Acute Care of the Cancer Patient

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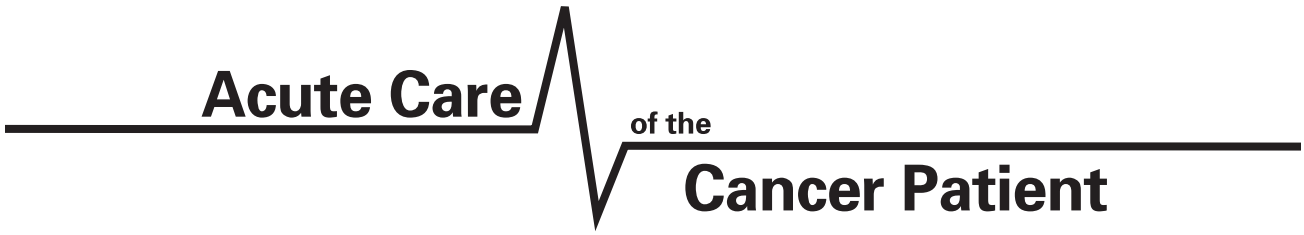
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This book is dedicated to the memory of Douglas Carter (1918–1999), a man whose integrity, flexibility and courage typified the qualities of those who would do battle with this dreadful disease. Let no operation be left untried, no drug remain untested and no compassion be spared for those who have no choice but to fight.

Introduction

The M.D. Anderson Cancer Center is a branch of The University of Texas with 1,000 faculty who focus their entire activities on our mission to eliminate cancer. Our integrated programs in patient care, research, education and prevention provide a wealth of knowledge on clinical care, gained partially from the outcome of extensive research and partly from experiences that have been incorporated into our practices.

This knowledge becomes especially important when skilled medical specialists who are not primarily cancer physicians are called upon to participate, and often temporarily lead, in care delivery for a cancer patient. The continuum of care provided by multidisciplinary teams of surgeons, medical oncologists, and radiation oncologists is frequently punctuated by acute episodes requiring these medical specialists to intervene, with both expertise and speed.

Unstable patients, who ordinarily would not be subjected to extensive surgery, must be stabilized and supported as best as possible when surgery is the only alternative for extending life. We deliberately expose patients to aggressive noninvasive treatments that compromise their ability to fight infection, maintain homeostasis, and prevent bleeding. When these types of complications occur, they become life threatening and require expert intervention. Here the cancer specialist is dependent upon his or her colleague's knowledge of the special problems that often complicate the cancer patient's care.

This book addresses the needs of physician specialists who inevitably become ''team members'' in the multidisciplinary care of the cancer patient. Most of the chapters focus upon the specialties of internal medicine, anesthesiology, and critical care. The special aspects of caring for pediatric patients and for end-stage cancer patients requiring palliative care are also addressed.

In addition, cancer specialists will find a wealth of information and experience, enabling better anticipation and fulfillment of their patients' needs.

The recommendations presented in this volume are documented from the research literature when available. Equally important, they draw upon the vast experience of internists, anesthesiologists, critical care specialists and oncologists at a major cancer center. In 2004, M.D. Anderson physicians saw over 60,000 cancer patients, including over 24,000 new patients, from all over the USA and worldwide. Over 12,000 patients participated in therapeutic clinical trials. We performed 12,463 surgeries, 250,035 courses of radiation therapy, and had over 750,000 patient visits in our clinics. All 13,000 employees, including faculty

and staff, are striving to improve cancer care and our understanding of this disease.

As our population ages, the incidence of cancer will double, even though the chances for curing individual patients are improving substantially. In my own lifetime, the 5-year disease-free survival rate has nearly doubled to 60 percent. New targeted therapies that hold great promise are under investigation. More and older patients who are symptomatic, even critically ill, will have treatment options that offer the possibility of prolonged life or even cure. The team effort required to sustain these patients will become more difficult, but also more promising. It is this hope for increased curability that motivates oncologists to push forward with new, aggressive treatments that often require intensive and rapidly responsive supportive care. Thus, acute cancer care is a timely and relevant topic.

I am pleased that the outstanding faculty at M.D. Anderson, together with collaborators from other institutions, have made this excellent book available to all who undertake the care of patients with cancer.

John Mendelsohn, M.D.
President
The University of Texas
M.D. Anderson Cancer Center
Houston, Texas, U.S.A.

Preface

This book has been written in an effort to collect in one place the knowledge and expertise of the many individuals who provide acute medical care for cancer patients while they receive chemotherapy, radiation treatment and/or undergo surgical resection. Over the past five years we have received many ''curbside consults'' from colleagues and friends in other institutions about how we do certain things or approach difficult oncological problems, all with the theme ''there's no book, so I called to ask.'' We have thus attempted to organize the ''para-oncological'' problems of cancer patients into logical groups, and then provide a contemporaneous account of what the issues are and how they are solved in each author's unit. We have divided the book into five sections, according to how we deal with these issues on a daily basis. Thus the first section describes the general principles of oncological practice — a primer for the non-specialist. The second section describes the perioperative care of patients undergoing cancer resection surgery, with surgical, anesthesiological and critical care perspectives in most cases. In the third section of the book we address the acute medical problems encountered by cancer patients, with an emphasis on critical care medicine and physiology. Section four deals with pediatric issues, while the final section covers the problems of pain management and palliative care. Each chapter has been written by one or more individuals whom we would trust to care for ourselves or our families, and thus whose opinions we trust. We feel that this is the ultimate test of faith in any one physician's skill, and was thus a natural benchmark when deciding whom we would invite to write each chapter. All of our authors have surpassed our expectations, and we think the result is a truly global collection of experience, skill and knowledge that was previously available only on individual cerebral hard drives. Inevitably there are differences in style when a book is written by more than 100 authors; however, we have tried to maintain consistency of philosophy wherever possible.

We hope that this book provides guidance to those who seek it, reassurance to those who are doubtful, and a challenge to those who may choose to do things a different way. It is our view that there are many ways to practice medicine, and not all are suitable in all places, for all patients, and for all physicians. Thus we have tried to emphasize themes, principles and approaches rather than to provide a recipe for every different situation. Please write and let us know what we did badly, so we may improve it next time around.

Andrew D. Shaw
Bernhard Riedel
Allen W. Burton
Alan I. Fields
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Cancer Growth, Progression, and Metastasis

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I. EVOLUTION OF THE PRIMARY TUMOR

The major clinical challenge for cancer therapy remains the eradication (or prevention) of metastatic disease. A principal barrier to destruction of disseminated cancer is the heterogeneous nature of cancer; tumors contain subpopulations of cells that are able to subvert host defenses and recruit infiltrating cells that supply needed growth factors and blood supply. Moreover, metastatic lesions can become autonomous with respect to homeostatic mechanisms of normal tissue architecture (1–3). Neoplastic transformation involves genetic alterations such as the activation or disregulation of oncogenes (4). There are probably continuous selection pressures for cells that are able to circumvent normal growth control mechanisms. The continual evolution of genetically unstable neoplasms eventually favors the emergence of cell subpopulations with metastatic potential. By the time of diagnosis of the primary tumor, malignant neoplasms contain multiple cell populations that are heterogeneous with respect to a variety of biological properties such as cell-surface characteristics, antigenicity, immunogenicity, growth rate, karyotype, sensitivity to chemotherapeutic drugs, and the ability to invade and metastasize (2,5–8). The existence of these subpopulations of cells presents a dilemma for the clinician. The emergence of drug-resistant variants during or subsequent to chemotherapy has been documented as having differences in the response of primary and metastatic tumors to therapeutic agents (2). The obstacle to chemotherapy that heterogeneity imposes may also affect the success of immunotherapy or the use of biological response modifiers (2,9–11).

Actually, the concept that tumors are heterogeneous is not new. Paget (12) analyzed the postmortem data of women who died of cancer and noticed the high frequency of metastasis to the ovaries and different incidence of skeletal metastases associated with different primary tumors. Paget concluded that the organ distribution of metastases is not a matter of chance and suggest that metastases develop only when the ''seed'' (certain tumor cells with metastatic ability) and the ''soil'' (colonized organs providing a microenvironment for growth advantage) are compatible. In recent years, Paget's hypothesis has received considerable experimental and clinical support (13–16). A current definition of the ''seed and soil'' hypothesis encompasses three principles. First, neoplasms are biologically heterogeneous (1,13). Second, the process of metastasis is highly selective, favoring the survival and growth of a small subpopulation of cells that pre-exist in the parent neoplasm (17). Third, the outcome of metastasis depends on multiple interactions of metastatic cells with homeostatic mechanisms. The majority of malignant tumors actually usurp

homeostatic mechanism to gain growth advantage. Neoplastic angiogenesis is an excellent example.

II. TUMOR ANGIOGENESIS

Because a tumor mass >0.25 mm in diameter exceeds the oxygen and nutrient diffusion limits of its vascular supply, to survive and grow, it must generate additional vasculature, i.e., angiogenesis (18–20). The process of angiogenesis consists of a series of sequential steps that result in the establishment of a new vascular bed. To generate capillary sprouts, endothelial cells proliferate, migrate, degrade the basement membrane, and form a structure, i.e., a new lumen organization (21). To stimulate angiogenesis, both tumor cells and host infiltrate cells (such as macrophages) secrete a variety of factors. More than a dozen of proangiogenic molecules have been reported, including basic fibroblast growth factor (bFGF), vascular endothelial growth factor (VEGF, also known as vascular permeability factor) (22–25), interleukin-8 (IL-8), angiogenin, angiotropin, platelet-derived growth factor (PDGF), transforming growth factor-α (TGF-α), transforming growth factor-β (TGF-β), epidermal growth factor (EGF), and tumor necrosis factor-α (TNF-α) (18–23). However, many tissues and tumors also generate factors that inhibit angiogenesis, such as angiostatin, endostatin, thrombospondins, interferon-α (IFN), and interferon-β (IFN-β) [O′R (26), O′ (27), Thrombosp (28–31)]. The angiogenic phenotype of an organ or a tumor is therefore determined by the net balance between positive and negative regulators of neovascularization (32). In normal tissues, factors that inhibit angiogenesis predominate (e.g., IFN-β), whereas in rapidly dividing tissues, factors that stimulate angiogenesis predominate. The type 1 interferons (α and β) are potent inhibitors of transcription of proangiogenic molecules, such as bFGF, matrix metalloproteinases 2 and 9 (MMP-2, MMP-9) and have antiangiogenic activity in treatment of vascular hemangiomas in humans and orthotopic murine tumor models (reviewed in Ref. 33).

Moreover, the structure and architecture of tumor vasculature can dramatically differ from those found in normal organs (34–36). Indeed, blood vessels in tumors are different than those found in wound healing and inflamed tissues. The blood flow through tumors can be tortuous and constantly modeled by regions of necrosis, rapid cell division, and presence of infiltrate cells. Receptors for VEGF (KDR in humans, Flt-1 in mice) are expressed specifically by tumor endothelium, as well as by the angiopoietin tyrosine kinase receptor, Tie-2 (37). In addition, receptors for PDGF and EGF are found on tumor endothelial cells (38–40).

The endothelium is fragile and upregulation of survival factors (such as Bcl-2 and survivin) by molecules found in abundance within the tumor microenvironment, such as VEGF and bFGF, help prevent apoptosis of new endothelium (41–44). There is increased leakiness to macromolecules (perhaps due to the presence of VEGF) (45,46), and vessels often lose distinct features of arteriole, capillary, and venule formation. Modern techniques, such as phage-display targeting, have defined "vascular addresses" that may be distinct for different organs, as well as tumors in those organs, and perhaps offer attractive targets for antivasculature therapy (47).

Angiogenic heterogeneity exists within a single tumor (zonal or intralesional) between different metastases even in a single organ and different neoplasms of the same histologic type is also documented (48,49). For example, the expression of proangiogenic molecules (and, therefore, blood vessel density) in murine or human tumors growing at orthotopic sites in athymic mice is zonal, i.e., demonstrates intralesional heterogeneity. Small tumors (3–4 mm in diameter) expressed more bFGF and IL-8 than large tumors (>10 mm in diameter), whereas more VEGF is expressed in large tumors. Immunostaining showed a heterogeneous distribution of these angiogenic factors within the tumor; expression of bFGF and IL-8 was highest on the periphery of a large tumor, where cell division was maximal. VEGF expression was higher in the center of the tumor (48). Similarly, heterogeneous dependence on angiogenesis was reported for cell subpopulations isolated from human melanoma xenografts having differential expression of hypoxia-inducing factor-1 (49).

Heterogeneity of blood vessel distribution in surgical specimens of human cancers is well documented (50,51). Benign neoplasms are sparely vascularized and tend to grow slowly in contrast to highly vascularized and rapidly growing malignant tumors (51). However, the distribution of vessels in a tumor is not uniform, and Weidner et al. (50,51) cautioned that, to predict the aggressive nature of human cancers, one must determine the mean vessel density (MVD) in the "areas of most intense neovascularization," i.e., tumors exhibit intralesional and zonal heterogeneity for MVD. Similarly, the expression of proangiogenic molecules in surgical specimens of human colon carcinoma was determined by in situ hybridization technique. Matrix metalloproteinase-9 and bFGF were overexpressed at the periphery of the tumor where cells were rapidly dividing, whereas VEGF expression was higher in the center of the lesions (52).

The extent of angiogenic heterogeneity in malignant neoplasms is also regulated by the organ microenvironment. For example, human renal carcinoma cells implanted into the kidney of athymic mice produced a high incidence of lung metastasis, whereas those implanted subcutaneously did not (53). Histopathologic examination of the tissues revealed that the tumors grown in the subcutis of nude mice had few blood vessels when compared with the tumors in the kidney. The subcutaneous tumors also had a significantly lower level of mRNA transcripts for bFGF than the tumor in the kidney, and the expression of the naturally occurring angiogenic inhibitor, IFN-β (which downregulates bFGF), was high in epithelial cells and fibroblasts surrounding the subcutaneous tumors. This was not detected in or around the tumors grown in the kidney (54). The production of IL-8 by melanoma cells is regulated by complex interactions with skin keratinocytes (55). Interleukin-8 expression can be increased by coculture of melanoma cells with skin keratinocytes, and this expression is inhibited by coincubation of melanoma cells with hepatocytes from the liver (56). The organ microenvironment also influences the expression of VEGF. Human gastric cancer cells implanted into the stomach were highly vascularized and expressed high levels of VEGF when compared with implantation in to an ectopic (subcutaneous) site, such as the skin. In addition, metastasis only occurred from the tumor implanted in the stomach (57).

The molecular cross-talk that occurs with tumor cells and endothelium within the tumor microenvironment results in sufficient recruitment of a vascular supply that has physiological properties that allow migration and eventual escape of subpopulations of tumor cells able to complete a cascade of events necessary for metastasis.

III. DETERMINANTS OF METASTASIS

The process of metastasis consists of a series of sequential steps, which can only be completed by an extremely small proportion of cells within the primary tumor (5). Metastasis begins by invasion into host stroma surrounding the primary neoplasm. This is facilitated by the production of enzymes such as the metalloproteinases, cathepsin B, and plasminogen activators (58–60). The invasive process is completed by dissolution of the basement membrane, enhanced motility of some tumor cells, and eventual penetration of blood vessels or lymphatics (61). Reduced expression of the E-cadherin–catenin complex is critical for intercellular adhesion and maintenance of both normal and malignant tissue architecture. Reduced expression of this cohesive complex is associated with tumor invasion, metastasis, and unfavorable prognosis (62). During blood-borne metastasis, tumor cells must survive transport in the circulation, interact with immune cells, and eventually express favorable adhesion molecules that allow arrest in a distant capillary bed. Using radiolabeled melanoma cells, it was found that, at 24 hr after entry of tumor cells into the circulation, $<1\%$ of the cells were viable and $<0.1\%$ eventually formed an experimental metastasis (63). This strengthens the concept that the mere presence of circulating tumor cells does not in itself constitute a prognosis for metastases. The subsequent interactions of metastatic cells with cells of the vascular endothelium include not only nonspecific lodgment of cell emboli, but also the formation of stable adhesions between tumor cells and small-vessel endothelial cells. Extravasation from the luminal side of the blood vessel and subsequent continued growth of the metastatic cell population require response to motility factors, enhanced enzyme expression, upregulation of growth factor receptors, and induction of an angiogenesis within the local environment (reviewed in Ref. 13). Organ-specific properties of the tumor cells result in interactions that enhance tumor growth and survival. For example, subsequent to a partial hepatectomy, the liver undergoes raid cell division termed "regeneration" without simultaneous cell division occurring in other organs, like the kidneys. In contrast, subsequent to nephrectomy, the contralateral kidney compensates by hypertrophy and hyperplasia, but the liver does not (64). When human colon carcinoma cells were implanted in nude mice that were subjected to nephrectomy, partial hepatectomy, or sham-surgery (as a control), it was observed that liver regeneration in nude mice actually stimulated the growth of the colon carcinoma, whereas nephrectomy specifically stimulated the growth of human renal cell carcinoma (64). Human colon carcinoma cells capable of growing in the liver parenchyma (Dukes' stage D) express a higher number of functional receptors for TGF-α (a ligand for the EGF-receptor) and hepatocyte growth factor (c-met) than do cells with low metastatic potential (Dukes' stage B) (65,66).

This concept was expanded to include an examination of the expression of metastasis-related genes such as E-cadherin, MMP-2, MMP-9, bFGF, VEGF, and IL-8. Analysis of the results indicated that these genes could be the predictors of patient survival and metastatic potential of a patient's colorectal carcinoma (67–69), gastric carcinoma (70), prostate carcinoma (71), pancreatic carcinoma (72), lung cancer (73), renal cell carcinoma (74), and ovarian cancer (75). Furthermore, the ratio between expression of collagenase type IV (mean of the expression of MMP-2 and MMP-9)

and E-cadherin (the MMP–E-cadherin ratio, measured at the periphery of each tumor analyzed) correlated with malignant phenotype; a lower MMP–E-cadherin ratio was associated with significantly longer survival and reduced disease recurrence. Studies using DNA microarray analysis on primary breast tumor specimens found that gene expression profiles are strong predictors of prognosis (76).

IV. IMPLICATIONS FOR THERAPY OF CANCER

A. Molecular Targeting in Clinical Studies

The hallmark of the malignant diagnosis is invasion of cytologically abberant cells into the surrounding normal tissue architecture. The primary tumor contains subpopulations of cells that are heterogeneous with respect to a variety of biological, immunological, biochemical, and metastatic properties. This heterogeneity results in the need for multilevel treatment strategies, as conventional therapies are selected for resistant cells. The identification of molecular interactions between tumor cells and tumor endothelium that promote tumor growth also identifies potential avenues for targeted therapy. Moreover, therapeutic strategies may identify unique targets on both tumor cells and their associated blood vessels. New drug development has focused upon targeting growth factor receptors and proangiogenic molecules found in the tumor microenvironment.

Inhibition of growth factor receptors has been accomplished with two main approaches: antibody inhibition of receptor signaling and highly specific inhibitors of intracellular activation (autophosphorylation) of the receptors. These receptors and mutant derivatives of the family of these receptors are often constitutively activated or overexpressed in cancer cells and confer chronic signaling for cell proliferation. The HER2/Neu family of receptors is often found in breast cancer and serves as a target for trastuzumab, the anti-HER2 antibody. This therapy has been used as a single agent, and best results in HER2+ patients were observed when this form of anti-EGF therapy was combined with conventional chemotherapy (77,78). Encouraging clinical results have been obtained using the anti-EGF-R antibody, IM-C225 (cetuixmab), in combination with chemotherapy or radiation in treatment of patients with recurrent or refractory squamous cell carcinoma of the head and neck (79).

Rapid clinical approval was obtained for a small molecule inhibitor of the BCR-ABL kinase (related to c-kit and the PDGF-receptor) for imatinib mesylate (Gleevec, STI-571) in therapy of chronic myeloid leukemia (80) with subsequent approval for use in gastrointestinal stromal tumors (81). These initial and dramatic results motivated clinical evaluation of a myriad of tyrosine kinase inhibitors (TKIs) that are highly specific for different families of growth factor receptors (reviewed in Ref. 82). ZD1839 (Iressa), a TKI of EGF-R, has been approved for advanced non-small cell lung cancer. Phase I and II trials indicated promising activity of this compound, even though patients were not selected for EGF-R expression (83). Therapies that rely upon specific expression of target molecules will eventually show much more efficacy in the patient population when molecular profiles of responders and nonresponders are defined (83).

Interestingly, animal experiments have defined mechanisms regarding the use of inhibitors of proangiogenic factors (and their receptors) that result in a concept of two-compartment targeting, i.e., therapy directed against dividing tumor cells and tumor-associated endothelium. This ''dual'' targeting occurred using both antibody and small molecule-mediated inhibition of growth factor receptor signaling.

B. Blockade of Epidermal Growth Factor Receptor Signaling

Bruns et al. (84) demonstrated regression of human pancreatic carcinoma growing orthotopically in nude mice by therapy with IM-C225 antibody plus gemcitabine. Although both gemcitabine and IM-C225 had activity in this model and are used as single agents, superior results, as measured by tumor burden and incidence of liver metastasis, were achieved by combination therapy. Of particular interest was the finding that apoptosis of tumor-associated endothelial cells was induced by treatment with IM-C225 (due to a coordinate downregulation of VEGF and IL-8 production of the pancreatic carcinoma cells by binding of the IM-C225 antibody). This striking observation, namely, inhibition of growth factor production or receptor signaling could lead to endothelial cell apoptosis, was confirmed using IM-C225 in an orthotopic bladder tumor model using combination therapy with paclitaxel (85).

The use of small molecule inhibitors of growth factor receptor signaling (TKI) has been extensively studied in animal tumor models. Using the orthotopic pancreatic model of human cancer in nude mice, Bruns et al. (86) reported that the modest activity of single agent use of either PKI-166 (EGF-R TKI) or gemcitabine was markedly improved by the combination of these agents (reduction in tumor burden of 85%). This combination therapy also inhibited lymph node and

liver metastasis. This form of therapy resulted in apoptosis of both tumor cells and tumor-associated endothelium.

The selective nature of EGF-R expression within tumors was demonstrated when human prostate tumor cells were injected into the tibia of nude mice (87). Immunohistochemical analysis revealed that the PC-3MM2 cells growing adjacent to the bone expressed high levels of EGF-R and activated EGF-R, whereas tumor cells in the adjacent musculature did not. Moreover, endothelial cells within the bone tumor lesions, but not within uninvolved bone or tumors in the muscle, expressed high levels of activated EGF-R. Oral administration of PKI-166 or PKI-166 plus paclitaxel reduced the incidence and size of bone tumors and the destruction of bone. The combination therapy resulted in a significant inhibition of phosphorylation of EGF-R on tumor and endothelial cells and induced significant apoptosis of endothelial cells within the tumor lesions.

Baker et al. (88) used four different orthotopic animal models, namely, bladder carcinoma, (253J-BV, EGF/TGF-α+), pancreatic carcinoma (L3.6pl, EGF/TGF-α+), EGF/TGF-α-negative renal cell carcinoma (SN12-PM6), and EGF/TGF-α+ renal cell carcinoma (RBM1-IT). Treatment with orally administered PKI-166 alone, intraperitoneal paclitaxel alone (253J-BV), gemcitabine alone (SN12-PM6), or combination of PKI-166 and chemotherapy produced 60%, 32%, or 81% reduction in the tumor volume of 253J-BV bladder tumors, respectively, and 26%, 23%, or 51% reduction in the tumor volume of SN12-PM6 kidney tumors, respectively. Immunohistochemical analyses demonstrated downregulation of phosphorylated EGF-R in the EGF/TGF-α+ and the EGF/TGF-α– tumors taken from mice treated with PKI-166, although apoptosis of tumor-associated endothelial cells was observed in mice whose tumors secreted EGF/TGF-α. These data strongly suggested that optimal combination therapy occurred in tumors that were positive for the respective growth factor receptors and secreted the ligand (which upregulated the receptor on tumor-associated endothelium, thus being vulnerable to TKI-mediated apoptosis). This dual targeting is not limited to EGF-R inhibition.

C. Blockade of Vascular Endothelial Growth Factor Receptor Signaling

Using a mouse-specific antibody (DC101) against the VEGF receptor, Bruns et al. (89) demonstrated inhibition of tumor growth, decrease in metastasis, and induction of apoptosis in both tumor cells and the tumor-associated endothelium in the human pancreatic tumor model in nude mice. Together, these data suggest that either deprivation of growth factors (caused by a decrease in their production) or blockade of receptor signaling leads to dual targeting within the tumor microenvironment. Solorzano et al. (90) demonstrated the inhibition of growth and liver metastasis of human pancreatic cancer implanted into the pancreas of nude mice by combination therapy with gemcitabine and PTK787/ZK222584, an inhibitor of the VEGF receptor. While both agents were active and used alone, superior results in reduction of tumor volume and incidence of lymph node and liver metastasis were achieved with combination therapy of gemcitabine plus PTK787. In addition, apoptosis of tumor cells and tumor-associated endothelial cells was observed. The use of TKI was taken a step further when Baker et al. (91) showed that combining PTK787 (VEGF-R TKI) plus PKI-166 (EGF-R TKI) in combination with gemcitabine resulted in a 97% reduction of pancreatic tumor volume in the orthotopic animal model, and the efficacy correlated with a decrease in circulating proangiogenic molecules (VEGF, IL-8) decreases in staining for dividing cells as measured by proliferating cell nuclear antigen and increases in apoptosis of tumor cells and endothelial cells.

