am Dent Assoc.* 1987;**114:**316-22.
270. **Keene HJ, Fleming TJ.** Prevalence of caries-associated microflora after radiotherapy in patients with cancer of the head and neck. *Oral Surg Oral Med Oral Pathol.* 1987;**64:**421-6.
271. **Sonis ST.** Oral complications of chemotherapy. In: DeVita VT, Hellman S, Rosenberg, SA, eds. *Cancer: Principle and Practice of Oncology.* Philadelphia: J.B. Lippincott; 1985:2014-21.
272. **Murray CG, Herson J, Daly TE, Zimmerman S.** Radiation necrosis of the mandible: a 10-year study. Part I. Factors influencing the onset of necrosis. *Int J Radiat Oncol Biol Phys.* 1980;**6:**543-8.
273. **Ravindranathan MP, Paul VJ, Kuriakose ET.** Cataract after busulfan treatment. *Br Med J.* 1972;**1:**218-9.
274. **Fraunfelder F, Hanna C, Dreis MW, Cosgrove KW Jr.** Cataracts associated with allopurinol therapy. *Am J Ophthalmol.* 1982;**94:**137-40.
275. **Crews S.** Posterior subscapular cataracts. *Am J Ophthalmol.* 1963;**56:**307-8.
276. **Deeg HJ, Flournoy N, Sullivan KM, et al.** Cataracts after total body irradiation and marrow transplantation: a sparing effect of dose fractionation. *Int J Radiat Oncol Biol Phys.* 1984;**10:**957-64.
277. **Haidak DJ, Hurwitz BS, Yeung KY.** Tear-duct fibrosis (dacryostenosis) due to 5-fluorouracil. *Ann Intern Med.* 1978;**88:**657.
278. **Seiff SR, Shorr N, Adams T.** Surgical treatment of punctual-canalicular fibrosis from 5-fluorouracil therapy. *Cancer.* 1985;**56:**2148-9.
279. **Parker RG, Berry HC.** Late effects of therapeutic irradiation on the skeleton and bone marrow. *Cancer.* 1976;**37:**1162-71.
280. **Ihde DC, DeVita VT.** Osteonecrosis of the femoral head in patients with lymphoma treated with intermittent combination chemotherapy (including corticosteroids). *Cancer.* 1975;**36:**1585-8.
281. **Smith DB.** Rehabilitation of the cancer patient with an ostomy. In: Gunn AE, ed. *Cancer Rehabilitation.* New York: Raven Press; 1984:101-20.
282. **Schimpff SC, Diggs CH, Wiswell JG, Salvatore PC, Wiernik PH.** Radiation-related thyroid dysfunction: implications for the treatment of Hodgkin's disease. *Ann Intern Med.* 1980;**92:**91-8.
283. **Sklar CA, Kim TH, Ramsay NK.** Thyroid dysfunction among long-term survivors of bone marrow transplantation. *Am J Med.* 1982;**73:**688-94.
284. **Markoe AM, Saluk PH.** Combined effects of radiation and chemotherapy on the lymphohemopoietic system with special reference to the immune response. *Front Radiat Ther Oncol.* 1979;**13:**175-93.
285. **Slater JM, Ngo E, Lau BH.** Effect of therapeutic irradiation on the immune responses. *AJR.* 1976;**126:**313-20.