D. Blockade of Platelet-Derived Growth Factor Receptor Signaling

Recent studies have shown that the use of TKI of PDGF-R signaling, STI-571, in combination with paclitaxel reduced the tumor incidence and bone lysis of human prostate cancer cells injected into the tibia of nude mice (92). This was associated with decreased phosphorylation of PDGF-R on tumor cells and tumor-associated endothelial cells and induction of apoptosis in both cell types. The benefits of targeting both pericytes (stromal supporting cells for endothelium, see Ref. 37) and endothelial cells within the tumor with kinase inhibitors have also been discussed (93).

E. Antiangiogenic Properties of Interferon-α

The antiangiogenic properties of IFN-α have been defined by studies using syngeneic murine tumor models and human tumors implanted into nude mice. As found with the chronic administration of IFN-α in hemangiomas (33), frequent, low doses of free-form IFN-α administered to mice implanted with syngeneic bladder carcinoma cells result in downregulation of angiogenesis-related genes (bFGF, MMP-9) and reduction of tumor burden (94). This was not observed with high-dose IFN-α, demonstrating that the optimal

therapeutic dose was not the maximally tolerated dose. These studies were expanded to include therapy of pancreatic cancer in nude mice (low dose IFN-α plus gemcitabine), and the 87% reduction in tumor volume observed using combination therapy was demonstrated to be due to inhibition of the expression of bFGF, MMP-9 and induction of apoptosis in both tumor cells and tumor-associated endothelium (95). Similar findings were reported using low-dose schedules of pegylated IFN-α in combination with paclitaxel in human ovarian cancer implanted into the peritoneal cavity of nude mice (96) and combination therapy with pegylated IFN-α and docetaxel in an orthotopic tumor model of human prostate cancer (97).

Molecular-based targeting of both tumor-associated endothelium and tumor cells will eventually depend upon the identification of unique profiles of human cancers that can be defined prior to therapy. In addition to targeting dividing endothelial cells, additional targets may be identified for existing tumor vasculature (as opposed to strict targeting of angiogenic endothelium) (98).

REFERENCES

1. Fidler IJ, Hart IR. Biological diversity in metastatic neoplasms: origins and implication. Science 1982; 217: 998–1003.
2. Fidler IJ, Balch CM. The biology of cancer metastasis and implications for therapy. Curr Prob Surg 1987; 24: 131–233.
3. Killion JJ, Fidler IJ. The biology of tumor metastasis. Semin Oncol 1989; 16:106–115.
4. Bishop MJ. The molecular genetics of cancer. Science 1987; 235:305–311.
5. Poste G, Fidler IJ. The pathogenesis of cancer metastasis. Nature 1980; 283:139–146.
6. Heppner G. Tumor heterogeneity. Cancer Res 1984; 44: 2259–2265.
7. Nicolson GL. Generation of phenotypic diversity and progression in metastatic tumors. Cancer Metastasis Rev 1984; 3:25–42.
8. Killion JJ, Kollmorgen GM. Isolation of immunogenic tumor cells by cell-affinity chromatography. Nature 1976; 259:674–676.
9. Kerbel RS. Implications of immunological heterogeneity in tumors. Nature 1979; 280:358–360.
10. Killion JJ. Immunotherapy with tumor subpopulations. II. Therapy of drug-resistant L1210 leukemia and E14 lymphoma. Cancer Immunol Immunother 1979; 5: 21–26.
11. Malkovska V, Sondel PM, Malkovsky. Tumor immunotherapy. Curr Opin Immunol 1989; 1:883–890.
12. Paget S. The distribution of secondary growths in cancer of the breast. Lancet 1889; 1:571–573.
13. Fidler IJ. Critical factors in the biology of human cancer metastasis: twenty-eighth G.H.A. Clowes memorial award lecture. Cancer Res 1990; 50:6130–6138.
14. Fidler IJ. Experimental orthotopic models of organ-specific metastasis by human neoplasms. Adv Mol Cell Biol 1994; 9:191–215.
15. Price JE. Host–tumor interaction in progression of breast cancer metastasis. In Vivo 1994; 8:145–154.
16. Hart IR. "Seed and soil" revisited: mechanisms of site-specific metastasis. Cancer Metastasis Rev 1982; 1: 5–16.
17. Fidler IJ, Kripke ML. Metastasis results from preexisting variant cells within a malignant tumor. Science 1977; 197:893–895.
18. Fidler IJ, Ellis LM. The implication of angiogenesis to the biology and therapy of cancer metastasis. Cell 1994; 47:185–188.
19. Folkman J. Angiogenesis in cancer, vascular, rheumatoid, and other disease. Nat Med 1995; 1:27–31.
20. Liotta LA, Steeg PS, Stetler-Stevenson WG. Cancer metastasis and angiogenesis: an imbalance of positive and negative regulation. Cell 1991; 64:327–336.
21. Auerbach W, Auerbach R. Angiogenesis inhibition: a review. Pharmacol Ther 1994; 63:265–311.
22. Folkman J, Klagsbrun M. Angiogenic factors. Science 1987; 235:444–447.
23. Bouck N, Stellmach V, Hsu SC. How tumors become angiogenic. Adv Cancer Res 1996; 69:135–174.
24. Folkman J. Seminars in medicine of the Beth Israel Hospital, Boston, MA. Clinical applications of research on angiogenesis. N Engl J Med 1995; 333:1757–1763.
25. Cockerill GW, Gamble JR, Vadas MA. Angiogenesis: models and modulators. Int Rev Cytol 1995; 159: 113–160.
26. O'Reilly MS, Holmgren L, Shing Y, Chen C, Rosenthal RA, Moses M, Lane WS, Cao Y, Sage EH, Folkman J. Angiostatin: a novel angiogenesis inhibitor that mediates the suppression of metastases by a Lewis lung carcinoma. Cell 1994; 79:185–188.
27. O'Reilly MS, Boehm, T, Shing Y, Fukai N, Vasios G, Lane WS, Flynn E, Birkhead JR, Olsen BR, Folkman J. Endostatin: an endogenous inhibitor of angiogenesis and tumor growth. Cell 1997; 88:277–285.
28. Miyata Y, Koga S, Takehara K, Kanetake H, Kanda S. Expression of thromobspondin-derived 4N1K peptide-containing proteins in renal cell carcinoma tissues is associated with a decrease in tumor growth and angiogenesis. Clin Cancer Res 2003; 9:1734–1740.
29. Folkman J. How is blood vessel growth regulated in normal and neoplastic tissue? G.H.A. Clowes memorial award lecture. Cancer Res 1986; 46:467–473.
30. Fidler IJ, Ellis LM. The implications of angiogenesis for the biology and therapy of cancer metastasis. Cell 1994; 79:185–188.
31. Singh RK, Llansa N, Bucana CD, Sanchez R, Koura A, Fidler IJ. Cell density-dependent regulation of basic fibroblast growth factor expression in human renal cell carcinoma cells. Cell Growth Differ 1996; 7:397–404.

32. Hanahan D, Folkman J. Patterns and emerging mechanisms of the angiogenic switch during tumorigenesis. Cell 1996; 86:353–364.
33. Fidler IJ. Regulation of neoplastic angiogenesis. J Natl Cancer Inst Monogr 2000; 28:10–14.
34. Ebhard A, Kahlert S, Goede V, Hemmerlein B, Plate KH, Augustin HG. Heterogeneity of angiogenesis and blood vessel maturation in human tumors: implications for antiangiogenic tumor therapies. Cancer Res 2000; 60:1388–1393.
35. Nels V, Denzer K, Drenchahn D. Pericyte involvement in capillary sprouting during angiogenesis in situ. Cell Tissue Res 1992; 270:469–474.
36. Nor JE, Polverni PJ. Role of endothelial cell survival and death signals in angiogenesis. Angiogenesis 1999; 3: 101–116.
37. Liu, W, Ahmad SA, Reinmuth N, Shaheen RM, Jung YD, Fan F, Ellis LM. Endothelial cell survival and apoptosis in the tumor vasculature. Apoptosis 2000; 5: 323–328.
38. Uehara H, Kim SJ, Karashima T, Shepherd DL, Fan D, Tsan R, Killion JJ, Logothetis C, Mathew P, Fidler IJ. Effects of blocking platelet-derived growth factor-receptor signaling in a mouse model of experimental prostate cancer bone metastases. J Natl Cancer Inst 2003; 19:458–470.
39. Veenendall LM, Jin H, Ran S, Cheung L, Navone N, Marks JW, Waltenberger J, Thorpe P, Rosenblum MG. In vitro and in vivo studies of a VEGF121/r Gelonin chimeric fusion toxin targeting the neovasculature of solid tumors. Proc Natl Acad Sci USA 2002; 99: 7866–7871.
40. Suhardja A, Hoffman H. Role of growth factors and their receptors in proliferation of microvascular endothelial cells. Microsc Res Tech 2003; 60:70–75.
41. Wang JH, Wu QD, Bouchier-Hayes D, Redmond HP. Hypoxia upregulates Bcl-2 expression and suppresses interferon-gamma induced antiangiogenic activity in human tumor derived endothelial cells. Cancer 2002; 15: 2745–2755.
42. Mesri M, Morales-Ruiz M, Ackermann EJ, Bennett CF, Pober JS, Sessa WC, Altieri DC. Suppression of vascular endothelial growth factor-mediated endothelial cell protection by surviving targeting. Am J Pathol 2001; 158:1757–1765.
43. Gerber HP, Dixit V, Ferrara N. Vascular endothelial growth factor induces expression of the antiapoptotic proteins Bcl-2 and A1 in vascular endothelial cells. J Biol Chem 1998; 273:13313–13316.
44. Karsan A, Yee E, Poirier GG, Zhou P, Craig R, Harlan JM. Fibroblast growth factor-2 inhibits endothelial cell apoptosis by Bcl-2-dependent and independent mechanisms. Am J Pathol 1997; 151:1775–1784.
45. Jain RK. Transport of molecules across tumor vasculature. Cancer Metastasis Rev 1987; 6:559–563.
46. Dvorak HF. Leaky tumor vessels: consequences for tumor stroma generation and for solid tumor therapy. Prog Clin Biol Res 1990; 354A:317–330.
47. Pasqualini R, Arap W, McDonald DM. Probing the structural and molecular diversity of tumor vasculature. Trends Mol Med 2002; 8:563–571.
48. Kumar R, Kuniyase H, Bucana CD, Wilson MR, Fidler IJ. Spatial and temporal expression of angiogenic molecules during tumor growth and progression. Oncol Res 1998; 10:301–311.
49. Yu JL, Rak JW, Carmeliet P, Nagy A, Kerbel RS, Coomber BL. Heterogeneous vascular dependence of tumor cell populations. Am J Pathol 2001; 158: 1225–1234.
50. Weidner N, Semple JP, Welch JR, Folkman J. Tumor angiogenesis and metastasis-correlation in invasive breast cancer. N Engl J Med 1991; 324:1–8.
51. Weidner N, Folkmna J, Pozza F, Bevilacqua P, Allred EN, Moore DH, Meli S, Gasparini G. Tumor angiogenesis: a new significant and independent prognostic indicator in early-stage breast carcinoma. J Natl Cancer Inst 1992; 84:1875–1887.
52. Kitadai Y, Bucana CD, Ellis LM, Anzai H, Tahara E, Fidler IJ. In situ hybridization technique for analysis of metastasis-related genes in human colon carcinoma cells. Am J Pathol 1995; 147:1238–1247.
53. Singh RK, Bucana CD, Gutman M, Fan D, Wilson MR, Fidler IJ. Organ site-dependent expression of basic fibroblast growth factor in human renal cell carcinoma cells. Am J Pathol 1994; 145:365–374.
54. Singh RK, Gurman M, Bucana CD, Sanchez R, Llansa N, Fidler IJ. Interferons alpha and beta down-regulate the expression of basic fibroblast growth factor in human carcinomas. Proc Natl Acad Sci USA 1995; 92: 4562–4566.
55. Herlyn M. Human melanoma: development and progression. Cancer Metastasis Rev 1990; 9:101–112.
56. Gurman M, Singh RK, Xie K, Bucana CD, Fidler IJ. Regulation of interleukin-8 expression in human melanoma cells by the organ environment. Cancer Res 1995; 55:2470–2475.
57. Takahasi Y, Mai M, Wilson MR, Ellis LM. Site-dependent expression of vascular endothelial growth factor, angiogenesis and proliferation in human gastric carcinoma. Int J Oncol 1996; 8:701–705.
58. Sloane BF, Honn KV. Cysteine proteinase and metastasis. Cancer Metastasis Rev 1984; 3:249–265.
59. Jones PA, DeClerck YA. Extracellular matrix destruction by invasive tumor cells. Cancer Metastasis Rev 1982; 1:289–319.
60. Liotta LA, Rao CN, Barksy SH. Tumor invasion and the extracellular matrix. Lab Invest 1983; 49:636–649.
61. Liotta LA, Stetler-Stevenson WG. Metalloproteinases and cancer invasion. Semin Cancer Biol 1990; 1: 99–106.
62. Bremnes RM, Veve R, Hirsch FR, Franklin WA. The E-cadherin cell–cell adhesion complex and lung cancer invasion, metastasis, and prognosis. Lung Cancer 2002; 36:115–124.
63. Fidler IJ. Metastasis: quantitative analysis of distribution and fate of tumor emboli labeled with

125I-5-iodo-2′-deoxyuridine. J Natl Cancer Inst 1970; 45:773–782.
64. Gutman M, Singh RK, Price JE, Fan D, Fidler IJ. Accelerated growth of human colon cancer cells in nude mice undergoing liver regeneration. Invasion Metastasis 1994; 14:362–371.
65. Radinsky R, Bucana CD, Ellis LM, Sanchez R, Clearly KR, Brigati DJ, Fidler IJ. A rapid colorimetric in situ messenger RNA hybridization technique for analysis of epidermal growth factor receptor in paraffin-embedded surgical specimens of human colon carcinomas. Cancer Res 1993; 53:937–943.
66. Radinsky R, Risin S, Fan D, Dong Z, Bielenberg, D, Bucana CD, Fidler IJ. Level and function of epidermal growth factor receptor predict the metastatic potential of human colon carcinoma cells. Clin Cancer Res 1995; 1:19–31.
67. Kitadai Y, Ellis LM, Tucker SL, Greene GF, Bucana CD, Cleary KR, Takahashi Y, Tahara E, Fidler IJ. Multiparametric in situ mRNA hybridization analysis to predict disease recurrence in patients with colon carcinoma. Am J Pathol 1996; 149:1541–1551.
68. Kitadai Y, Ellis LM, Takahashi Y, Bucana CD, Anzai H, Tahara E, Fidler IJ. Multiparametric in situ messenger RNA hybridization analysis to detect metastasis-related genes in surgical specimens of human colon carcinomas. Clin Cancer Res 1995; 1:1095–1102.
69. Kitadai Y, Bucana CD, Illis LM, Anzai H, Tahara E, Fidler IJ. In situ mRNA hybridization technique for analysis of metastasis-related genes in human colon carcinoma cells. Am J Pathol 1995; 147:1238–1247.
70. Anzai H, Kitadai Y, Bucana CD, Sanchez R, Omoto R, Fidler IJ. Expression of metastasis-related genes in surgical specimens of human gastric cancer can predict disease recurrence. Eur J Cancer 1998; 34:558–565.
71. Greene GF, Kitadai Y, Pettaway CA, von Eschenback AC, Bucana CD, Fidler IJ. Correlation of metastasis-related gene expression with metastatic potential in human prostate carcinoma cells implanted in nude mice using an in situ messenger RNA hybridization technique. Am J Pathol 1997; 150:1572–1582.
72. Kuniyasu H, Ellis LM, Evand DB, Abbruzzese JL, Fenoglio CJ, Bucana CD, Cleary KR, Tahara E, Fidler IJ. Relative expression of E-cadherin and type IVC collagenase genes predicts disease outcome in patients with resectable pancreatic carcinoma. Clin Cancer Res 1999; 5:25–33.
73. Herbst RS, Yano S, Kuniyasu H, Khuri FR, Bucana CD, Guo F, Liu D, Kemp B, Lee JJ, Hong WK, Fidler IJ. Differential expression of E-cadherin and type IV collagenase genes predicts outcome in patients with stage I non-small cell lung carcinoma. Clin Cancer Res 2000; 6:790–797.
74. Slaton JW, Inoue K, Perrotte P, El-Naggar AK, Swanson DA, Fidler IJ, Dinney CP. Expression levels of genes that regulate metastasis and angiogenesis correlate with advanced pathological stage of renal cell carcinoma. Am J Pathol 2001; 158:735–743.
75. Herrera CA, Xu L, Bucana CD, Silva VG, Hess KR, Gershenson DM, Fidler IJ. Expression of metastasis-related genes in human epitheilial ovarian tumors. Int J Oncol 2002; 20:5–13.
76. Van't Veer LJ, Dai H, van de Vijver MJ, He YD, Hart AA, Mao M, Peterse HL, van der Kooy K, Marton MJ, Witteveen AT, Schreiberr GJ, Kerkhoven RM, Roberts C, Linsley PS, Bernards R, Friend SH. Gene expression profiling predicts clinical outcome of breast cancer. Nature 2002; 415:530–536.
77. Arteaga CL. Trastuzumab, an appropriate first-line single-agent therapy for HER2-overexpressing metastatic breast cancer. Breast Cancer Res 2003; 5:96–100.
78. Christodoulou C, Klouvas G, Pateli A, Mellou S, Sgouros J, Skarlos DV. Prolonged administration of weekly paclitaxel and trastuzumab in patients with advanced breast cancer. Anticancer Res 2003; 23: 737–744.
79. Herbst RS, Hong WK. IMC-C225, an anti-epidermal growth factor receptor monoclonal antibody for treatment of head and neck cancer. Semin Oncol 2002; 29: 18–30.
80. Peggs K, Mackinnon S. Imatinib mesylate—the new gold standard for treatment of chronic myeloid leukemia. New Engl J Med 2003; 348:1048–1050.
81. Patel SR. Recent advances in systemic therapy of soft tissue sarcomas. Expert Rev Anticancer Ther 2003; 3: 179–184.
82. Fabbro D, Ruetz S, Buchdunger E, Cowan-Jacob SW, Fendrich G, Liebetanz J, Mestan J, O'Reilly T, Traxler P, Chaudhuri B, Fretz H, Zimmermann J, Meyer T, Caravatti G, Furet P, Manley PW. Protein kinases as targets for anticancer agents: from inhibitors to useful drugs. Pharmacol Ther 2002; 93:79–98.
83. Ranson M, Thatcher N. Commentary on ZD1839 (Iressa) in non-small cell lung cancer. Lung Cancer 2003; 40:77–78.
84. Bruns CJ, Harbison MT, Davis DW, Portera CA, Tsan R, McConkey DJ, Evans DB, Abbruzzese JL, Hicklin DJ, Radinsky R. Epidermal growth factor receptor blockade with C225 plus gemcitabine results in regression of human pancreatic carcinoma growing orthotopically in nude mice by antiangiogenic mechanisms. Clin Cancer Res 2000; 6:1936–1948.
85. Inoue K, Slaton JW, Perrotte P, Davis DW, Bruns CJ, Hicklin DJ, McConkey DJ, Sweeney P, Radinsky R, Dinney CP. Paclitaxel enhances the effects of the anti-epidermal growth factor receptor monoclonal antibody ImClone C225 in mice with metastatic human bladder transitional cell carcinoma. Clin Cancer Res 2000; 6: 4874–4884.
86. Bruns CJ, Solorzano CC, Harbison MT, Ozawa S, Tsan R, Fan D, Abbruzzese J, Traxler P, Buchdunger E, Randinsky R, Fidler IJ. Blockade of the epidermal growth factor receptor signaling by a novel tyrosine kinase inhibitor leads to apoptosis of endothelial cells and therapy of human pancreatic carcinoma. Cancer Res 2000; 60:2926–2935.

87. Kim SJ, Uehara, H, Karashima T, Shepherd DL, Killion JJ, Fidler IJ. Blockade of epidermal growth factor receptor signaling in tumor cells and tumor-associated endothelial cells for therapy of androgen-independent human prostate cancer growing in the bone of nude mice. Clin Cancer Res 2003; 9:1200–1210.
88. Baker CH, Kedar D, McCarty MF, Tsan R, Weber KL, Bucana CD, Fidler IJ. Blockade of epidermal growth factor receptor signaling on tumor cells and tumor-associated endothelial cells for therapy of human carcinomas. Am J Pathol 2002; 161:929–938.
89. Bruns CJ, Shrader M, Harbison MT, Portera C, Solorzano CC, Jauch KW, Hicklin DJ, Radinsky R, Ellis LM. Effect of the vascular endothelial growth factor receptor-2 antibody DC101 plus gemcitabine on growth, metastasis and angiogenesis of human pancreatic cancer growing orthotopically in nude mice. 2002; 102:101–108.
90. Solorzano CC, Baker CH, Bruns CJ, Killion JJ, Ellis LM, Wood J, Fidler IJ. Inhibition of growth and metastasis of human pancreatic cancer growing in nude mice by PTK787/ZK222584, an inhibitor of the vascular endothelial growth factor receptor tyrosine kinases. Cancer Biother Radiopharm 2002; 16:359–370.
91. Baker CH, Solorzano CC, Fidler IJ. Blockade of vascular endothelial growth factor receptor and epidermal growth factor receptor signaling for therapy of metastatic human pancreatic cancer. Cancer Res 2002; 62:1996–2003.
92. Uehara H, Kim SJ, Karashima T, Shepherd DL, Fan D, Tsan R, Killion JJ, Logothetis C, Mathew P, Fidler IJ. Effects of blocking platelet-derived growth factor-receptor signaling in a mouse model of experimental prostate cancer bone metastases. J Natl Cancer Inst 2003; 95:458–470.
93. Bergers G, Song S, Meryer-Morse N, Bergsland E, Hanahan D. Benefits of targeting both pericytes and endothelial cells in the tumor vasculature with kinase inhibitors. J Clin Invest 2003; 111:1287–1295.
94. Slaton JW, Perrotte P, Inoue K, Dinney CPN, Fidler IJ. Interferon-α-mediated down-regulation of angiogenesis-related genes and therapy of bladder cancer are dependent on optimization of biological dose and schedule. Clin Cancer Res 1999; 5:2726–2734.
95. Solorzano CC, Hwang R, Baker CH, Bucana CD, Pisters PW, Evans DB, Killion JJ, Fidler IJ. Administration of optimal biological dose and schedule of interferon alpha combined with gemcitabine induces apoptosis in tumor-associated endothelial cells and reduces growth of human pancreatic carcinoma implanted orthotopically in nude mice. Clin Cancer Res 2003; 9: 1858–1867.
96. Tedjarati S, Baker CH, Apte S, Huang S, Wolf JK, Killion JJ, Fidler IJ. Synergistic therapy of human ovarian carcinoma implanted orthotopically in nude mice by optimal biological dose of pegylated interferon alpha combined with paclitaxel. Clin Cancer Res 2002; 8: 2413–2422.
97. Huang SF, Kim SJ, Lee AT, Karashima T, Bucana C, Kedar D, Sweeney P, Mian B, Fan D, Shepherd D, Fidler IJ, Dinney CP, Killion JJ. Inhibition of growth and metastasis of orthotopic human prostate cancer in athymic mice by combination therapy with pegylated interferon-alpha-2b and docetaxel. Cancer Res 2002; 62: 5720–5726.
98. Thorpe PE, Chaplin DJ, Blakey DC. The first international conference on vascular targeting: meeting overview. Cancer Res 2003; 63:1144–1147.

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Principles of Clinical Cancer Staging

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I. INTRODUCTION

The first half of the 20th century was marked by a growing recognition that not all tumors at a given anatomic site share the same prognosis or require the same type of treatment. In the breast, for example, the radical mastectomy recommended by Halsted in the 19th century was needlessly disfiguring for some women with small tumors, while doing little to affect survival for those with advanced disease. This growing recognition of the heterogeneity of cancer resulted in attempts to define characteristics that would be useful in assessing prognosis and determining appropriate treatment for individual tumors.

By the 1940s, there was a widespread consensus that the major anatomical attributes of a tumor that determine its behavior are: size of the primary tumor (T), presence and extent of regional lymph node involvement (N), and presence of distant metastases (M). Starting in 1942, Pierre Denoix began the development of a cancer-staging system based on these attributes (1). Clinical stage classifications for cancers of the breast and larynx were first presented in 1958 (2). Recommendations for 23 other body sites were published in brochures by the International Union against Cancer (UICC), and consolidated into the ''TNM Classification of Malignant Tumors'' published by the UICC in 1968 (3). Second and third editions were published in 1974 and 1978, and the third edition was enlarged and revised in 1982.

The American Joint Committee on Cancer (AJCC) was first organized in 1959 as the American Joint Committee for Cancer Staging and End-Point Results Reporting, with the goal of developing a clinical-staging system that was acceptable to the American medical profession. The first formal edition of the cancer-staging manual from the AJCC appeared in 1977. The second edition, published in 1983, revised and expanded the earlier edition, and also moved to ensure conformity between the AJCC system and the UICC system. By ensuring this conformity, a uniform ''language'' is maintained for the exchange of clinical information among national and international treatment centers. Subsequent revisions of the TNM-staging system have been driven by significant advances in diagnosis and treatment, with the underlying goals of improving the assessment of prognosis and the ability to make appropriate treatment decisions. The latest revision of the TNM-staging system was published in 2002 (4,5) and officially adopted for use in tumor registries in January 2003.

The TNM-staging system includes four classifications: clinical, pathologic, retreatment, and autopsy. Clinical classification (TNM or cTNM) is based on

evidence that is gathered before initial treatment of the primary tumor, and is used to make treatment recommendations. Pathologic classification (pTNM) includes the results of clinical staging, as modified by evidence obtained from surgery and from pathologic examination of the primary tumor, lymph nodes, and distant metastases (if present). It is used to assess prognosis and to make recommendations for adjuvant treatment. Retreatment classification (rTNM) includes all information available at the time when further treatment is needed for a tumor that has recurred after a disease-free interval. Autopsy classification (aTNM) is used for cancers discovered after the death of a patient, when the cancer was not detected prior to death.

The T, N, and M classifications are separately defined for tumors at each anatomic site. Although TNM staging offers a valuable platform for assessing tumors at most sites, certain cancers require a different approach to staging. Both Hodgkin's and non-Hodgkin's lymphoma, for example, are staged by distribution and symptomatology, rather than local extent of the disease. Primary tumors of the central nervous system have not been amenable to TNM staging. In the brain, the size of the tumor is not as important for outcome as the histology and location. There are no lymph nodes in the brain, so an "N" classification is not possible. Finally, most patients with brain cancer tend to have a short survival time, so distant metastases do not have time to develop or cannot pass through the blood–brain barrier.

This review will cover the general principles used in clinical staging with the TNM system (4,5). Besides its current importance for primary treatment selection, clinical staging will have growing importance in cancer treatment as clinicians explore noninvasive modalities for tumor ablation. Noninvasive approaches currently under study include percutaneous radiofrequency ablation, cryosurgery, laser ablation, and MRI-guided focused sonography. Accurate clinical staging will be critical to ensure proper patient selection for such procedures, and will also be increasingly important in determining appropriate adjuvant treatment, since the primary tumor will be destroyed during the initial procedure.

II. PRINCIPLES OF CLINICAL CANCER STAGING USING THE TNM SYSTEM

A. General Rules

The natural history of a specific tumor is determined by a variety of factors. Cancers that develop in the same site (e.g., breast or prostate) and have similar histology can be expected to have roughly similar patterns of growth. Beyond that, increasing size of the tumor is one of the key indicators of outcome. As the primary tumor becomes larger, it is more likely to be associated with lymph node involvement and, ultimately, distant metastases. For some tumors, other factors have been found to significantly influence prognosis, and are also considered. For example, histologic grade is considered in the staging of soft-tissue sarcoma and prostate adenocarcinoma, and histologic type and patient age are considered in the staging of thyroid carcinoma.

Evidence for T, N, and M categories is acquired before any treatment of the primary tumor (including neoadjuvant systemic therapy), using the results from clinical examination. (If classification is performed during or following neoadjuvant therapy or other initial multimodality therapy, which might alter the original pathology, the TNM or pTNM categories are identified by a "y" prefix, e.g., ypTNM.) A variety of imaging studies and additional tests (endoscopy, surgical exploration, curettage, etc.) are used as appropriate for specific sites (see Table 1, for examples). All

Table 1 Evidence Used for Clinical Cancer Staging

Cancer site	Staging evidence
Salivary gland	Neurologic evaluation of cranial nerves; radiologic studies (MRI or CT) to examine deep tissue extent, bone invasion
Thyroid	Indirect laryngoscopy, radioisotope thyroid scan, MRI, or CT
Colon and rectum	Sigmoidoscopy, colonoscopy with biopsy, special examinations to demonstrate extracolonic metastases (chest films, liver function tests, liver scans)
Gall bladder	Ultrasound, CT, surgical exploration.
Melanoma	"T" classification based on thickness and ulceration, as determined by excisional biopsy (punch biopsy, fusiform ellipse, or saucerization)
Cervix	Colposcopy, endocervical curettage, hysteroscopy, cystoscopy, proctoscopy, intravenous urography, x-ray of lungs and skeleton
Prostate	Digital rectal exam, transrectal ultrasound, sextant needle biopsy
Kidney	CT, laparoscopy, biopsy of distant sites

cases must be confirmed microscopically for TNM staging. A biopsy (excisional, fine needle aspiration, core) is used to determine histologic type and grade, and to establish a diagnosis of cancer. The clinical stage of the primary tumor is not changed on the basis of additional information gathered during treatment. If there is any doubt about the appropriate T, N, or M category, the less advanced category is chosen.

B. The ''T'' Classification

The size of the primary tumor is clinically assessed through direct visualization, palpation, or imaging studies, and is represented as the linear measurement of the greatest dimension. Biopsy results are not used for clinical assessment of tumor size. The clinical estimation of tumor size by palpation may differ from that obtained on imaging studies. For example, it is relatively common to obtain different size estimates by physical examination and mammography in patients with breast cancer (6,7). In such cases, an average of the two values may be used (8). Clinical tumor size is classified as:

TX	Primary tumor cannot be assessed
T0	No evidence of primary tumor
Tis	Carcinoma in situ
T1, T2, T3, T4	Increasing size and/or local extent of the primary tumor

In cases where there are multiple simultaneous tumors in one organ, the T category is assigned according to the size of the largest tumor, rather than a combination of tumor sizes. The clinical record should indicate either the presence of multiple tumors [e.g., T2 (m)] or the number of tumors [e.g., T2 (5)].

C. The ''N'' Classification

The N classification reflects metastases of the primary tumor to regional lymph nodes. Lymph nodes are clinically assessed through palpation or imaging studies or through biopsy (e.g., FNA) of suspicious nodes. They are classified as:

NX	Regional lymph nodes cannot be assessed
N0	No regional lymph node metastases
N1, N2, N3	Increasing involvement of regional lymph nodes

Direct extension of a tumor into a lymph node is classified as a lymph node metastasis. Metastasis in any lymph node other than a regional node is considered to be a distant metastasis. Although biopsy of suspicious nodes is used for some tumors (e.g., thyroid carcinoma), sentinel lymph node assessment is *not* considered a part of clinical staging. The sentinel lymph node is the first node (or nodes) to receive drainage from the primary tumor, and its status (positive or negative for metastases) is predictive of the status of the other lymph nodes in that basin. Sentinel lymph node dissection is considered as part of the pathologic classification.

D. The ''M'' Classification

Distant metastases are typically detected through the use of imaging or through surgical exploration, often initiated as a result of patient symptomatology. They are classified as:

MX Distant metastasis cannot be assessed
M0 No distant metastasis
M1 Distant metastasis

The M1 category can be further categorized to reflect the site of the distant metastasis: pulmonary (PUL), osseous (OSS), hepatic (HEP), etc.

E. Assigning a Stage

After assigning a T, N, and M category, the categories are combined into stages. The clinical stage assigned to a specific tumor is used to select the appropriate initial treatment for that tumor. The TNM stages range from Stage 0 to IV. Carcinoma in situ is categorized as Stage 0 and, for most sites, the presence of distant metastases is categorized as Stage IV. Stages I, II, and III represent increasing anatomic extent of the tumor, characterized by increasingly poor outcomes. The TNM stages are defined such that the tumors represented in each stage are relatively homogeneous with regard to survival. Survival rates associated with different stages are defined separately for different cancer sites.

III. CHANGES IN THE TNM-STAGING SYSTEM

A. The Importance of Stability

The TNM-staging system is not a static set of rules. Since its inception, it has evolved because of advances in detection, diagnosis, and treatment for every tumor site. Significant advances in clinical imaging have enabled physicians to use these noninvasive technologies to more accurately determine tumor size and nodal involvement. Improved survival as the result of developments in systemic treatment has resulted in alterations to both clinical and pathologic staging in some cases. For example, metastases to the supraclavicular lymph nodes (SCLN) in patients with breast cancer are associated with a poor prognosis, and the 1997 revision of the TNM-staging system classified

SCLN metastases as distant metastases (M1), resulting in a designation of Stage IV (9). Such patients were generally considered to be end-stage and were given only palliative care. However, Brito et al. (10) found that when SCLN-positive breast cancer patients received aggressive multimodal treatment, their survival time was equivalent to that seen in Stage IIIB patients without distant metastases. Thus, in the new edition of the TNM-staging system, metastases to the SCLN are classified as N3c rather than M1.

However, changes in the TNM system are not undertaken lightly. The TNM-staging system represents a shorthand whereby clinical experience can be accurately conveyed to other practitioners, and the results of clinical studies in different institutes and different countries can be compared directly. The use of TNM staging in the United States is a mandatory requirement for admission to cancer-approved hospitals, and TNM staging is used in the accrual and sorting of cancer outcome data in national data bases. Thus, it is important for the TNM system to remain relatively consistent over extended time periods, and to incorporate only those changes that are supported by strong clinical data and represent a current consensus among medical practitioners.

To assess the difficulties that can arise even when necessary changes are made to the TNM-staging system, Woodward et al. (11) examined records from 1350 breast cancer patients who had received mastectomy and doxorubicin-based chemotherapy at M.D. Anderson Cancer Center. They assigned pathologic stage according to both the 1988 and the 2003 AJCC-staging criteria. Only about 60% of the patients who were Stage II in the 1988 classification system were still Stage II with the 2003 system. A significant percentage of patients with Stage IIb disease were upstaged to Stage IIIa in the new system, resulting in improved survival for both Stage II and Stage III.

B. The Future of the TNM System

1. *Morphological Markers*

In addition to amendments to the existing TNM system, researchers have investigated the potential usefulness of adding additional morphological and nonmorphological variables to the staging system. For some sites, this has already been done. Histology, patient age, and tumor grade are currently used in staging for some sites. The incorporation of grade has also been considered for breast cancer staging, and this will likely occur in the near future (4). Additional tumor characteristics, such as vascular invasion of tumor emboli into the lymphatic spaces or blood vessels, or patient characteristics, including ethnicity, may also prove to be useful.

2. *Nonmorphological Markers*

The use of nonmorphological markers in the staging of cancer has been actively pursued over the last 10 years. This research has been fueled by developing technologies in immunogenetics and molecular biology, with the ultimate goal of being able to define cancer prognosis on an individual basis for each patient.

The major drawback in the use of molecular markers for cancer staging has been the sheer complexity involved. The process of tumorigenesis involves the synergistic interplay of dozens of genes and gene products that regulate cell proliferation, apoptosis, tumor suppression, etc. Table 2 shows a list of 24 molecular markers that have been investigated to determine prognostic significance in breast cancer. A comprehensive review of the literature indicated that only two of these markers (cathepsin-D and Ki-67 labeling index) appeared to be independently correlated with survival in patients with early stage breast cancer (12). Even for these two markers, there is considerable controversy,

Table 2 Potential Molecular Markers for Prognosis in Breast Cancer

Marker type	Potential molecular markers
Proliferation	Ki-67 labeling index
	Proliferation cell nuclear antigen
Apoptosis	bcl gene family
Tumor suppressor genes	P53
	Nm23
Oncogenes	c-myc
	h-ras
Proteases	Cathepsin-D
	Urokinase-type plasminogen activator
	Matrix metalloproteinases
Breast cancer specific genes	BRCA1
	BRCA2
Growth factors	Epidermal growth factor receptor
	HER2/*neu*
	Transforming growth factor-alpha
	Insulin-like growth factor
	IGF-binding protein
Regulation of the cell cycle	Cyclin D1
	Cyclin D2
	Cyclin E
	Telomerase
Other	Estrogen/progesterone receptor
	ps2
	Heat shock proteins

in part due to technical difficulties in obtaining measurements that are consistent between laboratories and, sometimes, within the same laboratory. For example, Tandon et al. (13) published a report in which cathepsin-D was reported to be a good prognostic factor for early stage breast cancer, but were unable to duplicate this finding in a later study that used a different immunologic reagent to detect cathepsin-D (14).

A potential approach to dealing with the complexity of genetic interactions involved in tumorigenesis lies with the new technique of microarray analysis to create a genetic fingerprint of the tumor. In this technique, RNA from tumor cells is isolated and used to prepare complementary RNA (cRNA), which is then labeled and hybridized to microarray panels containing up to 25,000 oligonucleotides. Positive labeling, indicating binding of an oligonucleotide to a cRNA molecule, indicates that the genetic material was being actively expressed in the tumor cells. Van't Veer et al. (15) have used RNA-based microarrays to investigate the relationship between gene expression profiles and breast cancer prognosis. Using RNA isolated from 98 primary breast tumors, they hybridized onto microarrays containing probes from 25,000 genes. They established a profile of 70 genes associated with prognosis. Not surprisingly, a poor prognosis was associated with upregulation of genes related to the cell cycle, invasion, metastasis, angiogenesis, and signal transduction. In a follow-up study from the same researchers (16), the 70-gene expression profile was a more powerful predictor of 10-yr overall survival rates for young patients with breast cancer than standard prognostic indicators based on clinical and histologic criteria. While these studies were carried out using tumor samples obtained from surgical excision, it seems likely that these techniques can be readily adapted to use samples obtained through biopsy, and thus be useful for clinical staging. Microarray analysis may become an important tool in determining optimal treatment strategies for patients based on an individualized assessment of tumor aggressiveness.

Another approach that may refine our ability to establish accurate clinical staging involves the use of immunohistochemical or molecular biologic techniques to identify isolated tumor cells/clusters of cells. These isolated tumor cells are frequently identified during histologic examination of lymph nodes, where their significance has been the subject of much debate (4). Isolated tumor cells have also been identified in peripheral blood, where it is hypothesized that they may be significantly correlated with degree of malignancy. A recent study by Huang et al. (17) used nested reverse transcriptase–polymerase chain reaction to analyze mRNA expression of cancer-specific antigens [carcinoembryonic antigen, cytokeratin-19 (CK19)], cytokeratin-20) in peripheral blood from patients with gastrointestinal carcinoma, patients with inflammatory gastrointestinal disease, and healthy volunteers. Among patients with gastrointestinal carcinoma, 74.2% were positive for at least one marker, while only one blood sample from a healthy control was positive for a marker. A similar approach has been used in several studies examining the correlation between CK19-positive peripheral blood cells and outcome in patients with breast cancer. In a report from Stathapoulou et al. (18), CK19 mRNA was detected in the peripheral blood of 3.7% of healthy controls, 30% of patients with early breast cancer, and 52% of patients with metastatic breast cancer. By multivariate analysis, detection of peripheral blood CK19-positive cells was an independent prognostic factor for disease relapse and death. Kahn et al. (19) reported CK19-positive peripheral blood samples from 30% of patients with node-negative breast cancer, 36% of patients with node-positive breast cancer, and 71% of patients with metastatic disease.

IV. CONCLUSIONS

For almost 50 years, the TNM-staging system has been the best available tool for assessing prognosis and determining treatment options for a variety of human cancers. Its usefulness has been the result of a careful balance between the need to preserve a stable system and the requirement for change to represent current clinical consensus. For much of the 50 years, revisions to TNM have been largely concerned with fine-tuning the assessment of tumor size and regional and distant metastases. Gradually, however, the system has been diversifying, as different markers (e.g., tumor grade, serum factors) have shown themselves to be of prognostic significance for specific types of cancer. In the current environment of explosive change in our technical abilities to find and analyze tumor cells, it is to be expected that the diversification of the TNM system will increase in the future. With the incorporation of new tools of molecular biology, the staging system of the future is likely to approach the goal of becoming patient-specific.

REFERENCES

1. Denoix PF. Tumor, node and metastasis (TNM). Bull Inst Nat Hyg (Paris) 1944; 1:1–69.
2. UICC Committee on Clinical Stage Classification and Applied Statistics. Clinical stage classification and presentation of results, malignant tumors of the breast and larynx. Paris: International Union Against Cancer, 1958.

3. UICC Committee on Clinical Stage Classification and Applied Statistics. TNM Classification of Malignant Tumors. Geneva: International Union Against Cancer, 1968.
4. Greene FL, Page DL, Fleming ID, Fritz AG, Balch CM, Haller DG, Morrow M, eds. AJCC Cancer Staging Manual. 6th ed. New York: Springer, 2002.
5. Sobin LH, Wittekind C, eds. International Union Against Cancer (UICC): TNM Classification of Malignant Tumors. 6th ed. New York: Wiley, 2002.
6. Fornage BD, Tonbas O, Morel M. Clinical, mammographic, and sonographic determination of preoperative breast cancer size. Cancer 1987; 60:765–771.
7. Pain JA, Ebbs SR, Hern RP, Lowe S, Bradbeer JW. Assessment of breast cancer size: a comparison of methods. Eur J Surg Oncol 1992; 18:44–48.
8. Wittekind C, Henson DE, Hutter RVP, Sobin LH, eds. TNM Supplement. 2nd ed. New York: Wiley, 2001.
9. Fleming ID, Cooper JS, Henson DE, Hutter RVP, Kennedy BJ, Murphy GP, O'Sullivan B, Sobin LH, Yarbro JW, eds. AJCC Cancer Staging Manual. 5th ed. New York: Lippincott-Raven, 1997.
10. Brito RA, Valero VV, Buzdar AU, Booser DJ, Ames F, Strom E, Ross M, Theriault RL, Frey D, Kau SW, Asmer L, McNeese M, Singletary SE, Hortobagyi GN. Long-term results of combined-modality therapy for locally advanced breast cancer with ipsilateral supraclavicular metastases: The University of Texas M.D. Anderson Cancer Center experience. J Clin Oncol 2001; 19:628–633.
11. Woodward WA, Strom EA, McNeese MD, Perkins GH, Schechter NR, Singletary SE, Theriault RL, Hortobagyi GH, Hunt KK, Buchholz TA. Changes in the 2003 AJCC staging for breast cancer dramatically affect stage-specific survival. J Clin Oncol 2003; 21:3244–3248.
12. Mirza AN, Mirza NO, Vlastos G, Singletary SE. Prognostic factors in node-negative breast cancer: a review of studies with sample size more than 200 and follow-up more than 5 years. Ann Surg 2002; 235:10–26.
13. Tandon AK, Clark GM, Chamness GC, Chirgwin JM, McGuire WL. Cathepsin-D and prognosis in breast cancer. N Engl J Med 1990; 322:297–302.
14. Ravdin PM, Tandon AK, Allred DG, Clark GM, Fuqua SA, Hilsenbeck SH, Chamness GC, Osborne CK. Cathepsin-D by western blotting and immunohistochemitry: failure to confirm correlations with prognosis in node-negative breast cancer. J Clin Oncol 1994; 12:467–474.
15. Van't Veer LJ, Dai H, van de Vijver MJ, He YD, Hart AA, Mao M, Peterse JL, van der Kooy K, Marton MJ, Witteveen AT, Schreiber GJ, Kerkhoven RM, Roberts C, Linsley PS, Bernards R, Friend SH. Gene expression profiling predicts clinical outcome of breast cancer. Nature 2002; 415:530–536.
16. Van de Vijver MJ, He YD, Van't Veer LJ, Dai H, Hart AA, Voskuil DW, Schreiber GJ, Peterse JL, Roberts C, Marton MJ, Parrish M, Atsma D, Witteveen A, Glas A, Delahaye L, van der Velde T, Bartelink H, Roden S, Rutgers ET, Friend SH, Bernards R. A gene-expression signature as a predictor of survival in breast cancer. New Eng J Med 2002; 347:1999–2009.
17. Huang P, Wang J, Guo Y, Xie W. Molecular detection of disseminated tumor cells in the peripheral blood in patients with gastrointestinal cancer. J Cancer Res Clin Oncol 2003; 129:192–198.
18. Stathapoulou A, Vlachonikolis I, Mavroudis D, Perraki M, Kouroussis C, Apostolaki S, Malamos N, Kakolyris S, Kotsakis A, Xenidis N, Reppa D, Georgoulias V. Molecular detection of cytokeratin-9-positive cells in the peripheral blood of patients with operable breast cancer: evaluation of their prognostic significance. J Clin Oncol 2002; 20:3404–3412.
19. Kahn HJ, Yang LY, Blondal J, Lickley L, Holloway C, Hanna W, Narod S, McCready DR, Seth A, Marks A. RT-PCR amplification of CK19 mRNA in the blood of breast cancer patients: correlation with established prognostic parameters. Breast Cancer Res Treat 2000; 60:143–151.

3

Principles of Surgical Cancer Care

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I. INTRODUCTION

Surgery is the oldest and continues to be the primary modality of cancer therapy. Over the last few decades, cancer treatment has improved dramatically due to an improved understanding of the natural history of malignancy, contemporary diagnostic imaging, novel adjuvant and multimodality therapies, advanced surgical, anesthetic and critical care techniques, and the creation of an unique surgical discipline, surgical oncology, to embrace this ever-expanding body of knowledge (1).

The curative role of surgery in cancer therapy is a development of the last century (2). Original attempts at conservative tumor resection resulted in extremely high rates of local recurrence and subsequent patient mortality. In the late 19th century, complete en bloc resections and amputations were used to treat patients with malignant lesions. Although these techniques yielded improved results, the procedures were ablative and mutilating. The early foundations of radical surgery included the Halsted radical mastectomy and the Moynihan abdominoperineal resection for rectal cancer (3). These operations emphasized the need to remove regional lymph nodes. With the advent of effective complementary treatment modalities, notably radiation therapy in the 1920s, and chemotherapy in the 1950s, the trend of surgical tumor resection once again became conservative. Even in the contemporary era of multimodality cancer therapy, surgery continues to be the mainstay of treatment for patients with solid tumors. In general, the addition of adjuvant chemotherapy alone or in combination with radiation therapy, for patients with a high likelihood of recurrence due to microscopic residual disease has improved disease-free survival and prolonged quality of life for patients who have been rendered free of gross disease by prior surgical resection.

Surgical techniques and expertise are applicable to many facets of oncology care including prevention, diagnosis, definitive treatment, and palliation. Advances in oncology have expanded the field such that a relatively new specialty in surgical oncology has emerged. The surgical oncologist is a surgeon who not only treats cancer but is familiar with the natural history of particular tumors, as well as all aspects of treatment principles including radiation therapy, chemotherapy, and newer modalities including available clinical trials.

II. HISTORICAL PERSPECTIVE

In the second century A.D., Galen published his classification of tumors and cautioned that cancer was a systemic disease not amenable to cure by surgery. It

was not until the 18th century that advances in anatomic pathology by Morgagni, Le Dran, and Da Salva established that there was an initial period of local tumor growth prior to distant dissemination. However, in the era prior to the advent of safe general anesthetics, cancer surgery consisted primarily of amputation or cauterization of surface tumors of the trunk or extremities because patients were unwilling to submit to the pain of tumor surgery when there was little likelihood of positive survival impact.

The first recorded elective tumor resection was performed in 1809 by an American surgeon, Ephraim McDowell. He successfully removed a 22-lb ovarian tumor from a patient who subsequently survived 30 years. McDowell's work, which included 12 more ovarian resections, stimulated greater interest in elective surgery for cancer patients. In 1842, ether was first used for general anesthesia and the first published account of ether anesthesia (1846) was for the elective removal of a tongue carcinoma.

Even with the advent of antisepsis and general anesthesia, surgical tumor resection in the second half of the 19th and early 20th centuries was associated with high patient mortality rates. Cancer was rarely diagnosed in the early stages; consequently, few patients were considered candidates for curative surgery. Surgeons who attempted excision of malignant lesions were hindered by crude instruments, rudimentary anesthesia, and lack of antibiotics. Additionally, there was no appreciation for the importance of margin negative resection and surgeons relied on gross visual assessment of the tumor perimeter. Gradual recognition of principles of meticulous surgical technique, gentle tissue handling, and applications of Listerian principles led to rapid advancements in the field of surgical oncology. Pioneers such as Albert Theodore Bilroth (first gastrectomy, laryngectomy, and esophagectomy) and William Stewart Halsted (en bloc resection, radical mastectomy) led to the advent of contemporary surgical oncology (2).

III. PATIENT ASSESSMENT

A. Staging

Accurate cancer staging is essential (see Chapter 2). The goal of clinical staging is to define the extent of disease in order to recommend therapy, advise about prognosis, avoid unnecessary interventions, and perform comparisons of new treatment regimens. Tumor staging is a system used to describe the anatomic extent of a specific malignant process in an individual patient. Staging systems cluster relevant prognostic factors about the primary tumor, such as size, grade, location, as well as information about dissemination to regional sites (e.g., lymph nodes) or distant metastatic loci. The American Joint Committee on Cancer (AJCC) (4) and the Union Internationale Contre Cancer (International Union Against Cancer, UICC) have adopted a shared TNM system that defines a cancer in terms of the primary tumor (T), the presence or absence of nodal metastases (N), and the presence or absence of distant metastases (M). For some tumor types, such as soft tissue sarcoma, a G for grade of malignancy is added to the system in recognition of its prognostic importance in particular diseases. High-grade tumors are less differentiated and tend to metastasize more readily.

The TNM system has four classifications; clinical, pathologic, retreatment, and autopsy. The *clinical* classification (cTNM) represents the extent of the disease *prior* to first definitive treatment as determined from physical examination, imaging studies, endoscopy, biopsy, surgical exploration, and any other relevant findings. Surgical staging may be required prior to undertaking major surgical procedures, such as laparoscopic staging prior to pancreaticoduodenectomy or gastrectomy, or para-aortic lymph node biopsy prior to esophagectomy. The *pathologic* classification (pTNM) incorporates the additional information derived from pathologic examination of a completely resected specimen which is useful in planning adjuvant therapy. The *retreatment* classification (rTNM) is used to stage a cancer that has recurred following a disease-free interval and the *autopsy* classification (aTNM) is based on postmortem examination.

B. Preoperative Considerations

Determining the risks associated with a given operation is a complicated and inexact process based on a number of factors (5,6). The physical status of the patient, including nutritional assessment and comorbid conditions, morbidity inherent to a specific operation, and the intent of surgical procedure (curative vs. palliative) are all pertinent to this assessment. The technical complexity of an operation and the relative experience of the involved health-care personnel can all impact on the complications of a procedure. The risk assessment for cancer patients should balance the risks associated with disease progression and those associated with the treatment (6).

The preoperative cancer patient is frequently in relatively poor physical condition. Patients often present with poor nutritional status, considerable pain, physiologic abnormalities (e.g., electrolyte disorders), and significant comorbid conditions. The etiology of anorexia in a cancer patient may be multifactorial: interference with normal alimentary function, as is often encountered with cancers of the mouth, pharynx,

esophagus, intestinal tract; pain that may contribute to anorexia; systemic tumor effects. Nutritional deficiencies should be corrected prior to surgery if possible, with hyperalimentation or total parenteral nutrition (TPN). Reconstitution of nutritional stores is a slow process, and the risks and benefits of delaying therapy vs. restoring positive nitrogen balance must be considered. Consideration should also be given to re-establishing depleted blood volume and correcting electrolyte abnormalities prior to major surgical resections. Physiologic status related to cardiopulmonary reserve and hepatic and renal function should also be assessed and optimized. Surgical morbidity and mortality following extensive cancer operations will predictably be problematic if critical physiologic and biochemical deficiencies are not corrected in advance.

Operative morbidity and mortality are defined as events that occur within 30 days of an operative procedure. For patients with cancer, the underlying disease as well as the procedure itself must be considered in the preoperative risk assessment. Various scales for risk assessment, such as the five-level physical status classification of the American Society of Anesthesiologists and the five-step performance status scale of the Eastern Cooperative Oncology Group, may be useful in assessing the appropriateness of a given operation for a specific patient. Advanced age alone should not disqualify a patient from a potentially curative surgical procedure.

The risk assessment for palliative surgical procedures is particularly difficult. The high incidence of postoperative complications must be weighed against the potential for symptom control. For example, palliative surgery in the context of intestinal obstruction secondary to carcinomatosis has a 20–30% perioperative mortality. In such circumstances, the risk-to-benefit ratio and ultimate surgical objectives must be defined as clearly as possible and accepted by patient, family, and surgeon.

A patient's psychologic make-up and life situation must also be considered in treatment planning. The potential risks and benefits of all available treatment options must be examined, and a patient who is unable to accept the morbidity associated with a given treatment should be offered other options. In particularly difficult situations, consultation with a psychiatrist experienced in cancer (a psycho-oncologist) may help a patient and family deal with the reality of the disease and its treatment. This is particularly true for surgical procedures that significantly alter a patient's appearance, such as mastectomy or colostomy.

The experience of the surgeon and the clinical team has been defined as critical factors in surgical outcomes for cancer patients and should be included in risk assessment (6,7). There have been a number of studies that have demonstrated significant variations in operative survival based on hospital case volume (7). Particularly for high-risk surgical interventions such as pancreaticoduodenectomy, esophagectomy, gastrectomy, pelvic exenterations and hepatic resections, these studies indicate that the more cases performed at an institution the better the results (7,8). There have also been a few studies performed in patients with cancer that have suggested that patient long-term survival is impacted by the training and expertise of the operating surgeon regardless of whether interventions are high risk or low risk (e.g., procedures for breast cancer) (9–12).

IV. ROLES FOR SURGERY

A. Prevention

There has been much effort on the part of the medical community and various organizations and advocacy groups to educate the public on the early signs and symptoms that may indicate the presence of early malignancies that are more likely to be cured (1). This awareness along with the adoption of screening programs has resulted in an increased proportion of early stage, curable malignancies (13).

The identification of genetic mutations that predispose to subsequent cancer development has emerged as a means of risk assessment. The utility of prophylactic surgical treatments must be examined carefully on an individual basis. There is a growing list of indications for the role of prophylactic surgery in conditions such as cryptorchidism associated with subsequent testicular carcinoma, ulcerative colitis or familial polyposis associated with colon carcinoma, multiple endocrine neoplasia syndromes associated with the development of medullary carcinoma of the thyroid, oral leukoplakia associated with subsequent development of squamous cell carcinoma, and familial breast and ovarian cancer. In familial conditions with a high incidence of cancer, it is often the responsibility of the surgeon to educate the family of the risks to other family members.

B. Diagnosis

The diagnosis of solid tumors requires localization and biopsy for histologic confirmation. Historically, significant errors have been made when biopsy confirmation of malignancy was not obtained prior to treatment, as in the radical mastectomies that were performed for benign conditions. Contemporary practice requires

that actual slides be obtained and reviewed at an institution prior to the commencement of therapy. This is particularly important for rare neoplasms in which an erroneous interpretation may have been made in the initial pathologic assessment.

There are a variety of biopsy techniques available which can be used to obtain tissue for histologic diagnosis including fine-needle aspiration, core biopsy, incisional biopsy, and excisional biopsy. Several general principles should be followed in the acquisition of tissues suspected of malignancy (14). First, the biopsy site, whether needle tracks or surgical scars should be carefully selected so that it can easily be excised as part of the subsequent definitive surgical resection. Second, adjacent tissue planes should not be contaminated during biopsy as a result of poor technique such as inadequate hemostasis. Third, the choice of biopsy technique should be selected based on the sample of tissue required for adequate evaluation by the pathologist. Lastly, biopsy material should be handled with care from the time of resection, in which precise orientation must be defined by the surgeon, and subsequent handling and processing.

Fine-needle aspiration (FNA) is a cytologic technique in which cells are aspirated from a tumor using a needle and syringe with the application of negative pressure. It is an acceptable method of diagnosing most solid tumors, particularly when the results correlate closely with clinical and imaging findings. However, the resulting aspirated tissue consists of disaggregated cells rather than intact tissue and should be performed for primary diagnosis of tumors only at centers with experienced cytopathologists. Because of the lack of intact tumor architecture, the diagnosis of malignancy depends entirely on the detection of abnormal intracellular features, such as nuclear pleomorphism, increasing the margin of error over other biopsy techniques. Fine-needle aspiration biopsy is the procedure of choice to confirm or rule out the presence of a metastatic focus or local recurrence.

Superficial lesions are often subjected to fine-needle aspiration biopsy in the clinic setting. Deeper tumors may require an interventional radiologist to perform the technique under sonographic or computed tomography guidance. The technique generally involves use of a 21- to 23-gauge needle that is introduced into the mass after appropriate cleansing of the skin and injection of local anesthetic. Negative pressure is applied, and the needle is pulled back and forth several times in various directions. After the negative pressure is released, the needle is withdrawn and the contents of the needle are used to prepare a smear. A cytopathologist then examines the slides to determine whether sufficient diagnostic material is present. If insufficient diagnostic material is obtained, a core needle biopsy should be performed.

Core needle biopsy is a safe, accurate, and economical diagnostic procedure. Core biopsies are performed with a large-bore needle, such as the Vim Silverman or Tru Cut type. This technique retrieves a small piece of intact tumor tissue, which allows the pathologist to study the invasive relationship between cancer cells and the surrounding microenvironment. The tissue sample obtained from a core needle biopsy is usually sufficient for several diagnostic tests, such as electron microscopy, cytogenetic analysis, and flow cytometry. Computed tomography guidance can enhance the positive yield rate of a core needle biopsy by accurately pinpointing the location of the tumor. Precise localization in the tumor mass is particularly important to avoid sampling nondiagnostic necrotic or cystic areas of the tumor. Computed tomography guidance also permits access to tumors in otherwise inaccessible anatomic locations or near vital structures.

Open or incisional biopsy involves removal of a small portion of the tumor mass. It is a reliable diagnostic method that allows adequate tissue to be sampled for definitive and specific histologic identification. It is best performed under circumstances where the incisional wound can be totally excised in continuity with the definitive surgical resection, in the event that any tumor cells are spilled at the time of biopsy. When adequate tissue for diagnosis cannot be obtained by fine-needle aspiration biopsy or core biopsy, incisional biopsy is indicated for deep or superficial tumors larger than 3 cm. Because open biopsy may have complications, incisional biopsies are usually performed as a last resort. Open biopsy should ideally be performed by the surgeon who will perform the definitive surgical resection. For extremity tumors, the biopsy incision should be oriented longitudinally to allow subsequent wide local excision to encompass the biopsy site, scar, and tumor en bloc. A poorly oriented biopsy incision often mandates an excessively large surgical defect for subsequent wide local excision. Another mandate of surgical technique is that adequate hemostasis must be achieved at the time of biopsy to prevent dissemination of tumor cells into adjacent tissue planes by hematoma.

Excisional biopsy completely removes the local tumor mass. It is used for small, discrete masses that are 2–3 cm in diameter, where complete removal will not interfere with a subsequent wider excision that may be required for definitive local control. Surgeons should always orient biopsy specimens with sutures or metal clips so that if removal is incomplete and further excision is needed, positive margins can be accurately identified in situ. Excisional biopsies are commonly used for polypoid lesions of the colon, thyroid and

breast nodules, small skin lesions, and when the pathologist cannot make a definitive diagnosis from tissue removed by incisional biopsy. Excisional biopsies rarely provide any benefit over other biopsy techniques and may cause postoperative complications that could ultimately delay definitive therapy. Ill-conceived incisions can unnecessarily contaminate tissue planes, necessitating wider radiotherapy fields or more extensive subsequent resection. The classic example involves tumors of the extremities, which are best biopsied using longitudinal incisions that can be encompassed at the time of definitive en bloc resection. The final caveat is that surgical biopsy incisions should be performed with meticulous hemostasis as postoperative hematomas can create widespread dissemination of tumor cells with contamination of adjacent tissue planes.

Special consideration with regard to anatomic location and specimen processing should be given to surgical lymph node biopsies. Selection of axillary nodes may be preferable to groin nodes if both are enlarged due to a decreased likelihood of postoperative infection. Cervical lymph nodes should not be biopsied until a careful search for a primary tumor has been made using nasopharyngoscopy, esophagoscopy, and bronchoscopy since the etiology of cervical adenopathy is usually metastasis from laryngeal, oropharyngeal, and nasopharyngeal tumors. In contrast, supraclavicular nodes more frequently represent metastases from primary tumors of the thoracic, abdominal cavities, or breast. For patients with unknown primary tumors and/or suspected lymphoma, cytogenetic analysis requires sterile tissue processing.

C. Treatment of Primary Tumors

Surgery remains the most effective treatment of localized solid tumors. In general, en bloc resection encompassing all gross and microscopic tumor is the goal and often requires resection of adjacent anatomic structures or organs. Over the last two decades, there have been major improvements in operative technique as well as the optimization of multimodality therapy enhancing the ability to achieve surgical resection. These techniques have significantly reduced the overall morbidity and mortality associated with the surgical treatment of solid neoplasms. Specific examples include breast-conserving surgery for patients with breast carcinoma (15), limb salvage procedures for patients with bone and soft tissue sarcomas (16), improved techniques such as total mesorectal excision for clearance of rectal tumors (17), and procedures with preserve sexual potency and urinary continence for patients with prostate cancer (18).

Once a decision has been made to proceed with surgical therapy, the operative procedure must be carefully planned recognizing that the opportunity for cure is often limited to the first surgical resection. When a previous biopsy has been performed, the entire biopsy scar and any drain exit sites should be encompassed within the operative field when possible. Intraoperative considerations include the potential risk of implanting cancer if the tumor is inadvertently violated during an operative procedure. Local recurrence can occur despite all efforts to isolate the tumor or avoid spilling cancer cells into the operative field. Reasons for local recurrence include malignant cells present in local lymphatics or blood-borne cells, which implant into a wound. Manipulation of the tumor at any time during the surgical procedure can greatly increase the number of cancer cells recovered from the bloodstream. Likewise, it is also important to use appropriately large incisions to minimize excessive manipulation of the tumor.

1. Types of Cancer Operations

Local resection with removal of an adequate margin of normal peritumoral tissue may be adequate treatment for some neoplasms including wide excision of primary melanoma, early stage colon cancers as well as low-grade neoplasms such as basal cell carcinomas and mixed tumors of the parotid gland. In contrast, neoplasms that infiltrate adjacent tissues, such as soft tissue sarcomas, esophageal and gastric carcinomas, must be excised with a wide margin of normal tissue. Even tumors, which appear encapsulated at the time of resection, often demonstrate pseudocapsules composed of a compression zone of normal tissue interspersed with neoplastic cells when examined microscopically. Simple enucleation of these tumors results in local recurrence in virtually all cases.

Wide local resection of some tumors requires sacrificing major vessels, nerves, joints, or bones. Occasionally, even amputation may be necessary as an initial surgical procedure if a curative result is to be obtained. The extent of operation must be based solely on the extent of resection needed to achieve negative tumor margins. During the operation, pathologic evaluation of resected margins may indicate the need to alter the initial operative plan. These decisions are often difficult and require experienced judgment. It is usually better to proceed with a potentially curative tumor extirpation unless there is unequivocal histologic confirmation that the lesion has extended beyond the boundaries of curative surgical resection. Issues of reconstruction should be approached separately and often require the participation of plastic and reconstructive surgeons and other surgical specialists who have been consulted prior to the resection.

Many neoplasms metastasize via the lymphatics, and operations have been designed to remove the primary neoplasm along with draining regional lymph nodes. Circumstances that favor this type of operative approach are when the lymph nodes draining the neoplasm are adjacent to the tumor bed or when there is a single avenue of lymphatic drainage that can be removed without sacrificing vital structures. When there is demonstrable metastatic spread to adjacent nodal basins, it is generally agreed that en bloc regional lymph node dissection is appropriate. However, in many such cases, the tumor has already spread beyond regional nodes and cure rates may be quite low. Regional lymph node involvement should not be viewed as a contraindication to surgical resection because en bloc removal of the involved lymph nodes may offer the only chance for cure and/or significant palliative local control. Nodal involvement should be viewed as a possible indication for adjuvant therapies, such as radiation or chemotherapy.

The value of elective or prophylactic lymph node dissection has been challenged, particularly with respect to radical nodal resections in gastric, pancreatic, esophageal, rectal, and lung cancer (3). It is not clear whether cure rates are enhanced when subclinically positive lymph nodes are removed. Actively accruing randomized clinical trials in a number of disciplines are currently addressing this question. Regardless of whether or not there is a direct therapeutic benefit, knowledge of regional node tumor status can have an impact on tumor staging and subsequent treatment recommendations. The ability to identify and assess sentinel lymph nodes has revolutionized cancer staging for patients with melanoma and breast cancer. As many as 30% of previously negative regional lymph nodes are identified to harbor occult metastases by contemporary histologic analysis of sentinel lymph nodes (19). Therapeutic lymph node dissection and adjuvant therapy can now be directed to patients with confirmed microscopic nodal disease. Current controversy pertains to the utility of subsequent complete nodal dissection in subsets of patients with minimal micrometastatic disease detected in sentinel lymph nodes.

Improvements in surgical technique, anesthesia, and supportive care allow radical operative resections to be performed for locally advanced tumors. Such heroic procedures, if safely executed, can be justified in select situations with curative intent. For example, pelvic exenteration that entails the removal of all pelvic organs (bladder, uterus, and rectum) is a potentially curative procedure for patients with recurrent cancers of the cervix and well-differentiated locally extensive adenocarcinomas of the rectum. Reconstruction following exenteration involves creation of a colostomy, urinary tract drainage, and possible tissue coverage in the perineum. Experienced multidisciplinary surgical teams are often required for the best functional outcome. In addition to technical expertise, postoperative emotional support and rehabilitation services are often required.

In select patients, surgical resection of locally recurrent neoplasms may produce long periods of remission. For example, surgical procedures are frequently successful in controlling recurrent soft tissue sarcomas, anastomotic recurrences of colon cancer, certain basal and squamous carcinomas of skin and local breast cancer recurrence following segmental mastectomy. Clinical judgment must be exercised when considering surgical resection of a locally recurrent tumor in a patient with synchronous metastatic disease. Under normal circumstances surgical resection should not be contemplated unless the entire local recurrence can be completely excised and there is some form of effective therapy available to treat the metastases.

2. *Emerging Surgical Techniques*

Several new procedures have become part of the armamentarium of the surgical oncologist. Sentinel lymph node mapping and biopsy have become the standard of care for staging patients with breast cancer and melanoma. Laparoscopic surgery, which has been in existence for years, is being defined in relation to oncology by way of clinical trials. Isolated regional perfusion with chemotherapy continues to be evaluated. Newer technologies, such as radiofrequency ablation (RFA) and breast ductal lavage, are currently being evaluated.

a. Sentinel Lymph Node Biopsy

Sentinel lymph node (SLN) biopsy techniques have become established techniques for the staging assessment of patients with breast carcinoma (20) and melanoma (21). Expanded indications for this technique are being evaluated in a number of other tumor histologies including gastrointestinal (22–25), genitourinary (26,27), gynecologic (28,29), and head and neck (30) malignancies.

In melanoma, remarkable progress has been made such that sentinel lymph node positivity in patients with clinically negative axillae is the most important single known prognostic factor for subsequent melanoma recurrence (31).

The role of sentinel lymph node biopsy also continues to mature in carcinoma of the breast. Recent refinements in technique have rendered application of this technology less cumbersome with the administration of radiolabeled sulfur colloid that is used to identify

the sentinel node 24 hr prior to surgical biopsy, relieving time constrictions inherent in immediate preoperative injection. Intraoperative assessment of sentinel node status using touch preparation techniques (32) has also been investigated as a means of obtaining immediate information allowing definitive surgical nodal dissections while preserving nodal tissue as compared to frozen section analysis for other clinical and research applications. Neoadjuvant chemotherapy has recently been shown not to affect sentinel node biopsy accuracy, rendering surgical consolidation less morbid in patients so treated (33). Other new applications such as in ductal carcinoma in situ (DCIS) are apparent in results from recent studies suggesting a 12% positive rate in the higher risk patients with DCIS, such as those with microinvasion (34). It can be anticipated that sentinel node biopsy technology will continue to develop as new uptake markers are applied and as analytic schema such as microarray technology are coupled with this minimal surgical approach.

b. Laparoscopic Surgery

Laparoscopic surgery has been used for the diagnosis, staging, and treatment of patients with malignancy. Despite contemporary radiologic imaging, laparoscopy has been demonstrated to have utility in tumor staging, particularly with upper gastrointestinal malignancies (35). A laparoscopic evaluation can provide additional information about the primary tumor nodal disease, as well as detect small hepatic and peritoneal diseases that cannot be appreciated on radiologic imaging. The addition of ultrasound techniques have been shown to increase the sensitivity of tumor staging beyond laparoscopy alone and radiologic imaging (36,37). Clinical trials are ongoing to determine the utility of laparoscopic oncologic resections.

c. Isolated Regional Perfusion

Isolated perfusion is a technique that was devised to administer concentrated dose of chemotherapy to tumors. The majority of the experience has been in isolated limb perfusion for in-transit melanoma and as a means of providing a limb sparing alternative for patients with locally advanced soft tissue sarcomas.

Isolated limb perfusion involves isolating the main artery and vein of the perfused limb from the systemic circulation. The choice of anatomic approach is determined by tumor site; external iliac vessels are used for thigh tumors, femoral or popliteal vessels for calf tumors, and axillary vessels for upper-extremity tumors. The vessels are dissected, and all collateral vessels are ligated. The vessels are then cannulated and connected to a pump oxygenator similar to that used in cardiopulmonary bypass. A tourniquet or Esmarch band is applied to the limb to achieve complete vascular isolation. For the lower limb, the Esmarch band is anchored at the anterior–superior iliac spine with the aid of a pin inserted into the pelvic bones. For the upper limb, the pin is anchored at the scapular and pectoral levels. Chemotherapeutic agents are then added to the perfusion circuit and circulated for 90 min. Systemic leakage from the perfused limb is monitored continuously by monitoring ^{99}Tc-radiolabeled human serum albumin injected into the perfusate. Radioactivity above the precordial area is recorded with a Geiger counter. The temperature of the perfused limb is maintained during the entire procedure by external heating and warming of the perfusate to 40°C. At the end of the procedure, the limb is washed out, the cannulas are extracted, and the blood vessels are repaired.

Despite a 40-year history of isolated limb perfusion being used, many questions remain to be answered. The choice of chemotherapeutic agent in the perfusion circuit, the benefits of hyperthermia, and the effectiveness of hyperthermic perfusion in the neoadjuvant or adjuvant setting remain to be elucidated. Studies published to date have involved heterogeneous patient groups and diverse chemotherapeutic agents.

With a similar intent, optimal cytoreduction and intraperitoneal hyperthermic peritoneal perfusion has been used for the treatment of patients with peritoneal implants from a variety of tumor histologies including pseudomyxoma peritonei (38), gastrointestinal carcinomatosis (39), intra-abdominal mesothelioma (40), ovarian cancer (41), and sarcomatosis (42).

d. Radiofrequency Ablation

Radiofrequency ablation is a technique by which tumor tissue is selectively destroyed by the transfer of heat energy from an electrode placed within the tumor and delivered as an alternating current. This approach has been used extensively in the context of unresectable primary and secondary hepatic malignancy (43). The technique has also been successfully utilized as an initial treatment in bilobar liver disease in conjunction with synchronous or sequential hepatic resection and in the treatment of hepatocellular carcinoma in patients with cirrhosis (44).

Based on the success of RFA in treating malignancy of the liver, attempts are being made to broaden its indications with investigations in the treatment of unresectable pancreatic carcinoma, retroperitoneal sarcoma, and other malignant diseases. A recent report has demonstrated the utility of RFA in early stage breast carcinoma where the need to preserve tissue may be a concern to many patients (45). This is currently being

evaluated in clinical trials in which patients undergo core needle biopsy to assess for residual viable tumor 4 weeks after RFA, and then undergo sequential or modified mastectomy only if the core needle biopsy is positive (46). Patients with negative core biopsies will receive radiation therapy without mastectomy. Approaches such as these indicate potential approaches for eliminating tumors without the necessity of ablative surgical resections in the future.

e. Breast Ductal Lavage

Breast ductal lavage is emerging as another minimally invasive surgical procedure to identify cellular abnormalities in the epithelial lining of the breast ductal system. The procedure consists of identifying fluid-yielding breast ducts by initial aspiration, followed by placement of small catheters into the fluid-yielding duct with infusion and then aspiration of normal saline effluent. The effluent is collected and examined using standard cytopathology techniques (47). The technique has been demonstrated to be sensitive in populations of patients at high risk for breast cancer. The ability to perform minimally invasive procedures that increase the sensitivity of detecting cellular atypia may ultimately become incorporated into surveillance strategies for asymptomatic patients at risk for developing breast cancer.

3. Surgery as a Component of Multimodality Therapy

Tumors that are at high risk for local and/or distant recurrence are often treated with multimodality therapies. The use of combined modality therapy (surgery in combination with radiation and chemotherapy) was pioneered by pediatric oncologists in the management of childhood neoplasms. Tumors such as retinoblastoma, Wilms' tumor, and embryonal rhabdomyosarcoma can often be cured using combinations of radiation, chemotherapy, and surgery. For example, the cure rate for patients with Wilms' tumor is 75% if surgical therapy is followed by radiation and chemotherapy, an increase of 40% over operation alone.

Until recently, the effectiveness of multimodality therapy was only occasionally demonstrable for adult neoplasms. Clinical trials have confirmed the benefit of combination surgical resection and radiation therapy for the local control of localized breast cancers (15) and skeletal and soft tissue sarcomas. In the past, surgical resection of these tumors as a single treatment resulted in frequent local recurrences. The addition of radiation to more conservative surgical resections (segmental mastectomy and limb-sparing tumor resection) can achieve rates of local control similar to mastectomy and amputation. With both types of neoplasms, survival and local recurrences were the same for patients treated with multimodality therapy; however, patients were spared the physical deformity and psychological stress associated with radical surgical procedures (3,48).

Surgical resection and radiation are the most successful means of treating cancer localized to the primary site and/or regional lymph nodes. Since these forms of therapy exert their effects loco-regionally, it is not usually considered curative once a tumor has metastasized beyond these sites. Chemotherapy, immunotherapy, and hormonal therapy are treatments that can potentially kill tumor cells that have metastasized to distant sites. These systemic modalities have a greater chance of cure in patients with minimal (or even subclinical) tumor burden as compared with those with clinically evident disease. Consequently, surgery and radiation therapy may be useful in decreasing a given patient's tumor burden, thereby maximizing the impact of subsequent systemic approaches. Evidence of such treatment benefit is the survival benefit seen in patients with stage III colon cancer who receive 5-FU and leukovorin following surgical resection.

An emerging element of the multimodality approach for some tumors is immunotherapy, treatment aimed at activation of the immune system. The concept of immunostimulation with biologic response modifiers or nonspecific immunomodulators is not new in cancer therapy. Nearly a century ago, William B. Coley developed the basis for nonspecific cancer immunotherapy using mixed bacterial vaccines (Coley's toxin). Since then, whole cell or cell fragment tumor vaccines have been introduced for active specific immunotherapy of neoplastic disease, and some of these have reached clinical applications. In melanoma, immunotherapy alone or in combination with chemotherapy is often used as an adjuvant to surgery for the treatment of regional disease or in attempts to prolong the survival of patients with distant metastases. Cytokines, such as interferon-α and interleukin-2, are also being used to modulate the immune response and have proven effective in some diseases, such as myeloid leukemia and hairy cell leukemia, melanoma, and renal cell carcinoma.

Historically, surgery was performed first in the sequence of therapies for solid neoplasms with the addition of radiation and/or chemotherapy following adequate healing of the surgical wound. There is increasing evidence that suggests that definitive surgical resection should follow chemotherapy and/or radiation. Postoperative surgical sites may be relatively hypoxic and resistant to radiation therapy, whereas the chemotherapeutic regimen may be tailored for efficacy with tumors in situ. Surgical resection may then be

employed to remove residual tumor. Frequently, sequencing chemotherapy and radiotherapy prior to surgical resection can cause shrinkage of tumor mass due to destruction of chemo- and radiosensitive tumors resulting in less ablative surgical resections with improved function. These concepts have been applied to patients with breast cancer, bone and soft tissue sarcomas and other neoplasms.

Treatment sequencing requires the input of a multidisciplinary team, which includes radiation, medical, and surgical oncologists. The surgical oncologist must be able to co-ordinate and integrate the efforts of the entire oncologic team if he or she is to retain a primary role in the management of the cancer patient.

D. Patterns of Tumor Spread

In general, tumors disseminate via direct infiltration of surrounding tissues, lymphatic invasion, vascular dissemination, or implantation in serous cavities. A combination of dissemination routes is also possible and the sequence may not be predictable. For example, patients with breast cancer or melanoma may manifest distant metastatic disease in the lungs, liver, or skeleton without ever developing evidence of lymph node metastases.

Direct extension through tissue planes is characteristic of adenocarcinomas of the stomach or esophagus, which can extend for a considerable distance (10–15 cm) along tissue planes beyond the palpable tumor mass. Soft tissue sarcomas are often described to have "finger-like" projections into the surrounding tissues resulting in high local recurrence rates for tumors that are not excised with wide margins. Also, central nervous system tumors may result in death by infiltrating surrounding brain tissue and affecting vital functions.

Tumor cells can readily enter the lymphatics and traverse these channels by permeation or embolization to lymph nodes. Lymphatic involvement is extremely common in epithelial neoplasms of all types, except basal cell carcinoma of the skin, which metastasizes to regional lymphatics in less than 0.1% of cases. Growth of tumor cells along the course of a lymphatic channel (permeation) is commonly seen in patients with breast cancer with involvement of the skin lymphatics and in patients with carcinoma of the prostate who demonstrate perineural lymphatics invasion. Lymphatic embolization is of great clinical importance in a number of neoplasms. Tumor cells traverse the lymphatic channels to regional lymph nodes and deposit initially in the subcapsular space. Eventually, the tumor cells are able to permeate the sinusoids and replace the nodal parenchyma. It is thought to spread directly from node to node. When tumor involved lymph nodes become enlarged, tumor can extend beyond the capsule into the perinodal fat, often indicating an ominous prognosis.

Lymphatic drainage from the lower extremities and intra-abdominal organs ultimately empties into the thoracic duct by way of the cisterna chyli. Ultimately, lymph flows into the left jugular vein creating a direct route for tumor cells to pass from the lymphatic system into the bloodstream. Alternatively, tumor cells may reach the bloodstream by direct invasion of blood vessels, most commonly through capillaries or veins. Vascular invasion is common in both carcinomas and sarcomas and is associated with a poor prognosis. Some types of neoplasms have a particular tendency to grow as a solid column along the course of veins. For example, renal cell carcinoma can grow into the renal vein and inferior vena cava extending to the right atrium. In such situations, en bloc removal requiring resection with cardiopulmonary bypass may still result in long-term survival or even cure.

Tumor cells occasionally gain entrance to serous cavities by growing through the wall of an organ. Many tumor cells can grow in suspension without a supporting matrix and may spread freely within the peritoneal cavity by attaching to serous surfaces. Widespread peritoneal seeding is common with gastrointestinal neoplasms including pseudomyxoma peritonei and ovarian tumors. Similarly, malignant gliomas may spread widely within the CNS via the cerebrospinal fluid.

Although much is known about the routes of tumor spread, the mechanisms underlying this process remain unclear. Some cancers are metastatic at the time of primary diagnosis, whereas other tumors of the same histologic type may remain localized for years. In some instances, metastases may dominate the presenting clinical picture, whereas the primary tumor remains latent and asymptomatic or even undetectable. For example, cerebral metastases from silent cancers in the bronchus or the breast are often mistaken for primary benign central nervous system neoplasms.

An en bloc tumor resection is intended to remove the primary neoplasm along with contiguous lymphatic and vascular channels that may contain tumor. Potential cure is achieved by the mechanical removal of all cancer cells. However, in many instances cancer cells can be found in operative washings, blood or lymphatics without subsequent distant recurrence indicating that the metastatic process is inefficient. Host immune mechanisms may also have a role in the salvage of patients undergoing resection of metastases in distant organs, such as the lung or liver. Particularly, in patients who undergo resection of metastatic disease, it is likely that they harbor subclinical metastases in other sites, which are presumably destroyed

by host immune mechanisms such that at least a subset of postresection patients subsequently become disease-free long-term survivors.

E. Surgical Emergencies

A number of surgical emergencies can emerge as a result of enlarging tumors including exsanguinating hemorrhage, perforated viscus, abscess formation, or impending obstruction of a hollow viscus, such as gastrointestinal organs, critical blood vessels, or respiratory structures. Additionally, surgical intervention may also be indicated to decompress tumors invading the central nervous system or destroying critical neurologic components by exerting pressure in closed spaces.

Specific issues pertaining to the evaluation of cancer patients for emergency surgical interventions include the effects of recent myelosuppressive chemotherapy. Potential catastrophes can sometimes be avoided by performing elective procedures on patients expectantly, just after they have gone through the nadir of their most recent myelosuppressive chemotherapy. In truly emergent situations, patient and families must be made aware of the increased surgical risks and the potential benefits of the proposed surgery, which is frequently only palliative.

F. Surgical Palliation

1. Metastatic Disease

It is recognized in general that if patients require heroic resections to obtain loco-regional control of their primary disease, it is likely that the disease has already disseminated to distant sites. Metastatic disease disseminated to vital organs is the cause of death in the majority of patients with cancer. Despite this, the removal of metastatic lesions in the lung, liver, or brain has occasionally produced prolonged survival and/or cure. Occasionally, even multiple metastases may be successfully resected. Extensive radiologic assessment should be performed prior to embarking on surgical resection of metastatic disease to ensure that metastatic spread is limited to region of the proposed surgery.

Examples of particular scenarios in which surgical resection has been demonstrated to be successful in patients with metastatic cancer include liver metastases in patients with colorectal carcinoma and pulmonary metastases in patients with sarcoma. Metastatectomy is considered in patients with colorectal cancer in whom the primary tumor has been controlled, there is no evidence of extrahepatic metastases, with resectable liver metastases (isolated primarily to hepatic lobe). Although only a minority of patients with colon cancer metastatic to the liver will meet these requirements of operability, approximately 25% of operable patients will survive more than 5 years following resection. The results for resection of pulmonary metastases for sarcoma have also been very satisfactory. For example, resection of a solitary or limited pulmonary metastasis for some tumor types, such as osteogenic sarcoma, results in a higher survival rate than does resection of primary bronchogenic carcinoma of the lung. Resection of pulmonary metastases may be indicated even when more than one metastatic lesion is present, particularly for tumors that have responded to systemic therapy or have a long doubling time.

2. Palliative Procedures

A surgical oncologist is often faced with a dilemma when a cancer has spread beyond the possibility of cure. Patients are generally deemed incurable if they have widespread distant metastases or evidence of extensive local tumor infiltration of critical anatomic structures. The goal of therapy in such situations is to treat symptomatic disease progression and maintain maximum activity and quality of life as long as possible (6,49). Histologic proof of distant metastases should be obtained before a patient is considered incurable. Occasionally, an exploratory celiotomy or thoracotomy may be necessary to determine the histology of ambiguous lesions in the lungs or liver. Within each anatomic region of the body, there are specific criteria defining whether a patient is unequivocally incurable. Although tumor invasion of some organs and contiguous structures may imply a poor prognosis, such scenarios may not indicate absolute incurability. In equivocal situations, patients should be explored with the intention and preparation for surgical cure.

A palliative operation may be justified to relieve pain, hemorrhage, obstruction, or infection. Particularly, invasive interventions must be balanced by "realistic expectations of achieving low morbidity and achieving durable palliation"(49). Palliative surgery may also be considered in circumstances when there are no better nonsurgical means of palliation with the potential for improving quality of life, even if it does not result in prolonged survival. In a review by Wagman (49), the primary considerations for patients and physicians considering a palliative procedure include: the complexity of the procedure, the duration of the hospitalization as well as overall recovery period, the likelihood of achieving the palliative goal, the interim evaluations that will be required to sustain palliation, the likely durability of palliation, and the anticipated malignant disease progression. Examples of palliative surgical procedures include: (1) colostomy, enterostomy, or gastrojejunostomy to relieve

gastrointestinal obstruction; (2) cystectomy to control hemorrhagic tumors of the bladder; (3) amputation for control of intractable pain; (4) soft tissue resections (e.g., mastectomy) for infection control of primary tumors for patients with metastatic disease; and (5) colon resection to prevent obstruction in the presence of hepatic metastases.

Cytoreduction, treatment that incompletely eradicates tumor, is a special application of palliative surgery. The basis for cytoreductive surgery is that in some patients extensive yet isolated local spread of malignancy precludes gross total resection of all disease. In such circumstances, removal of bulky symptomatic tumor often improves function and quality of life and theoretically may improve response to systemic therapies by reducing overall tumor burden (50). The benefits of cytoreductive surgery have been demonstrated in a number of tumor histologies including ovarian neoplasms (51), germ cell tumors (52), some gastrointestinal tumors (53), and metastatic neuroendocrine tumors (54). The risks associated with cytoreductive surgery can be significant and the particular tumor biology must be examined prior to embarking on an extensive cytoreductive resection (50). McCarter and Fong (50) outline several principles for identifying patients likely to benefit from cytoreductive surgery including patients with symptomatic, slow-growing tumors (favorable biologic behavior), likely to respond to additional therapies, and in whom cytoreductive resection can be performed safely.

In addition to surgical resection, a number of less invasive cytoreductive techniques have emerged including cryoablation, RFA, ethanol injection, and embolization, as a means of treating patients that are not candidates for surgical resection (54). Methods for applying these techniques safely and effectively using percutaneous applications are under investigation.

G. Special Situations

1. Vascular Access

Vascular access is commonly required in cancer patients requiring long-term nutritional and hematologic support, as well as for the administration of systemic therapies. Catheter technology has progressed over the past 35 years and there are a large variety of vascular access devices that can be inserted percutaneously depending on the intended use. Multi-lumen catheters are available which allow the simultaneous administration of otherwise incompatible agents, such as some blood products, antibiotics, and chemotherapies.

Catheter placement can be accomplished at the bedside, in the radiology procedure suite, or in the operating room and must be performed as a sterile surgical procedure. Postcatheter placement chest radiographs are required to confirm catheter tip location and rule out the presence of iatrogenic complications. Catheterization is associated with venous thrombosis so that for patients that require serial catheters, nuclear flow studies performed prior to subsequent catheterizations may detect chronic subclinical occlusion in a potential candidate recipient vessel.

There have been little data available upon which to base a decision of whether to use percutaneous venous access or a subcutaneously implantable venous access system. Results of a recently published Canadian randomized trial suggests that the majority of participants can receive satisfactory venous access percutaneously, with the added expense of an implantable system reserved for those patients who fail percutaneous access strategies (55). This latter approach has been the standard of practice at the University of Texas M.D. Anderson Cancer Center for more than a decade with comparably satisfactory results.

V. RECONSTRUCTION AND REHABILITATION

Developments in reconstructive surgery have remarkably improved the quality of life for many cancer patients following surgical resection of tumors (56). The routine application of microvascular anastomotic techniques has enabled the free transfer of composite grafts containing skin, muscle, and/or bone to surgical defects. Examples of these dramatic improvements in the combined surgical management of complex cancer problems include breast reconstruction after mastectomy (57,58), tissue transfers as part of radical resection of extremity tumors (59–61), aerodigestive reconstruction (62,63), and perineal reconstruction following radical pelvic surgery (64,65). Research is ongoing to define the applications of tissue engineering to extend the reconstructive armamentarium (66). It may be possible in the future to custom grow nerve, fat, muscle, bone cartilage, or other body components as replacement tissues for reconstruction of oncologic surgical defects.

VI. THE SURGICAL ONCOLOGIST

Surgical oncologists are surgeons who devote most of their time to the study and treatment of malignant neoplastic disease. They must possess the necessary knowledge, skills, and clinical experience to perform both the standard as well as extraordinary surgical procedures often required for patients with cancer. However, surgical oncology is more of a cognitive than

a technical surgical specialty. With the exception of a small cluster of index operations, such as regional pancreatectomy, limb salvage and retroperitoneal sarcoma surgery, isolated limb perfusion, and multisegment liver resection, most of the surgical procedures that are performed by surgical oncologists are similar to those performed by a surgeon not oncologically trained. What frequently differentiates these two types of surgeons is the knowledge of contemporary multimodality cancer care. Surgical oncologists must be able to diagnose tumors accurately and to differentiate aggressive neoplastic lesions from benign reactive processes. In addition, surgical oncologists should have a firm understanding of radiation oncology, medical oncology, pathology, and hematology.

Surgical oncologists have a shared role with medical oncologists as the ''primary-care physicians'' of cancer treatment. Almost all cancer patients will initially be managed by one of these two specialists who will bear the ultimate responsibility for co-ordinating appropriate multimodality care for the individual patient. As a member of a multidisciplinary team, the role of the surgical oncologist is to co-ordinate and assist with all aspects of a patient care including tumor diagnosis, surgical resection, follow-up and often palliative interventions. The cancer surgeon is commonly charged with the responsibility of establishing a tissue diagnosis by selection of biopsy technique, communicating biopsy findings to the patient, completing staging procedures and initiating the interaction with other members of the multimodality oncology team. During these initial interactions with patients and family, it is most often the cancer surgeon who educates and explains the sequence and rationale of the various treatment components that can be used to manage their specific malignancy. In this role, a cancer surgeon must be aware of the different therapeutic options, the natural history of a given malignancy, and how these factors will be integrated into a well-conceived and appropriate multimodality treatment algorithm.

Beyond the initiation of diagnosis and treatment, a surgical oncologist is also involved in decisions about follow-up care and surveillance to detect tumor recurrence. In this regard, the cancer surgeon, unlike almost any other surgical specialist, makes a patient commitment for the acute as well as the long-term components of their disease process (10).

Given the complexity of contemporary multidisciplinary approaches to the cancer patient, free-standing cancer centers have developed facilities to provide the needed planning expertise, clinical care, patient support services, and access points to clinical trials. These comprehensive cancer centers are frequently affiliated with academic medical institutions and offer the complete spectrum of oncologic therapies, clinical trials, rehabilitation and social services, as well as basic and translational research programs.

As part of a larger surgical community, the surgical oncologist is a critical conduit of cancer information to colleagues in general surgery and other surgical specialties. This function is often performed at academic surgical meetings, such as those of the American College of Surgeons or the Society of Surgical Oncology, as well as by service in directing hospital-based tumor boards and direct consultation on behalf of individual cancer patients. Because of their leading role in the initial diagnosis of cancer, it is not surprising that surgical oncologists are also frequently in leadership roles in cancer prevention and screening programs. Nation-based multimodality clinical trial groups also depend on surgical oncology expertise to help in trial design, establishing the criteria of surgical quality control, educating trial participants regarding standards of surgical care, as well as assistance in accurate data collection, analysis, and presentation of trial results.

VII. CONCLUSIONS

Within the next decade, cancer is predicted to replace cardiovascular disease as the most prevalent killer of Americans on an annual basis. At present, surgery remains the most promising treatment modality with the greatest chance of cure for solid tumors. As multimodality treatments increase in number and grow in complexity, surgical oncologists will have to become increasingly involved in basic science, technology development, and clinical trial design. Understanding the natural history of specific malignancies will require an expanded knowledge base about genetics and the molecular biology that drives solid tumor proliferation and metastasis. The contemporary surgical approach encompasses appropriate margins of resection including regional nodal basins with morbidity in proportion to the benefits of reducing recurrence (3). Cancer prevention and early diagnosis are the mainstays of increasing survival, whereas advances in adjuvant systemic therapies including molecularly targeted therapies may provide hope for those with advanced disease. Surgical oncologists must be flexible and examine new techniques scientifically as they become available. Risk assessments must be performed for all procedures, keeping in mind that doing nothing may at times be beneficial.

REFERENCES

1. Bremers AJ, Rutgers EJ, van de Velde CJ. Cancer surgery: the last 25 years. Cancer Treat Rev 1999; 25: 333–353.

2. Hill GJ. II. Historic milestones in cancer surgery. Semin Oncol 1979; 6:409–427.
3. Cady B. Fundamentals of contemporary surgical oncology: biologic principles and the threshold concept govern treatment and outcomes. J Am Coll Surg 2001; 192:777–792.
4. American Joint Committee on Cancer. Cancer Staging Manual. 6th ed. New York: Springer, 2002:221–226.
5. Rahlfs TF, Jones RL. Risks and outcomes in oncology patients undergoing anesthesia and surgery. Int Anesthesiol Clin 1998; 36:141–149.
6. Rew DA. Risk analysis in surgical oncology—part II: risk and the practicing surgeon. Eur J Surg Oncol 2000; 26:705–710.
7. Hillner BE, Smith TJ, Desch CE. Hospital and physician volume or specialization and outcomes in cancer treatment: importance in quality of cancer care. J Clin Oncol 2000; 18:2327–2340.
8. Begg CB, Cramer LD, Hoskins WJ, et al. Impact of hospital volume on operative mortality for major cancer surgery. JAMA 1998; 280:1747–1751.
9. Hodgson DC, Fuchs CS, Ayanian JZ. Impact of patient and provider characteristics on the treatment and outcomes of colorectal cancer. J Natl Cancer Inst 2001; 93:501–515.
10. Helsper JT. Impact of the surgeon on cancer management outcomes. J Surg Oncol 2003; 82:1–2.
11. McArdle CS, Hole D. Impact of variability among surgeons on postoperative morbidity and mortality and ultimate survival. BMJ 1991; 302:1501–1505.
12. Gillis CR, Hole DJ. Survival outcome of care by specialist surgeons in breast cancer: a study of 3786 patients in the west of Scotland. BMJ 1996; 312:145–148.
13. Cady B. Basic principles in surgical oncology. Arch Surg 1997; 132:338–346.
14. Rosenberg SA. Principles of cancer management: surgical oncology. In: Vincent T, DeVita J, Hellman S, Rosenberg SA, eds. Cancer: Principles and Practice of Oncology. Philadelphia: Lippincott Williams & Wilkins, 2001:253–264.
15. Fisher B, Anderson S, Bryant J, et al. Twenty-year follow-up of a randomized trial comparing total mastectomy, lumpectomy, and lumpectomy plus irradiation for the treatment of invasive breast cancer. N Engl J Med 2002; 347:1233–1241.
16. Rosenberg SA, Tepper J, Glatstein E, et al. The treatment of soft-tissue sarcomas of the extremities: prospective randomized evaluations of (1) limb-sparing surgery plus radiation therapy compared with amputation and (2) the role of adjuvant chemotherapy. Ann Surg 1982; 196:305–315.
17. Heald RJ, Ryall RD. Recurrence and survival after total mesorectal excision for rectal cancer. Lancet 1986; 1: 1479–1482.
18. Sokoloff MH, Brendler CB. Indications and contraindications for nerve-sparing radical prostatectomy. Urol Clin North Am 2001; 28:535–543.
19. Cote RJ, Peterson HF, Chaiwun B, et al. Role of immunohistochemical detection of lymph-node metastases in management of breast cancer. International Breast Cancer Study Group. Lancet 1999; 354:896–900.
20. Giuliano AE, Jones RC, Brennan M, et al. Sentinel lymphadenectomy in breast cancer. J Clin Oncol 1997; 15:2345–2350.
21. Morton DL. Lymphatic mapping and sentinel lymphadenectomy for melanoma: past, present, and future. Ann Surg Oncol 2001; 8:22S–28S.
22. Tanaka K, Kobayashi M, Konishi N, et al. Laparoscopic intraoperative detection of micrometastatic sentinel nodes by immunohistochemical staining in patients with early gastric cancer. Surg Endosc 2003; 28:28.
23. Tien HY, McMasters KM, Edwards MJ, et al. Sentinel lymph node metastasis in anal melanoma: a case report. Int J Gastrointest Cancer 2002; 32:53–56.
24. Yasuda S, Shimada H, Chino O, et al. Sentinel lymph node detection with Tc-99m tin colloids in patients with esophagogastric cancer. Jpn J Clin Oncol 2003; 33: 68–72.
25. Bilchik AJ, Nora DT, Sobin LH, et al. Effect of lymphatic mapping on the new tumor-node-metastasis classification for colorectal cancer. J Clin Oncol 2003; 21:668–672.
26. Tanis PJ, Lont AP, Meinhardt W, et al. Dynamic sentinel node biopsy for penile cancer: reliability of a staging technique. J Urol 2002; 168:76–80.
27. Wawroschek F, Wagner T, Hamm M, et al. The influence of serial sections, immunohistochemistry, and extension of pelvic lymph node dissection on the lymph node status in clinically localized prostate cancer. Eur Urol 2003; 43:132–137.
28. DuBeshter B, Deuel C, Gillis S, et al. Endometrial cancer: the potential role of cervical cytology in current surgical staging. Obstet Gynecol 2003; 101:445–450.
29. De Hullu JA, Van Der Zee AG. Sentinel node techniques in cancer of the vulva. Curr Womens Health Rep 2003; 3:19–26.
30. Pitman KT, Ferlito A, Devaney KO, et al. Sentinel lymph node biopsy in head and neck cancer. Oral Oncol 2003; 39:343–349.
31. Solorzano CC, Ross MI, Delpassand E, et al. Utility of breast sentinel lymph node biopsy using day-before-surgery injection of high-dose 99mTc-labeled sulfur colloid. Ann Surg Oncol 2001; 8:821–827.
32. Henry-Tillman RS, Korourian S, Rubio IT, et al. Intraoperative touch preparation for sentinel lymph node biopsy: a 4-year experience. Ann Surg Oncol 2002; 9:333–339.
33. Breslin TM, Cohen L, Sahin A, et al. Sentinel lymph node biopsy is accurate after neoadjuvant chemotherapy for breast cancer. J Clin Oncol 2000; 18:3480–3486.
34. Klauber-DeMore N, Tan LK, Liberman L, et al. Sentinel lymph node biopsy: is it indicated in patients with high-risk ductal carcinoma-in-situ and ductal

carcinoma-in-situ with microinvasion? Ann Surg Oncol 2000; 7:636–642.
35. Conlon KC, Minnard EA. The value of laparoscopic staging in upper gastrointestinal malignancy. Oncologist 1997; 2:10–17.
36. Finch MD, John TG, Garden OJ, et al. Laparoscopic ultrasonography for staging gastroesophageal cancer. Surgery 1997; 121:10–17.
37. John TG, Greig JD, Carter DC, et al. Carcinoma of the pancreatic head and periampullary region. Tumor staging with laparoscopy and laparoscopic ultrasonography. Ann Surg 1995; 221:156–164.
38. Sugarbaker PH. Cytoreductive surgery and perioperative intraperitoneal chemotherapy as a curative approach to pseudomyxoma peritonei syndrome. Tumori 2001; 87:S3–S5.
39. Glehen O, Mithieux F, Osinsky D, et al. Surgery combined with peritonectomy procedures and intraperitoneal chemohyperthermia in abdominal cancers with peritoneal carcinomatosis: a phase II study. J Clin Oncol 2003; 21:799–806.
40. Ma GY, Bartlett DL, Reed E, et al. Continuous hyperthermic peritoneal perfusion with cisplatin for the treatment of peritoneal mesothelioma. Cancer J Sci Am 1997; 3:174–179.
41. Atkins CD. Intraperitoneal chemotherapy for stage III ovarian cancer. J Clin Oncol 2003; 21:957; author reply 957–958.
42. Rossi CR, Foletto M, Mocellin S, et al. Hyperthermic intraoperative intraperitoneal chemotherapy with cisplatin and doxorubicin in patients who undergo cytoreductive surgery for peritoneal carcinomatosis and sarcomatosis: phase I study. Cancer 2002; 94:492–499.
43. Curley SA, Izzo F, Delrio P, et al. Radiofrequency ablation of unresectable primary and metastatic hepatic malignancies: results in 123 patients. Ann Surg 1999; 230:1–8.
44. Curley SA, Izzo F, Ellis LM, et al. Radiofrequency ablation of hepatocellular cancer in 110 patients with cirrhosis. Ann Surg 2000; 232:381–391.
45. Izzo F, Thomas R, Delrio P, et al. Radiofrequency ablation in patients with primary breast carcinoma: a pilot study in 26 patients. Cancer 2001; 92:2036–2044.
46. Singletary SE, Fornage BD, Sneige N, et al. Radiofrequency ablation of early-stage invasive breast tumors: an overview. Cancer J 2002; 8:177–180.
47. Dooley WC, Ljung BM, Veronesi U, et al. Ductal lavage for detection of cellular atypia in women at high risk for breast cancer. J Natl Cancer Inst 2001; 93: 1624–1632.
48. Karakousis CP. Radical versus conservative cancer surgery: an anachronism? J Surg Oncol 2001; 77:221–224.
49. Wagman LD. Palliative surgery: a modern perspective. J Surg Oncol 2002; 80:1–3.
50. McCarter MD, Fong Y. Role for surgical cytoreduction in multimodality treatments for cancer. Ann Surg Oncol 2001; 8:38–43.
51. Eisenkop SM, Friedman RL, Wang HJ. Complete cytoreductive surgery is feasible and maximizes survival in patients with advanced epithelial ovarian cancer: a prospective study. Gynecol Oncol 1998; 69:103–108.
52. Richie JP. Surgical aspects in the treatment of patients with testicular cancer. Hematol Oncol Clin North Am 1991; 5:1127–1142.
53. Gomez Portilla A, Deraco M, Sugarbaker PH. Clinical pathway for peritoneal carcinomatosis from colon and rectal cancer: guidelines for current practice. Tumori 1997; 83:725–728.
54. Miller CA, Ellison EC. Therapeutic alternatives in metastatic neuroendocrine tumors. Surg Oncol Clin N Am 1998; 7:863–879.
55. Bow EJ, Kilpatrick MG, Clinch JJ. Totally implantable venous access ports systems for patients receiving chemotherapy for solid tissue malignancies: a randomized controlled clinical trial examining the safety, efficacy, costs, and impact on quality of life. J Clin Oncol 1999; 17:1267.
56. Bland KI. Oncologic and plastic surgeons: colleagues, collaborators, teammates. Plast Reconstr Surg 1998; 102:1733–1747.
57. Petit J, Rietjens M, Garusi C. Breast reconstructive techniques in cancer patients: which ones, when to apply, which immediate and long term risks? Crit Rev Oncol Hematol 2001; 38:231–239.
58. Newman LA, Kuerer HM, Hunt KK, et al. Feasibility of immediate breast reconstruction for locally advanced breast cancer. Ann Surg Oncol 1999; 6:671–675.
59. Bickels J, Wittig JC, Kollender Y, et al. Distal femur resection with endoprosthetic reconstruction: a long-term followup study. Clin Orthop 2002; 1(400):225–235.
60. Zenn MR, Levin LS. Microvascular reconstruction of the lower extremity. Semin Surg Oncol 2000; 19: 272–281.
61. Hornicek FJ, Gebhardt MC, Sorger JI, et al. Tumor reconstruction. Orthop Clin North Am 1999; 30:673–684.
62. Haughey BH, Taylor SM, Fuller D. Fasciocutaneous flap reconstruction of the tongue and floor of mouth: outcomes and techniques. Arch Otolaryngol Head Neck Surg 2002; 128:1388–1395.
63. Losken A, Carlson GW, Culbertson JH, et al. Omental free flap reconstruction in complex head and neck deformities. Head Neck 2002; 24:326–331.
64. Arkoulakis NS, Angel CL, DuBeshter B, et al. Reconstruction of an extensive vulvectomy defect using the gluteus maximus fasciocutaneous V-Y advancement flap. Ann Plast Surg 2002; 49:50–54.
65. Rietjens M, Maggioni A, Bocciolone L, et al. Vaginal reconstruction after extended radical pelvic surgery for cancer: comparison of two techniques. Plast Reconstr Surg 2002; 109:1592–1597; discussion 1598–1599.
66. Miller MJ. Osseous tissue engineering in oncologic surgery. Semin Surg Oncol 2000; 19:294–301.

4

Principles of Chemotherapy

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I. INTRODUCTION

Chemotherapy may be used as the sole therapy for malignancy, but is more commonly used in combination with surgery, radiotherapy, or both. This strategy enhances local control and eradicates occult metastases. The dosage and schedule of chemotherapeutic agents are a balance between efficacy and toxic effects on vital organ systems. Many patients receiving chemotherapy may require elective or even emergent surgery, and the perioperative team members must have a clear understanding of the actions, interactions, and potential toxic effects of each agent in the chemotherapeutic regimen. The preoperative evaluation of the patient should include a detailed history of the exact type and dosing information for each antineoplastic agent used. Organ systems most likely to have been and to be affected should be thoroughly evaluated.

This chapter includes a brief discussion of the basic principles of chemotherapy, synopses of chemotherapeutic mechanisms of action and drug resistance, and a review of select classes of chemotherapeutic agents, namely: alkylating agents, platinum agents, antimetabolites, anthracyclines, topoisomerase inhibitors, microtubule inhibitors, and miscellaneous agents.

II. TUMOR GROWTH

Most antineoplastic drugs are designed to interfere with cell division by interfering with DNA synthesis, replication, transcription, and translation. Cells that are replicating more quickly are also usually more sensitive to chemotherapeutic agents. This balance between cell death and cell replication dictates the degree of response to treatment with a given agent.

Tumor cell kinetics and doubling time are not constant in all cancer cells within an affected individual. Moreover, the proliferating proportion of tumor cells varies among cancers, from 90% in some hematalogic malignancies (for example, lymphoma) to less than 20% in some solid tumors. However, within the tumor's proliferating subpopulation, the doubling time remains constant. As the tumor mass increases, the percentages of nondividing and dying cells will increase.

The smallest mass detectable on chest radiography (approximately 1 cm in diameter) represents approximately 1 g of tissue (1×10^9 cells). In such cases, the neoplastic cells have been present for some time, but vital organs are often not damaged until the tumor mass increases to 1×10^{12} to 10^{13} cells (approximately 1 to 10 kg of tissue). For cell division to be sustained within the body, the growing tumor must induce

neoangiogenesis to supply the tumor cells with adequate nutrients and oxygen; otherwise, necrosis will ensue. The resulting new blood vessels differ from the body's normal vasculature in that they are often densely packed, tortuous, and chaotically distributed.

Many solid tumors contain large quantities of nonproliferating cells that are resistant to the cytotoxic effects of chemotherapy. Proliferating cells are preferentially susceptible to chemotherapeutic agents; quiescent cells may also be killed, albeit less efficiently. This selectivity partially explains why many solid tumors are refractory to chemotherapeutic intervention. In addition, pre-existing genetically distinct tumor cell subclones may display accelerated growth and an ability to metastasize, a property often associated with larger primary tumors (1).

III. CHEMOTHERAPY AND THE CELL CYCLE

Different chemotherapeutic agents affect cells at different points in the cell's replicative cycle. Combining chemotherapeutic agents that target cells at different points in the cell cycle can be very effective, with additive or even synergistic effects in some cases. Certain normal cells such as those found in the bone marrow, hair follicle, and gastrointestinal mucosa are continually replenishing their numbers by traversing through the cell cycle. Chemotherapy may damage these normal cells resulting in side effects such as myelosuppression, alopecia, and mucositis.

A patient's tumor is composed of cells formed as a result of mitosis and consists of three subpopulations: cells that are nondividing and terminally differentiated, cells that are progressing through the cell cycle toward cell division, and resting cells that may return to the cell cycle (i.e., stem cells). All malignant solid tumors are composed of all three-cell populations.

Tumor cells that are proliferating traverse the mitotic cell cycle, which is composed of the G1, S, G2 and M phases. Cells that are resting (G0 phase) are able to divide again by re-entering the cell cycle at the G1 phase. Preliminary synthetic cellular processes occur, preparing cells to enter the DNA synthetic (S) phase. Specific protein signals regulate the cell cycle and allow replication of the genome, where the DNA content becomes tetraploid. After completion of the S phase, the cell enters a second resting phase, G2, before undergoing mitosis. The cell progresses to mitotic (M) phase, where the chromosomes separate and the cell divides (2,3).

Chemotherapeutic agents can be classified according to the phase of the cell cycle in which they are active (Table 1). This is not an arbitrary classification scheme. Agents whose action is consistent throughout all phases of the cell cycle (e.g., alkylating agents) have a linear dosage–response curve: the greater the dosage of the agent, the larger the percentage of cell kill. In contrast, drugs whose action is specific to a particular cell cycle phase plateau in their ability to kill cells since some cells will not be in that phase of the cell cycle. The percentage of cell kill will not increase with increasing drug dosage.

Table 1 Agents That Kill Tumor Cells in Specific Phases of the Cell Cycle

G1 phase	S phase	G2 phase	M phase
Asparaginase	Capecitabine	Bleomycin	Docetaxel
Corticosteroids	Cytarabine	Irinotecan	Etoposide
	Doxorubicin	Mitoxantrone	Paclitaxel
	Fludarabine	Topotecan	Teniposide
	Fluorouracil		Vinblastine
	Gemcitabine		Vincristine
	Hydroxyurea		Vinorelbine
	Mercaptopurine		
	Methotrexate		
	Prednisone		
	Procarbazine		
	Thioguanine		

IV. COMBINATION CHEMOTHERAPY

Chemotherapy combinations have been devised in order to maximize cell killing by using agents that target different points in the cell cycle, rather than combining agents that target the cells in the same phase. Combining different chemotherapeutic agents accomplishes at least three objectives: It provides overlapping and sometimes synergistic cell kill within the range of toxicity tolerated by the patient for each drug, it provides coverage for resistant tumor cell subclones in a heterogeneous tumor population, and it slows the development of new drug-resistant tumor cell subclones (4). Several general principles guide selection of agents used in combination regimens: (a) Drugs known to be active as single agents should be chosen, with preference for agents that induce complete remission. (b) Drugs with different mechanisms of action should be chosen, to allow for additive or synergistic effects on tumor cells. (c) Drugs with differing dose-limiting toxicities should be chosen, to allow for each drug to be given at the full therapeutic dosage. (d) The treatment-free interval between cycles should be the shortest time that allows for recovery of the most sensitive normal tissue. (e) Drugs with different

patterns of resistance should be combined to maximize killing of cells that may be resistant to a single agent.

V. DOSAGE INTENSITY

Dosage intensity is a phenomenon that has been observed to be a beneficial strategy in retrospective studies of colon cancer, ovarian cancer, breast cancer, and lymphoma (5). For chemotherapy-sensitive cancers, the factor limiting the capacity to cure is insufficient dosing. Suboptimal doses of chemotherapy most often result from the development of chemotherapy-related side effects. As the dosage of an agent is reduced, the cure rate significantly decreases, and there is an appreciable decline in the complete remission rate. Therefore, chemotherapy-sensitive cancer patients are commonly given, doses approaching the maximal tolerated dosage.

VI. DRUG RESISTANCE

Cancer is a genetic disease. Cancer cells are inherently more prone to genetic mutations than are normal cells, and spontaneous mutations occur in subpopulations of cells before exposure to chemotherapy. Some of these subpopulations are drug resistant and continue to proliferate after chemotherapy has eliminated the sensitive cell lines. The Goldie–Coldman hypothesis asserts that the probability of a tumor population containing resistant cells is a function of the total number of cells present (6,7). Several mechanisms for chemotherapeutic failure have been identified and are described below.

A. Single-Drug Resistance

Cell lines may become resistant to a single-drug class or to multiple drugs, depending on the type of resistance. Mechanisms by which tumors become more resistant to a single agent are increased production of catabolic enzymes to degrade drugs, direct drug inactivation by glutathione, reduced ability to repair DNA strand breaks, and alterations in transport proteins.

Exposure to a drug can result in gene amplification of DNA for specific catabolic enzymes. Upregulation of catabolic enzymes and the resulting decrease in effective drug levels causes drug resistance. Examples include increases in dihydrofolic reductase, which metabolizes methotrexate (8); deaminase, which deactivates cytarabine (9); and glutathione, which inactivates alkylating agents (10). Glutathione is not only essential for DNA synthesis but is a scavenger of free radicals and appears to play a role in drug resistance. The hypothesized mechanisms of glutathione-mediated drug resistance are inactivation of alkylating agents through direct binding, increased metabolism, detoxification, and repair of DNA damage.

Increased topoisomerase inhibition results in both inhibition of DNA replication and failure to repair strand breaks. DNA strands are wound together and attached to the nuclear matrix at regularly spaced domains. Topoisomerases bind to these domains, forming a "cleavable complex" that allows DNA to unwind in preparation for cell division. Topoisomerases later participate in the resealing of DNA molecules during cell division. Inhibition of topoisomerase causes both inhibition of DNA replication and failure to repair strand breaks (11). Camptothecin derivatives, such as irinotecan and topotecan, exert their effect by inhibiting topoisomerase I. Epipodophyllotoxin derivatives, such as etoposide, inhibit topoisomerase II. Both of these agents cause stable, and therefore lethal, DNA strand breaks. Alternatively, resistance to topoisomerase inhibitors may develop with decreased drug access to the enzyme, alteration of the enzyme structure or activity, increased rate of DNA repair or as the result of the action of a multidrug-resistance protein (12,13).

Drug exposure can also induce production of transport proteins that effectively lower intracellular concentrations of a drug and thus lead to drug resistance, possibly owing to smaller amounts of a drug entering a cell or larger amounts being carried out because of adaptive changes in cell membrane transport. Examples include methotrexate transport and multidrug-resistance gene-1 (MDR-1) (14).

B. Multidrug Resistance

Resistance can also arise to multiple drugs simultaneously. Induction or amplification of MDR-1 can result in multidrug resistance through increased production of a pump that rapidly transport hydrophobic chemicals out of the cell (14). Another product of normal cells that confers resistance to chemotherapy is P-170, found in healthy renal, colonic, and adrenal cells (15). P-170 can be induced by and mediates the transport of actinomycin D, anthracyclines, colchicines, epipodophyllotoxin, and vinca alkaloids.

Overexpression of certain gene products, such as BCL-2, suppress apoptosis. This suppression of apoptosis not only removes a major mechanism by which antineoplastic agents kill cells, but also allows cancer cells to accumulate genetic defects, resulting in preferential selection of more aggressive cancer cells (16).

VII. CHEMOTHERAPEUTIC AGENTS

Many patients with cancer who undergo elective or emergent surgery also will undergo or have undergone chemotherapy at some point in their treatment. The clinical benefits of chemotherapy are often limited by the toxic effects of these agents on vital organ systems (Tables 2 and 3). Members of the perioperative team must have a clear understanding of the actions, interactions, and toxic effects of the various chemotherapeutic agents that have been or will be used. During the perioperative evaluation, the exact type and dosages of chemotherapeutic agents used should be reviewed and the organ systems most likely to be affected should be carefully evaluated.

Chemotherapeutic agents can be grouped into several major classes on the basis of their underlying antineoplastic mechanism of action or the source from which they are derived. Table 2 lists several commonly used antineoplastic agents by class, along with the toxic effects associated with each drug. Rational use of systemic anticancer therapies is based on an understanding of tumor cell biology and clinical pharmacology. The choice of an appropriate chemotherapeutic agents depends, in part on the inherent sensitivity of a specific disease to the various classes of drugs that are currently available and on the ability to administer the agents

Table 2 Toxic Effects of Chemotherapeutic Agents Grouped by Class

Class	Agent(s)	Toxic effect(s)
Alkylating agents	Busulfan, chlorambucil, cyclophosphamide, ifosfamide, mechlorethamine, melphalan, thiotepa	Myelosuppression, pulmonary infiltrates, pulmonary fibrosis, hemorrhagic cystitis, alopecia, nausea, emesis
	Lomustine, carmustine	Myelosuppression, emesis
	Procarbazine, dacarbazine, temozolomide, hexamethylmelamine	Anorexia, myelosuppression, peripheral neuropathy
Platinum agents	Cisplatin	Nausea and emesis, nephrotoxicity, hypomagnesemia, neurotoxicity
	Carboplatin	Myelosuppression, emesis
Antimetabolites	Cytarabine, fludarabine, floxuridine, fluorouracil, 6-mercaptopurine, methotrexate, 6-thioguanine	GI mucositis, myelosuppression, alopecia, neurotoxicity
Anthracyclines	Doxorubicin, daunorubicin, epirubicin, idarubicin, mitoxantrone	GI mucositis, alopecia, myelosuppression, cardiotoxicity
Topoisomerase inhibitors	Etoposide, teniposide	Myelosuppression, alopecia, GI mucositis, blisters, neuropathy, anaphylaxis
	Irinotecan, topotecan	Myelosuppression, diarrhea, electrolyte disorders
Microtubule inhibitors	Paclitaxel, docetaxel	Myelosuppression, stomatitis, neuropathy, anaphylaxis, edema
	Vinblastine	Myelosuppression, GI toxicity, neuropathy, blisters, alopecia, hypertension, pulmonary toxicity
	Vincristine	Peripheral neuropathy, paralytic ileus, syndrome of inappropriate secretion of antidiuretic hormone, rash, alopecia, bladder atony
	Vinorelbine	Myelosuppression, alopecia
Other agents	Plicamycin	Myelosuppression, hypocalcemia, hepatotoxicity
	Mitomycin C	Myelosuppression, GI mucositis, hypercalcemia
	Dactinomycin	GI mucositis, myelosuppression, alopecia
	Bleomycin	Nausea, emesis, alopecia, pulmonary fibrosis
	Asparaginase	GI toxicity, somnolence, confusion, fatty liver
	Hydroxyurea	Myelosuppression
	Mitotane	Adrenal insufficiency, emesis, diarrhea, tremors
	Streptozocin	Hypoglycemia
	Levamisole	Rash, arthralgia, myalgia, fever, neutropenia
	Leucovorin	Allergy

Table 3 Types and Degrees of Toxic Effects of Chemotherapeutic Agents

Drug	Toxicity			
	Hematologic	Hepatic	Nephrotoxic	Cardiac
Actinomycin	3[a]	0	0	1
Amsacrine (AMSA)	2	1	0	3
Ara-C (cytarabine)	3	3	0	0
L-Asparaginase	0	3	0	0
Azathioprine	–	3	0	2
Bleomycin	0	0	0	1
Busulfan	–	1	0	0
Carboplatin	3	0	0	0
Carmustine (BCNU)	3	3	2	0
Chlorambucil	2	1	0	0
Cyclophosphamide	3	1	0	0
Dacarbazine (DTIC)	1	2	0	0
Deoxycoformycin	1	2	1	0
Daunomycin/doxorubicin	3	0	0	3
Etoposide/teniposide	2	2	0	0
Fludarabine	2	1	1	0
Fluorouracil	1–2	2	0	1
Hexamethylmelamine	1	0	0	0
Hydroxyurea	3	0	0	0
Ifosfamide	2	0	2	0
Lomustine (CCNU)	3	3	2	0
Melphalan	3	1	0	0
Mercaptopurine	2	3	0	0
Methotrexate	1–2	3	2	0
Mithramycin	1	3	3	0
Mitomycin C	1	0	2	1
Mitotane	–	0	0	0
Mitoxantrone	2	1	0	0
Nitrogen mustard	3	0	0	0
Procarbazine	2	0	0	0
Streptozocin	1	3	3	0
Taxol (paclitaxel)	3	2	0	3
Thioguanine (6-TG)	2	2	0	0
Thiotepa	–	0	0	0
Vincristine	1	2	0	1
Vinblastine	3	0	0	0
Vindesine	2	0	0	0

[a] Toxicity ratings: 0, rare or very mild; 1, occasional, usually not severe; 2, moderately severe; 3, frequent or severe.
–, Type of toxicity not reported to date in the general medical literature.

either as single agents or in combination, based on their combined toxic effects on critical organ systems.

A. Alkylating Agents

Alkylating agents were the first nonhormonal chemotherapeutic agents. Introduced in the 1940s, these agents have been increasingly used both as a primary treatment for cancer and, more important, as an adjuvant therapy to be administered in association with surgery or radiotherapy or both. The alkylating agents are a large group of agents that can impair cell function by transferring alkyl groups to amino, carboxyl, sulfhydryl, and phosphate groups. The common feature of these compounds is that they are composed of monofunctional or bifunctional alkyl groups linked to a core structure that confers pharmacologic and toxicologic differences on the alkylating moieties. The four drugs which have replaced nitrogen mustard in common clinical practices are L-phenylalanine mustard (LPAM; melphalan), ifosfamide, chlorambucil, and cyclophosphamide.

The common mechanistic feature of alkylating agents is that, upon entering cells, the alkyl groups bind to DNA, RNA, and proteins. This alkylation results in abnormal nucleotide sequences, miscoding of messenger RNA, cross-linked DNA strands that cannot replicate, breakage of DNA strands, and other damage to the transcription and translation of genetic material. These agents depend on cell pro liferation for activity but are not cell cycle-phase-specific.

1. Cyclophosphamide, Ifosfamide, Chlorambucil, Mechlorethamine, and Melphalan

Both cyclophosphamide and chlorambucil are orally bioavailable and are administered either intravenously or orally; ifosfamide is utilized by the intravenous route. Except for the requirement for hepatic metabolism of cyclophosphamide and ifosfamide, which prolongs its primary elimination as well as the disappearance of its metabolites (approximately 8 hr), elimination of the alkylating agents in the blood is rapid (less than 2 hr) owing to chemical decomposition.

The toxicity of alkylating agents is primarily hematopoietic. Some alkylating agents, such as mechlorethamine, have a more prominent effect on granulocytes; other agents, such as melphalan, induce relatively greater thrombocytopenia, although granulocytopenia often also occurs. The nadir of hematologic counts usually occurs 8–14 days after drug administration. The cyclophosphamide and ifosfamide metabolite acrolein can irritate the bladder mucosa, requiring strict attention to hydration and urine flow; ifosfamide metabolites, may also produce renal tubular injury. All alkylating agents can cause alopecia, nausea, emesis, and infertility. These agents are also associated with the rare development of treatment-related second malignancies. Clear evidence shows that alkylating agents are associated with the development of secondary leukemias, the frequency of which is related to the amount of alkylating agent received. The presumed mechanism of this effect is damage to the normal bone marrow stem cells resulting in mutagenic changes (17).

Alkylating agents are among the most widely used antineoplastic agents and form an important part of curative therapeutic regimens for lymphomas and important surgical adjuvant regimens for breast cancer and soft-tissue sarcomas. Alkylating agents are also the class of drugs with the steepest dose–response curves in vitro and, therefore, are also the antineoplastic drugs that are most readily dose escalated. Thus, these drugs are frequently employed in high dose chemotherapeutic regimens administered with autologous or allogeneic bone marrow support.

2. Nitrosoureas

Nitrosoureas are lipid soluble and appear to be the most effective agents for use in malignancies of the central nervous system (CNS). Their lipid solubility is believed to enhance penetration of these agents through the blood–brain barrier and hence delivery into the CNS. These agents have a unique pattern of toxicity for normal tissues, although their mechanism of tumor cell killing seems to be DNA cross-linking similar to that of the classic alkylating agents. Nitrosoureas tend to exert their most pronounced toxic effects on the hematopoietic system at a later time than do classic alkylating agents. After nitrosourea therapy with carmustine (bischloroethylnitrosourea, BCNU), for example, the nadir of myelosuppression occurs at days 30–36, although drug disappearance from the circulation is rapid; further, nitrosoureas appear to have the ability to damage bone marrow stem cells more effectively than do other classic alkylating agents. Nitrosoureas are also more commonly associated with pulmonary interstitial fibrosis than are other alkylating agents and can produce cumulative renal injury.

Other alkylating agents in clinical practice include busulfan, an alkane sulfonate used for treatment of chronic myelogenous leukemia, and dacarbazine, which methylates as well as binds to DNA and is used to treat soft-tissue sarcomas and malignant melanoma.

B. Platinum Agents

1. Cis-platinum

The finding that platinum salts are toxic to bacteria led to the discovery that such salts are also quite effective antineoplastic agents. The classic platinum coordination complex is the drug cisplatin (*cis*-diamminedichloroplatinum II), whose action is similar to those of alkylating agents. The platinum compound covalently links to biologically important macromolecules, for example the primary target for cisplatin damage in proliferating cells is DNA. ''Platinated'' DNA contains intra- and interstrand crosslinks that disrupt DNA function and replication. The clearance of cisplatin is primarily through endogenous inactivation via binding to biologic macromolecules, and the half-life of the unchanged parent molecule in plasma is short; hepatic metabolism and renal excretion play little role in the elimination of the drugs. The toxicity of cisplatin can be significant, with toxic effects that may include severe nausea and emesis; renal tubular impairment; damage to cochlear hair cells, with high-frequency hearing loss; and peripheral nerve damage resulting in a sensorimotor neuropathy. However, careful attention to enhanced intravenous hydration and urine

output can largely ameliorate the neurotoxicity of cisplatin, and the recent development of improved antiemetic regimens has dramatically reduced the emetogenic side effects of cisplatin administration. Myelosuppression induced by cisplatin, although modest, must also be carefully monitored.

The introduction of cisplatin into oncologic therapeutics has led to a remarkable change in the therapy for disseminated testicular germ cell cancer, significantly increasing the curability of this disease, as well as the management of advanced ovarian, small and nonsmall cell lung cancers, osteosarcomas, and squamous cancers of the head and neck.

2. *Carboplatin*

Carboplatin (diamine 1,1-cyclobutanedicarboxylatoplatinum II) is structurally similar to cisplatin, but differs markedly in its pharmacokinetics and spectrum of toxicity. The half-life of carboplatin is longer than that of cisplatin, and the clearance of carboplatin is determined primarily by renal excretion. Carboplatin is substantially less toxic to the kidneys and has a lesser propensity for causing nausea and emesis. Similarly, no neurotoxicity occurs with carboplatin except at high doses. Unlike cisplatin, carboplatin is associated with greater bone–marrow suppression. Platelets are affected more than are granulocytes. Generally, the antitumor activity of carboplatin appears to be equivalent to that of cisplatin, except in the treatment of germ cell malignancies. However, the precise dosage equivalents of these two drugs are uncertain. In combination chemotherapy, carboplatin's myelosuppressive effects can necessitate dosage reduction of both carboplatin and other myelosuppressive agents used at the same time. Tumor resistance to these agents appears to be related to the capacity of cells to repair nucleic acid damage and to inactivate the drugs by conjugation with glutathione (18,19).

C. Antimetabolites

Members of a substantial group of highly effective chemotherapeutic drugs known as antimetabolites disrupt the intermediary metabolism of malignant cells. These compounds can inhibit important enzymes or serve as inhibitory substances, resulting in incorporation of a "fraudulent" molecule into biologically active molecules. Several antimetabolites are widely used as part of curative chemotherapeutic regimens for treatment of childhood malignancies, acute leukemias, lymphomas, osteosarcomas, and for palliation in patients with common solid tumors.

1. *Methotrexate*

Methotrexate, the most widely used folate antagonist, is the prototype of the antimetabolite class. First developed for treatment of childhood leukemias in the late 1940s, methotrexate, a folate analogue, binds to and inhibits dihydrofolate reductase (DHFR), thereby inhibiting DNA replication. Methotrexate is water-soluble and is cleared by glomerular filtration, with a terminal half-life of 8 hr. Impaired renal function and pleural effusions can considerably alter the pharmacokinetics and toxicity of methotrexate. Because methotrexate impairs the genesis of reduced folates, the toxicity and efficacy of the agent can, in part, be inhibited by concomitant administration of exogenous reduced folates, such as leucovorin (citrovorum factor). However, when the toxic effects of methotrexate, such as renal dysfunction, myelosuppression, or mucositis, become clinically evident, reduced folates play little role in their resolution. Methotrexate has broad activity in the treatment of acute lymphocytic leukemia, osteosarcoma, and head and neck cancer (20).

2. *Fluoropyrimidines*

The fluoropyrimidines 5-fluorouracil (5-FU) and 5-fluorodeoxyuridine (FUdR) alter metabolic conversion and, in the presence of reduced folates, bind to the DNA synthetic enzyme thymidylate synthase in place of the normal substrate, uracil, forming a covalent complex and inactivating the enzyme. Fluoropyrimidines can also be directly incorporated into RNA in place of uracil, leading to impaired RNA processing. They are cleared rapidly by hepatic metabolism, with a half-life in plasma of 10–15 min; the large capacity of the liver to detoxify these drugs provides a pharmacologic advantage when they are infused directly into the liver, causing a high local drug concentration with modest or no systemic drug exposure or toxicity. Hepatic artery infusion of fluoropyrimidines is modestly successful in the treatment of hepatic metastases from colorectal cancer. Recently, patients with partial or complete deficiencies of dihydropyrimidine dehydrogenase, the key enzyme in fluoropyrimidine catabolism, have been described; these individuals are at markedly increased risk of developing severe side effects after treatment with fluoropyrimidine. The toxicity of fluoropyrimidines is manifested as reversible, usually mild myelosuppression and potentially severe diarrhea and stomatitis, with very occasional cerebellar dysfunction and minimal alopecia, principally occurring 8–14 days after completion of therapy. Fluoropyrimidines are important components of combination regimens utilized for breast cancer and are the most active compounds in a wide variety of gastrointestinal

malignancies. Because the binding of fluoropyrimidines to thymidylate synthase can be enhanced by increasing the intracellular concentration of reduced folates, 5-FU and leucovorin have been combined. This combination has proved to be one of the most active regimens for the treatment of colorectal cancer in both the advanced disease and the adjuvant settings. However, treatment with this combination is associated with an increased risk of severe mucositis or diarrhea (21).

3. *Cytosine Arabinoside*

Cytosine arabinoside (Ara-C) is a "fraudulent" nucleoside consisting of a purine cytosine linked to arabinose, a sugar that is not naturally produced by humans. The Ara-C is metabolized by the same enzymes necessary for synthesis of cytosine triphosphate (CTP), which is incorporated into DNA. Incorporation of the fraudulent base Ara-C inhibits DNA replication and repair, and leads to impaired cellular proliferation, in part through induction of apoptosis. The efficacy of Ara-C is directly related to the rate of formation of Ara-CTP, a process that can be enhanced by administering the drug at high dosages. Ara-C is rapidly catabolized in the liver, peripheral tissues, and serum by the enzyme cytidine deaminase, with a terminal half-life of 2 hr. The major toxic effects of Ara-C are bone–marrow suppression, stomatitis, and intrahepatic cholestasis. Higher doses of Ara-C may have toxic effects on the CNS consisting of disorientation, cerebellar dysfunction, and coma. The primary use of Ara-C is in the treatment of acute myelogenous leukemia (22,23).

4. *Gemcitabine*

Like Ara-C, the cytidine analogue gemcitabine (2′2′-difluorodeoxycytidine; dFdC), is activated by deoxycytidine kinase and detoxified by cytidine deaminase. Gemcitabine exerts antineoplastic effects by incorporation of its major intracellular metabolite into DNA. The dose-limiting toxicity of gemcitabine is myelosuppression, with neutropenia occurring more frequently than thrombocytopenia. Fever, skin rash, and flu-like symptoms may occur. Gemcitabine has been shown to improve the quality of life of patients with advanced pancreatic cancer and has a palliative benefit in the treatment of nonsmall cell lung cancer, soft-tissue sarcomas, ovarian cancer, and breast cancer (24).

D. Anthracyclines

The anthracyclines doxorubicin and daunorubicin were isolated from *Streptomyces* species and thus have been termed antitumor antibiotics. However, these drugs interact significantly with a wide range of biochemical systems in tumor cells; many of these interactions contribute to their broad antineoplastic activity. Anthracyclines appear to exert their antitumor activity, at least in part, by the following mechanisms: binding to the nuclear enzyme topoisomerase II to form a "cleavable complex" that interferes with the ability of the enzyme to reduce torsional strain in DNA; generation of reactive oxygen species that interfere with mitochondria functions and critical macromolecules; and activation of signal transduction pathways that ultimately lead to stimulation of apoptosis. The pharmacokinetics of doxorubicin and daunorubicin, as well as epirubicin, the anthracycline analogue most frequently used in Europe, demonstrate triexponential decay, with a long terminal half-life in plasma (approximately 10 hr). All anthracyclines are metabolized primarily by the liver and excreted, in part, into the bile; individuals with liver dysfunction may exhibit considerably enhanced anthracycline toxicity because of delayed drug clearance. The toxicity profile of anthracyclines includes myelosuppression and damage to oral and gastrointestinal mucosa, resulting in stomatitis and diarrhea. Alopecia is a universal effect of anthracycline administration. Anthracycline antibiotics are also potent vesicants; extravasation of these agents into soft-tissue results in extensive necrosis and soft-tissue damage. Consequently, great care must be exercised when anthracyclines are administered intravenously. Continuous infusion must be done through indwelling central venous catheters.

A unique toxicity of anthracyclines is cumulative, dose-dependent myocardial damage. This toxicity is enhanced by the high iron content of myocardial tissue. Recent studies that have employed either gated cardiac blood pool scanning or endomyocardial biopsy as end points for functional or histopathologic confirmation of cardiac toxicity of doxorubicin have demonstrated that the incidence of measurable heart damage begins to climb when the cumulative dose exceeds 350–400 mg/m^2 if the drug has been administered by short intravenous infusion (a "bolus" injection is often given over 30 min). Thus, in patients who begin therapy with normal cardiac function, anthracyclines can be administered with low risk of myocardial dysfunction. However, in individuals with a history of hypertensive heart disease or prior left chest wall irradiation, the maximum safe dose of doxorubicin may be lower. Data indicate that infusional therapy with anthracyclines (e.g., 72- to 96-hr continuous infusion) allows for a much higher cumulative dose to be administered with diminished risk of cardiac toxicity. Dexrazoxane is a novel agent that chelates iron, minimizing the myocardial toxicity of doxorubicin administered as a bolus.

Anthracyclines have a broad range of antineoplastic activities and form an important component of combination therapies for non-Hodgkin's lymphoma, Hodgkin's disease, breast cancer, osteosarcoma, soft-tissue sarcomas, and a variety of pediatric solid tumors. Daunorubicin, idarubicin, and doxorubicin are also the most active drugs for the treatment of lymphoid and myeloid leukemias (25,26).

E. Topoisomerase Inhibitors

1. *Podophyllotoxins*

Etoposide (VP-16) and teniposide (VM-26) are the two podophyllotoxin derivatives now commonly used. The antiproliferative effects of podophyllotoxin derivatives have been known for many years. These agents exert their anticancer activity through interaction with the enzyme topoisomerase II, which facilitates the uncoiling of DNA before DNA replication. VP-16 and VM-26 are metabolized by the liver; about 40% of a dose of etoposide is excreted by the kidney. The terminal half-lives of both drugs are 8–10 hr in plasma after intravenous administration.

VP-16 is the most frequently used podophyllotoxin and can be administered either intravenously or orally. Recent data suggest that continuous low-dose oral VP-16 is active when intermittent schedules have failed. The primary toxic effects of these agents are leukopenia, thrombocytopenia, and mild to moderate alopecia; at high dosages, stomatitis occurs. An unfortunate late effect of VP-16 is the development of secondary leukemia. VP-16 is active in germ cell tumors, small cell carcinomas of the lung, Hodgkin's and non-Hodgkin's lymphomas, and myeloid and lymphoid leukemias (27,28).

2. *Campothecins*

Camptothecin and its derivatives inhibit the nuclear enzyme topoisomerase I, a protein that plays a critical role in relieving torsional strain in DNA during replication, and thus resulting in cell death. The camptothecin derivatives topotecan and irinotecan (CPT-11) are useful for the treatment of advanced ovarian and colorectal carcinoma, respectively. The major toxic effect of topotecan is myelosuppression, especially neutropenia, which occurs approximately 10 days after administration. Irinotecan is excreted into the urine and bile; SN-38, the active metabolite of irinotecan, is also excreted into the bile. In addition to neutropenia, treatment with irinotecan can produce two forms of diarrhea that may be dose-limiting: the early type of diarrhea, which occurs within hours of drug administration, is probably cholinergic and is associated with cramping and diaphoresis; it can be prevented by pretreatment with atropine. More difficult to control is the late-onset diarrhea that is frequently seen after the second or third weekly dose of irinotecan; this effect can produce dehydration if not aggressively managed with loperamide and fluid replacement. Topotecan has demonstrated moderate activity in patients with platinum-refractory ovarian cancer. Irinotecan clearly can produce objective remission in patients with fluoropyrimidine-refractory colorectal cancer (29,30).

F. Microtubule Inhibitors

1. *Vinca Alkaloids*

The two most commonly utilized vinca alkaloids, vincristine, and vinblastine are complex molecules whose mechanism of action is based on disruption of microtubular function through microtubular aggregation. This action results in disruption of the formation of the mitotic spindle and inhibition of cells progressing through the cell cycle at the stage of mitosis. Vinca alkaloids are metabolized primarily by the liver, and their toxicity is considerably enhanced in individuals with severe hepatic dysfunction. The primary toxicity of vincristine is neurologic. Vincristine administration may result in a peripheral neuropathy or ileus. The peripheral neuropathy is related to nerve damage associated with axonal microtubular disruption, while the ileus is thought to be due to damage to autonomic nerves supplying the gastrointestinal tract.

Vinca alkaloids are components of effective combination therapies for a wide variety of tumors. They are most active in hematologic malignancies and germ cell tumors. Activity in small, non-small cell lung cancer, and breast cancer is limited but does occur. The primary toxic effect of vinblastine is myelosuppression affecting both granulocytes and platelets; neuropathy is an uncommon side effect of vinblastine administration (31,32).

2. *Taxanes*

Paclitaxel was the first clinically useful compound in the taxane class of antimicrotubule agents. The drug was originally isolated from the bark of the pacific yew, *Taxus brevifolia*, but is now semisynthetically derived. This agent has a wide spectrum of antineoplastic activity and a unique mechanism of cytotoxicity. Paclitaxel interacts with microtubules but, rather than inhibiting their formation as the vinca alkaloids do, stabilizes microtubules and inhibits their dissolution, upsetting the dynamic balance between microtubule formation and dissolution upon which many intracellular processes depend. The most obviously

affected process is mitosis, which requires microtubules for chromosome separation and cell division. Although both paclitaxel and vinca alkaloids inhibit microtubular function, cells resistant to one class of drugs are not always resistant to the other. Paclitaxel is cleared primarily by the liver; dosage adjustment is required for patients with moderate elevations of hepatic enzymes. The primary toxic effects of paclitaxel are myelosuppression and peripheral neuropathy. Toxic effects of paclitaxel that complicate its development are hypotension and anaphylactoid reactions, which appear to be related to the vehicle in which paclitaxel is prepared (Cremophor-EL). The hypersensitivity reactions have been averted by administration of antihistamines and corticosteroids. Paclitaxel is active in refractory ovarian cancer, small and nonsmall cell lung cancers, and breast cancer.

The taxane analogue docetaxel is a product of semisynthetic approaches. Docetaxel, like paclitaxel, is metabolized by the liver. Because of its enhanced solubility, docetaxel is prepared in a vehicle different from that of paclitaxel and thus does not produce as many immediate hypersensitivity reactions. However, unlike paclitaxel, docetaxel can produce a capillary leak syndrome characterized by peripheral edema, ascites, or pleural effusion. Prior premedication with dexamethasone can decrease and delay the onset of this syndrome (33,34). There is incomplete cross-resistance between docetaxel and paclitaxel. Docetaxel is very active in the treatment of breast, lung, and ovarian cancers.

G. Other Agents

1. *Actinomycin D*

A byproduct of *Streptomyces*, Actinomycin D is used for the treatment of childhood malignancies, particularly soft-tissue sarcomas and neuroblastoma. The drug's mechanism of action is inhibition of RNA and protein synthesis that occurs after DNA intercalation, with RNA chain elongation being principally affected. The drug is excreted in part by the kidney and into the bile as the unchanged parent molecule with a long terminal half-life (over 30 hr). The major toxic effects of actinomycin D are myelosuppression, which may be severe; alopecia; nausea and emesis; diarrhea and mucositis; and the potential for extravasation injury if the drug leaks from a vein into the surrounding soft tissues (35).

2. *Mitomycin C*

Like actinomycin D, mitomycin C was isolated from a species of *Streptomyces* yeast. This unique molecule combines quinine and aziridine moieties, both of which play important roles in the agent's reductive intracellular activation to a potent alkylating species and in the generation of reactive oxygen molecules. Under hypoxic conditions, reductive alkylation appears to be responsible for tumor cell killing. Mitomycin C is metabolized by the liver and excreted in part by the kidney, with a terminal half-life of 30–60 min. Its major toxic effects include myelosuppression (which may be delayed up to 4–5 weeks after treatment), alopecia and stomatitis, hemolytic–uremic syndrome, extravasation injury, and exacerbation of anthracycline-induced cardiac toxic effects. The major therapeutic roles of mitomycin C are in the treatment of superficial bladder cancer, for which the drug is administered by direct instillation, and in palliative therapy for gastrointestinal, breast, and nonsmall cell lung cancers (36,37).

3. *Bleomycin*

Bleomycin is a complex mixture of peptides isolated from the *Streptomyces verticillus* fungus plays an important role in the treatment of testicular germ cell neoplasms and non-Hodgkin's lymphoma. The agent's unique mechanism of tumor cell killing involves the formation of metal–bleomycin complex, which rapidly binds oxygen; the activated metal (usually ferrous iron)–oxygen–bleomycin complex is stabilized by and actively cleaves DNA, producing both single and double strand breaks. Bleomycin is metabolized by a hydrolase that is found in both normal and malignant cells but at low concentrations in skin and lung, two organs that are particularly sensitive to the drug. Bleomycin is excreted in the urine, with an elimination half-life in plasma of approximately 3 hr; the pharmacokinetics of the drug is markedly altered in patients with abnormal renal function. Bleomycin produces little myelosuppression, but its administration is frequently associated with fever and occasionally with acute allergic reaction. The major side effect of bleomycin is a cumulative pulmonary toxicity, the etiology of which remains unclear; however, the clinical picture of bleomycin-induced lung damage is well known and is characterized by nonproductive cough and shortness of breath, with minimal findings on physical examination, and occasionally patchy interstitial infiltrate on chest radiography. Pulmonary function studies demonstrate a reduced diffusion capacity, especially in patients who have received a total dose greater than 240 mg. Pulmonary function testing is recommended prior each cycle of therapy (every 3–4 weeks). Discontinuation of the drug may lead to complete resolution of signs and symptoms of respiratory impairment over

a period of months to years; however, all patients exposed to bleomycin remain at risk of developing acute respiratory failure postoperatively if exposed to high oxygen tensions during the perioperative period (38,39).

VIII. DEFINITION OF RESPONSE

The word "response" is used by oncologists to determine whether a therapy is shrinking a given solid tumor. This is commonly used as a surrogate marker to determine the efficacy of a given chemotherapy in solid tumors. Radiographic imaging or physical examination is used to determine the baseline size of a tumor prior to chemotherapy. After a certain number of treatments (usually 2 cycles of chemotherapy, or 6–8 weeks), the size of the solid tumor is once again measured. Treatment continues until the patient does not tolerate further chemotherapy, or there is evidence that the tumor has grown. In 1994, the task force reviewed and updated the criteria used to evaluate response to treatment of solid tumors. The task force concluded that for a baseline lesion to be termed measurable the longest diameter must be $\geq$20 mm using conventional imaging or $\geq$10 mm with spiral CT scanning, all lesions with smaller diameters are considered nonmeasurable. All the following lesions are also considered nonmeasurable: ascites, bone lesions, cystic lesions, inflammatory breast disease, leptomeningeal disease, lymphangitis, pericardial effusion, pleural/pericardial effusion, and cutis/pulmonis, as well as any abdominal masses that are not confirmed and followed up using imaging techniques. Tumors located in a previously irradiated area might be considered measurable.

To assess overall tumor burden, the sum of the longest diameters of all measurable lesions up to a maximum of five lesions per organ and 10 lesions total should be calculated and recorded (these tumors are considered the target lesions). All other lesions or sites of disease should be recorded as baseline "nontarget" lesions.

The definition of "tumor response" has changed somewhat from the original definition in the *WHO Handbook*. Using only the longest diameter for all lesions, a *complete response* is currently defined as the disappearance of all target lesions; a *partial response* is at least a 30% decrease in the sum of the longest diameters of all target lesions, taking as a reference the sum of the longest diameters of the target lesions since the treatment started. *Stable disease* is shrinkage insufficient to meet the definition of, partial response or increase in tumor diameters insufficient to qualify for progressive disease, taking as a reference the smallest sum of the longest diameter since the treatment started. *Progressive disease* is at least a 20% increase in the sum of the longest diameters of all target lesions, taking as a reference the smallest sum of the longest diameters recorded since the treatment started, or as the appearance of one or more new lesions.

IX. CONCLUSION

Cancer chemotherapy has had a profound influence on the treatment and survival of patients with both primary and metastatic cancers. Since these agents have potentially lethal side effects, yet must be used at an adequate therapeutic dose, the clinicians caring for these patients are engaged in a delicate balance of risks and benefits. Knowledge of the type of cancer, the stage of disease in the individual patient, and the side effects of the chemotherapeutic agents must be used to achieve maximal therapeutic benefit with minimal adverse events. This information will enhance the likelihood of success in the care of patients with cancer.

REFERENCES

1. Shackney SE, McCormack GW, Cuchural GJ Jr. Growth rate patterns of solid tumors and their relation to responsiveness to therapy: an analytical review. Ann Intern Med 1978; 89:107–121.
2. Hartwell LH, Weinert TA. Checkpoints: controls that ensure the order of cell cycle events. Science 1989; 246:629–634.
3. Hartwell LH, Kastan MB. Cell cycle control and cancer [rev] [101 refs]. Science 1994; 266:1821–1828.
4. DeVita VT Jr, Young RC, Canellos GP. Combination versus single agent chemotherapy: a review of the basis for selection of drug treatment of cancer. Cancer 1975; 35:98–110.
5. Levin L, Hryniuk WM. Dose intensity analysis of chemotherapy regimens in ovarian carcinoma. J Clin oncol Off J Amer Soc Clin Oncol 1987; 5(5):756–767.
6. Goldie JH, Coldman AJ. Quantitative model for multiple levels of drug resistance in clinical tumors. Cancer Treatment Rep 1983; 67(10):923–931.
7. Goldie JH, Coldman AJ. A mathematic model for relating the drug sensitivity of tumors to their spontaneous mutation rate. Cancer Treatment Rep 1979; 63(11–12):1727–1733.
8. Schrecker AW, Mead JA, Greenberg NH, Goldin A. Dihydrofolate reductase activity of leukemia L1210 during development of methotrexate resistance. Biochem Pharmacol 1971; 20(3):716–718.
9. Steuart CD, Burke PJ. Cytidine deaminase and the development of resistance to arabinosyl cytosine. Nat New Biol 1971; 233(38):109–110.

10. Puchalski RB, Fahl WE. Cancer Research, U.O. Expression of recombinant glutathione s-transferase pi, Ya, or Yb1 confers resistance to alkylating agents. Proc Natl Acad Sci USA 1990; 87(7):2443–2447.
11. Hsiang YH, Hertzberg R, Hecht S, Liu LF. Camptothecin induces protein-linked DNA breaks via mammalian DNA topoisomerase I. J Biol Chem 1985; 260(27): 14873–14878.
12. Benedetti P, Fiorani P, Capuani L, Wang JC. Camptothecin resistance from a single mutation changing glycine 363 of human DNA topoisomerase I to cysteine. Cancer Res 1993; 53(18):4343–4348.
13. Knab AM, Fertala J, Bjornsti MA. Mechanisms of camptothecin resistance in yeast DNA topo isomerase I mutants. J Biol Chem 1993; 268(30): 22322–22330.
14. Gros P, Fallows DA, Croop JM, Housman DE. Chromosome-mediated gene transfer of multidrug resistance. Mol Cell Biol 1986; 6(11):3785–3790.
15. Weide R, Dowding C, Paulsen W, Goldman J. The role of the MDR-1/P-170 mechanism in the development of multidrug resistance in chronic myeloid leukemia. Leukemia 1990; 4(10):695–699.
16. Strasser A, Huang DC, Vaux DL. The role of the bcl-2/ced-9 gene family in cancer and general implications of defects in cell death control for tumourigenesis and resistance to chemotherapy. Biochimica et biophysica acta 1997; 1333(2):F151–F178.
17. Sandoval C, Pui CH, Bowman LC, Heaton D, Hurwitz CA, Raimondi SC, Behm FG, Head DR. Secondary acute myeloid leukemia in children previously treated with alkylating agents, intercalating topoisomerase II inhibitors, and irradiation. J Clin Oncol Off J Amer Soc Clin Oncol 1993; 11(6):1039–1045.
18. Lind MJ, Thatcher N. Alkylating agents. Curr Opinion Oncol 1989; 1:192–197.
19. Meyn RE, Murray D. Cell cycle effects of alkylating agents. Pharmacol Therapeutics 1984; 24:147–163.
20. Chabner BA, Myers CE, Coleman CN, Johns DG. The clinical pharmacology of antineoplastic agents (first of two parts). New England J Med 1975; 292: 1107–1113.
21. Myers CE. The pharmacology of the fluoropyrimidines. Pharmacol Rev 1981; 33:1–15.
22. Stentoft J. The toxicity of cytarabine. Drug Safett 1990; 5:7–27.
23. Hamada A, Kawaguchi T, Nakano M. Clinical pharmacokinetics of cytarabine formulations. Clin Pharmacokinetics 2002; 41:705–718.
24. Hui YF, Reitz J. Gemcitabine: a cytidine analogue active against solid tumors. Amer J Health Syst Pharmacy 1997; 54:162–170; quiz 197–168.
25. Danesi R, Fogli S, Gennari A, Conte P, Del Tacca M. Pharmacokinetic-pharmacodynamic relationships of the anthracycline anticancer drugs. Clin Pharmacokinetics 2002; 41:431–444.
26. Hortobagyi GN. Anthracyclines in the treatment of cancer. An overview. Drugs 1997; 54(suppl 4):1–7.
27. Gray R, Slevin ML. The clinical pharmacology of etoposide. BMJ 1991; 302:1100–1101.
28. Carney DN. The pharmacology of intravenous and oral etoposide. Cancer 1991; 67:299–302.
29. Mathijssen RH, Sparreboom, A, Verweij J, Karlsson MO. Pharmacology of topoisomerase I inhibitors irintoecan (CPT-11) amd topotecan. J Clin Oncol 2002; 20:3293–3301.
30. Verweij J, Loos WJ, de Bruijn P, Nooter K, Sparreboom A, Abang AM. The clinical pharmacology of topoisomerase I inhibitors. Br J Cancer 2002; 87:144–150.
31. Budman DR. New vinca alkaloids and related compounds. Seminars Oncol 1992; 19:639–645.
32. Rahmani R, Zhou XJ. Pharmacokinetics and metabolism of vinca alkaloids. Cancer Surveys 1993; 17: 269–281.
33. Crown J. The taxanes: an update [comment]. Lancet 2000;355:1176–1178.
34. Rowinsky EK, Donehower RC. Paclitaxel (taxol) [erratum appears in N Eng J Med 1995 Jul 6; 333(1)75]. New England J Med 1995; 332:1004–1014.
35. Sekine I, Fukuda H, Kunitoh H, Saijo N. Cancer chemotherapy in the elderly. Jap J Clin Oncol 1998; 28:463–473.
36. Bradner WT, Mitomycin C. A clinical update. Cancer Treatment Rev 2001; 27:35–50.
37. Sugai M, Komatsuzawa H, Hong YM, Suginaka H, Tomasz A, Verweij J, Mitomycin C. Mechanism of action, usefulness and limitations. Proc Natl Acad Sci USA 1995; 92:285–289.
38. Johnson RK, Mattern MR, Wang X, Hecht SM, Beck HT, Ortiz A, Kingston DG. Bleomycin: new perspectives on the mechanism of action. J Nat Products 2000; 63:217–221.
39. Dorr RT. Bleomycin pharmacology: mechanism of action and resistance, and clinical pharmacokinetics. Seminars Oncol 1992; 19:3–8.

5

Endocrine Evaluation and Management of the Perioperative Cancer Patient

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I. INTRODUCTION

There are a variety of endocrine and metabolic disorders that impact the management of the perioperative or critically ill patient in the cancer environment. Most are similar to clinical disorders seen in the general population; a subset is unique to patients with cancer and may be caused by the malignancy or by its treatment. This chapter will describe succinctly the major endocrine disorders in patients with cancer and focus on those areas of endocrinology and metabolism most likely to impact upon the perioperative patient.

A. Preoperative Evaluation

Several endocrine system disorders can have a major impact on perioperative morbidity and mortality. These include diabetes mellitus, diabetes insipidus (DI), hypopituitarism, thyroid disorders, abnormalities of adrenal medullary and cortical function, and calcium and electrolyte disorders. Failure to identify these disorders in the preoperative period can lead to acute medical problems in the intra- or postoperative periods. Most of these disorders can be easily identified and treated if recognized in advance. Initial evaluation should include simple questions focused on personal or family history for these disorders (Table 1).

II. MANAGEMENT OF THE CANCER PATIENT WITH DIABETES MELLITUS

With over 151 million patients diagnosed worldwide, diabetes mellitus has become a leading cause of morbidity and mortality (1). Not surprisingly, it coexists frequently with another highly prevalent disorder, i.e. cancer.

A. Glucose Metabolism During Acute Illness

Acute illness, as well as surgical procedures, in healthy persons causes several physiological alterations that may lead to hyperglycemia and its complications. Stress responses associated with illness or surgery result in elevations of hormones such as glucagon, epinephrine, cortisol, and growth hormone (GH) that

Table 1 Preoperative Evaluation for Endocrine and Metabolic Disorders

History
Personal or family history of:
Diabetes mellitus or hypoglycemia, polyuria or polydipsia
Hyper- or hypothyroidism or thyroid hormone replacement
Hypertension or hypotension, tachycardia, adrenergic symptoms
Adrenal cortical surgery, excessive cortisol production
Pituitary surgery or symptoms of hypopituitarism, polyuria, DI
Kidney stones, tetany, hypercalcemia, or other symptoms of hyper- or hypocalcemia
Physical examination
Physical findings suggestive of endocrine disorders
Hypertension or hypotension may indicate pituitary or adrenal disorder; bradycardia or tachycardia may indicate thyroid or adrenal disorder
Skin—examination for scars of prior pituitary, thyroid, or adrenal surgery; signs of corticoid excess (bruising, centripetal obesity, loss of muscle mass, rounded facies) or deficiency (increased pigmentation in Addison disease or pallor in hypopituitarism)
Eyes—visual field abnormalities
Thyroid—enlargement or nodularity
Cardiovascular system—bradycardia or tachycardia may indicate thyroid disorder
Genitalia—small testicular size may indicate pituitary insufficiency
Laboratory
Routine—glucose, electrolytes, blood urea nitrogen, creatinine
Tests suggested by historical or physical findings—free thyroxine, TSH, gonadotropins, prolactin, GH, insulin-like growth factor I, serum testosterone, 8 AM serum cortisol, plasma catecholamines and metanephrines

counter the effects of insulin. Increased circulating levels of these hormones result in a hypercatabolic state, with lipolysis, ketogenesis, glycogenolysis, and gluconeogenesis, resulting in increased circulating levels of free fatty acids, glucose, and ketone bodies. Medications used to treat acute illnesses may alter glucose metabolism by decreasing insulin secretion, increasing insulin resistance, or increasing the clearance of antidiabetic medications (Table 2) (2). The end result is hyperglycemia.

Hyperglycemia inhibits host defenses against infections by diminishing chemotaxis, phagocytosis, granulocyte adhesion, and bactericidal function (3,4). It also leads to osmotic diuresis, leading to whole body and cellular dehydration, which is associated with increased morbidity and mortality. Hyperglycemia can also cause endothelial dysfunction, which may contribute to adverse cardiovascular outcomes (5). Thus, in a hospitalized patient who already has a variably compromised immune system or cardiovascular status, hyperglycemia and insulin resistance increase the risks for infection and vascular disease.

At the other end of the glycemic spectrum, hospitalized patients face many situations that may increase their propensity to develop hypoglycemia . The patient may be kept fasting for prolonged periods in preparation for surgical or diagnostic procedures, or the disease itself or its treatment may cause anorexia, nausea, and/or vomiting, limiting caloric intake. If renal insufficiency, liver failure, or sepsis develops, the capacity for glycogenolytic or gluconeogenic responses to hypoglycemia is impaired and the plasma clearance of hypoglycemic medications, including insulin, may be prolonged. The patient then becomes very prone to developing hypoglycemia. Several medications commonly administered to hospitalized patients may also cause hypoglycemia by increasing the circulating levels of insulin, transiently improving insulin sensitivity, depleting glycogen stores, or impeding gluconeogenesis (Table 2) (2).

1. *Special Considerations in the Patient with Cancer*

Many neoplastic disorders are associated with changes in carbohydrate metabolism. Impaired glucose tolerance has been described as an early and prominent metabolic complication of cancer (6). The plasma levels of GH, a counter regulatory hormone, may be elevated, aggravating whole body insulin resistance (7). Glucocorticoids are frequently used to treat cancer patients, and these agents can cause significant hyperglycemia in a diabetic or glucose intolerant patient (7). Cancer patients are frequently immunosuppressed, making them susceptible to infections. Infections can aggravate hyperglycemia, which in turn complicates effective treatment of the infections. Hospitalized cancer patients are also prone to developing hypoglycemia, especially if they have pre-existing diabetes and are taking oral antidiabetic agents or insulin. Such

Table 2 Medications That Alter Glucose Metabolism

Hyperglycemia	Hypoglycemia
α-Interferon	α-Agonists
β-Adrenergic agonists	β-Blockers
β-Blockers	ACE inhibitors
Alcohol and illicit drugs	Acetaminophen
Amiodarone	Aluminum hydroxide
Amoxapine	Anabolic steroids
Atypical antipsychotic agents	Diphenhydramine
Aripiprazole	Disopyramide
Clozapine	Doxepin
Olanzapine	Encainide
Quetiapine	Ethanol
Risperidone	Fibric acid derivatives
Ziprasidone	Fluoxetine
Calcium channel blockers	Ganciclovir
Central α-blockers	Haloperidol
Cyclosporine	Indomethacin
Dilantin	Isoproterenol
Dopamine	Lidocaine
Droperidol	Lithium
Ephedrine	Monoamine oxidase inhibitors
Epinephrine	Octreotide
Glucocorticoids	Orphenadrine
Growth hormone	Ouabain
L-Dopa	Para-aminosalicylic acid
Lithium	Pentamidine
Loop diuretics	Quinidine
Morphine	Quinolones
Nucleoside reverse transcriptase inhibitors	Salicylates
Octreotide	Tricyclic antidepressants
Oral contraceptives	Trimethoprim-sulphamethoxazole
Phenothiazines	Warfarin
Protease inhibitors	
Quinolones	
Thiazides	
Thyroid hormone	

common complications of cancer or its treatment as anorexia, nausea, vomiting, and ileus can result in decreased caloric intake and nutrient absorption, setting the stage for hypoglycemia (7).

2. Goals of Glycemic Control

A growing body of data from carefully conducted clinical trials suggests that the attainment and maintenance of normoglycemia or near-normoglycemia is associated with significantly improved outcomes when compared with a more relaxed approach (8–11). It is reasonable to extrapolate from these data that normalizing plasma glucose levels should also be the goal in a hospitalized patient with complications associated with cancer. Some experts advocate a less aggressive glycemic target of 140–200 mg/dL (12) or 150–250 mg/dL (7). However, there are no well-controlled studies on optimal levels of glycemic control in hospitalized cancer patients, although there are excellent outcome studies that support the use of tight glycemic control in hospitalized patient with other illnesses (8–11). Hence, we advocate a glycemic target of 100–140 mg/dL, with due care to avoid hypoglycemia. This can be achieved effectively and safely by careful bedside glucose monitoring coupled with rational insulin therapy.

3. Terminally Ill Patients

In these patients, intensive glucose control may not be warranted due to the increased discomforts of multiple insulin injections and the risk of hypoglycemia. On the other hand, uncontrolled hyperglycemia may result in unnecessary and preventable complications such as ketoacidosis or hyperosmolality. A reasonable approach therefore would be to maintain blood glucose in a range of 140–200 mg/dL.

B. Preoperative Assessment of the Cancer Patient for Diabetes Mellitus

The preoperative assessment of the patient with diabetes must take several important issues into account as listed below.

1. Type of Diabetes

a. Type 1 Diabetes Mellitus

It should go without saying that a patient known to have type 1 diabetes has no endogenous insulin production and therefore needs continuous insulin replacement. A cardinal principle is that such a patient needs insulin even in the fasted state in order to prevent severe hyperglycemia and ketoacidosis. Hence, meal-based "sliding scale" regimens of short-acting insulins without a constant supply of basal insulin are completely inadequate. Table 3 provides some recommendations for specific circumstances in hospitalized patients with type 1 diabetes.

b. Type 2 Diabetes Mellitus

These patients may still have endogenous insulin production, so they may not require exogenous insulin. Still, it is important to monitor the blood glucose levels during the hospitalization, as they may develop significant hyperglycemia. Many apparently "type 2" diabetic patients lose β-cell function several years after

Table 3 Recommendations for the Management of Diabetes Mellitus in Specific Circumstances

	Diabetes mellitus	
Circumstances	Type 1	Type 2
Intraoperative and prolonged procedures	Major operation or procedure: continuous IV insulin and glucose infusions	Major operation or procedure: continuous IV insulin and glucose infusions
	Minor operation or procedure: 50–75% of long acting insulin, monitor glucose levels. If glucose >140 mg/dL, consider continuous IV insulin and glucose infusions	Insulin requiring, minor operation or procedure: 1/2 to 2/3 of long acting insulin, monitor glucose levels. If glucose >140 mg/dL, consider continuous IV insulin and glucose infusions.
		Noninsulin requiring: hold oral medications, monitor glucose levels. If glucose >140 mg/dL, consider continuous IV insulin and glucose infusions
Intensive care unit	Continuous IV insulin and glucose infusions	Continuous IV insulin and glucose infusions
Parenteral nutrition and continuous tube feeding	Continuous IV insulin	Continuous IV insulin
Glucocorticoid therapy	Small dose: increase basal insulin and monitor glucose levels. If glucose >140 mg/dL, consider continuous IV insulin and glucose infusions	Small dose, insulin requiring: increase basal insulin and monitor glucose levels. If glucose >140 mg/dL, consider continuous IV insulin and glucose infusions
	Intermediate dose: increase basal and preprandial insulin and monitor glucose levels. If glucose >140 mg/dL, consider continuous IV insulin and glucose infusions	Small dose, noninsulin requiring: monitor glucose levels. If glucose >140 mg/dL, consider long acting insulin
	High dose: continuous IV insulin and glucose infusions	Intermediate dose, insulin requiring: increase basal and preprandial insulin and monitor glucose levels. If glucose >140 mg/dL, consider continuous IV insulin and glucose infusions
		Intermediate dose, noninsulin requiring: start basal insulin and monitor glucose levels. If glucose >140 mg/dL, consider continuous IV insulin and glucose infusions
		High dose insulin and noninsulin requiring: continuous IV insulin and glucose infusions

diagnosis, and these patients will require continuous exogenous insulin. If the patient is not insulin-dependent, and no significant change in the diet is anticipated, oral antidiabetic medications should be continued. If the patient is to be kept fasting for any reason, the oral agents should be withheld. The patient on metformin therapy is at high risk of developing lactic acidosis, so this medication should be withheld if the patient has or is expected to experience any situation that might lead to a lowering of the glomerular filtration rate (e.g., renal insufficiency, cardiac or hepatic failure, volume depletion, hemorrhage). Sulfonylureas also should be withheld if the patient has renal insufficiency or liver failure. Thiazolindinedione drugs should be withheld if the patient has cardiac failure or hepatitis. The alpha-glucosidase inhibitors should be withheld if the patient has diarrhea. Table 3 provides recommendations for some specific conditions.

2. *Management of Exogenous Insulin*

a. *Insulin Administration in a Stable Patient*

In a patient who is already taking insulin, the same dosage and frequency of insulin injections should be maintained as long as there are no major changes in daily caloric intake. If the patient is to be kept fasting for any length of time beyond the usual sleeping hours, or if caloric intake is expected to decrease significantly, short-acting insulin should be withheld, but subcutaneously administered long-acting or "basal" insulin should be continued or initiated at 50–60% of the total usual daily dose of insulin. This dose should be "titrated" appropriately on the basis of close monitoring of blood glucose at the bedside. A continuous source of calories is essential to prevent hypoglycemia, if the patient is to be treated with daily intermediate- or long-acting insulin preparations.

b. *Continuous Insulin Infusions*

Many patients who require intensive care, or who are undergoing surgery or a prolonged procedure, are better managed with a continuous, intravenous infusion of insulin together with potassium and glucose. There is considerable experience with the use of this combination infusion, which permits flexibility of treatment with ease of attaining normoglycemia. Table 4 displays a typical algorithm we use to guide the adjustments needed to achieve and maintain normoglycemia.

C. Perioperative Management of Diabetes Mellitus

The length and type of diabetes should guide perioperative management. Table 3 summarizes different approaches for specific circumstances.

Patients with type 1 diabetes require a continuous supply of exogenous insulin to preserve life. For minor procedures, short acting insulin should be withheld and 50–75% of the basal insulin requirement should be administered in the form of NPH or Lente insulin, with frequent monitoring of blood glucose during the procedure. Continuous insulin and glucose infusions should be considered, if the blood glucose levels remain >140 mg/dL. For longer procedures, infusions of insulin and glucose are ideal. Type 2 diabetic patients who are completely insulin dependent should be managed as if they have type 1 diabetes. For the noninsulin requiring type 2 diabetic patient undergoing a minor procedure, oral hypoglycemic medications should be

Table 4 Intravenous Insulin and Glucose Infusion Rates in the ICU

Capillary blood glucose (mg/dL)	Insulin infusion[a] rate (U/hr)	Glucose infusion[b] rate (cc/hr)	Additional glucose (IV push)/action
< 80	0	50	25 cc of 50% dextrose
80–100	1.0	40	–
101–140	2.0	30	–
141–200	3.0	20	–
201–250	6.0	10	–
251–300	8.0	5	–
301–350	10.0	2.5	Call physician
351–400	13.0	2.5	Call physician
401–450	15.0	2.5	Call physician
> 450	18.0	2.5	Call physician

[a] In 100 cc of normal saline, add 100 U of regular insulin and 60 mEq of KCl.
[b] 10% Dextrose.

Table 5 Scale for Premeal Insulin, Lispro or Aspart

Capillary blood glucose (mg/dL)	Insulin dose (U)	Addition glucose or action	Size of meal (calories)	Additional insulin dose (U)
<60	0	25 cc of 50% dextrose (intravenous push) page physician		
60–80	0	30 cc of orange juice	<300	–2
81–100	2	–	300–500	0
101–140	3	–	501–700	+1
141–200	4	–	701–800	+2
201–250	5	–	801–1000	+3
251–300	6	–		
>300	7	Call physician		

held, with frequent glucose monitoring; if blood glucose levels remain consistently >140 mg/dL, continuous insulin and glucose infusions should be considered. For longer procedures, the noninsulin requiring type 2 diabetic patient is also better managed with the continuous insulin and glucose infusions.

D. Postoperative Management

1. *Bedside Glucose Monitoring*

Capillary blood glucose testing at the bedside is essential in the management of any hospitalized patient with diabetes. The frequency of bedside glucose testing with a glucometer should be determined by the patient's condition and specific clinical situation. At a minimum, in a nonintensive-care setting such as for a stable patient admitted for elective surgery or an uncomplicated illness, bedside glucose testing should be performed before each meal and at bedtime. Tables 5 and 6 present specific recommendations for the use of short acting pre-meal insulin and adjustment of night-time insulin doses based on blood glucose values. For patients who are not likely to be consuming regular meals or who are receiving continuous intravenous insulin, monitoring should be more frequent.

Table 6 Sliding Scale for the Adjustment of the Bedtime Insulin Dose

Prebreakfast capillary blood glucose (mg/dL)	Change in insulin dose (U)
<60	−3
60–80	−2
81–100	−1
101–140	0
141–200	+1
201–250	+2
251–300	+3
301–350	+4
351–400	+5
>400	+6

2. *Special Considerations in Patients Receiving Glucocorticoids*

Patients with various malignancies are frequently treated with high doses of glucocorticoids, which can lead to severe hyperglycemia and ketoacidosis. It is of paramount importance to anticipate this effect, intensify blood glucose monitoring, and prepare to increase insulin doses when therapy with glucocorticoids is planned. It is usually necessary to increase the dosage of twice-daily NPH insulin rapidly to keep up with increasing hyperglycemia during the active treatment phase. For nondiabetic patients, the risk for developing diabetes should be assessed before initiating glucocorticoid therapy (Table 3).

III. MANAGEMENT OF THE CANCER PATIENT WITH THYROID DISEASE

The production and secretion of thyroid hormones are regulated by the hypothalamus, pituitary, and the thyroid gland. The hypothalamus secretes thyrotropin-releasing hormone (TRH), which stimulates the thyrotroph cells in the anterior pituitary to secrete thyroid-stimulating hormone (TSH). Thyroid-stimulating hormone, in the presence of an optimal supply of dietary iodine, stimulates the synthesis and release of thyroxine (T4) and triiodothyronine (T3) from the thyroid. T3, the active hormone, is also generated at the target organs by selective 5′-deiodination of T4. T3 feeds back on the hypothalamus and anterior pituitary to downregulate TRH and TSH secretion. This exquisitely regulated system maintains circulating T4 and T3 levels within narrow physiologic limits. The plasma concentrations of T4 and T3 (and of their "free" or unbound

components) are also affected by binding proteins, predominantly thyroxine binding globulin produced by the liver.

Maintenance of a normal "euthyroid" state depends on the proper functioning of all of these regulatory steps. Therefore, pathologic conditions that specifically disrupt each of these steps can result in hyper- or hypothyroidism. Unfortunately, the TRH–TSH–T4–T3 axis can also be affected by a variety of drugs, as well as by both acute and chronic stress or illness, resulting in the so-called "euthyroid sick" state. It is important to differentiate "true" disorders of thyroid function from those in which thyroid function test values are altered due to nonthyroidal illness.

Severe thyrotoxicosis can lead to a life-threatening condition associated with high mortality sometimes termed "thyroid storm", whereas severe hypothyroidism can evolve into the serious condition of myxedema coma. However, it is important to recognize that milder degrees of thyroid dysfunction can also complicate the clinical course of patients undergoing surgical operations.

Mild hyperthyroidism and hypothyroidism are extremely common, affecting 6% and 12% of the elderly, respectively. They often go undiagnosed before the patient presents for surgery. The symptoms of hyperthyroidism may be muted, especially in the elderly or chronically ill. Even "subclinical" hyperthyroidism is associated with a doubling of the risk of cardiac arrhythmias in the elderly and a small increase in the risk of systemic embolism. Furthermore, acute illness, surgical procedures, administration of iodine in radiocontrast materials, and induction of anesthesia can precipitate severe, life-threatening thyrotoxicosis in a patient with subclinical hyperthyroidism. Therefore, it is important to detect and diagnose hyperthyroidism and hypothyroidism, be alert to situations in the intra- and perioperative periods that might precipitate a thyrotoxic or myxedematous crisis, and treat these conditions promptly and appropriately.

A. Preoperative Assessment for Thyroid Disease

1. Patients with known hyperthyroidism should be rendered euthyroid before elective surgery, to avoid precipitating thyroid storm. Standard measures to control hyperthyroidism include the use of thionamides such as propylthiouracil (PTU) or methimazole and beta-blockers, or, if time permits, they include ablation of the gland with radioactive iodine. This management is best undertaken by an experienced endocrinologist with the knowledge that it may take as long as 6–8 weeks to achieve euthyroidism. In the more acute setting of an urgently required surgical procedure, high doses of PTU or methimazone and beta-blockers should be administered, with additional measures to block the release of preformed thyroid hormones from the gland and/or the peripheral conversion of T4 to T3, such as administration of iodine in the form of saturated solution of potassium iodide (SSKI), sodium ipodate or Lugol's iodine, glucocorticoids, and in rare circumstances, lithium. Treatment becomes more complicated in the patient with a dysfunctional bowel or severe upper small intestinal obstruction, since the first-line antithyroid drugs, PTU and methimazole, are not available in parenteral form. However, both the antithyroid agents and sodium iodide are very well absorbed via the rectal route, even in patients with severely compromised small intestinal function. These measures are effective and may achieve sufficient control to permit emergent surgery without serious metabolic decompensation. In rare situations, where it is necessary to proceed with a particular oncologic treatment on an emergent basis that cannot be safely performed in the presence of hyperthyroidism, an emergent thyroidectomy may be appropriate following extensive beta-adrenergic blockade.
2. Hypothyroidism is extremely common (13,14) and causes widespread dysfunction of physiologic functions and metabolism. It is associated with impaired myocardial contractility, diminished cardiac output, depressed baroreceptor function, decreased oxygen consumption, increased peripheral vascular resistance (15), hypoglycemia, hyperlipidemia (16), and hyponatremia. Patients with untreated hypothyroidism also have expanded plasma volumes and reduced GFR (17), with distinctly abnormal rates of hepatic drug metabolism (18,19). Hypothyroidism also induces a hypercoagulable state (20). Importantly, many of these metabolic and physiologic disturbances—e.g., the impaired ventilatory responses (21)—can be reversed by thyroid hormone replacement therapy for as short a period as 1 week.
3. Hypothyroid patients should be treated to achieve euthyroidism before planning elective surgery. The treatment options include levothyroxine (LT4, half-life 7 days) and LT4 plus liothyronine (T3, half-life 36 hr) (Goodman). Levothyroxine is the preferred treatment in stable patients not requiring urgent surgery

and, at the proper dose, will render a patient euthyroid in several weeks. In an emergent situation, such as in the patient with myxedema coma, it may be necessary to use a combination of LT4 and T3 to reverse organ dysfunction more rapidly. However, caution must be exercised in administering these hormones, especially in combination, in very ill patients. Treatment in such circumstances requires the experience of an endocrinologist to avoid potentially severe adverse cardiac effects such as myocardial ischemia or infarction (22). Varying doses and routes of administration of thyroid hormones have been used to treat myxedema coma. Arlot et al. (23) compared the oral and parenteral routes of thyroxine administration and found that although absorption is variable with oral T4 administration, clinical response occurs quickly even in patients with ileus; the intravenous route involves high peaks of plasma T4 and T3 with the peripheral conversion of T4 to T3 allowing gradual T3 delivery to organ systems, and the levels diminished slowly over 5–9 days.

4. Primary hypothyroidism may be associated with primary adrenal insufficiency. Hypothyroid patients also exhibit a blunted response to glucocorticoids, even to "stress doses" of steroid. Hence, it is advisable to test patients with recently diagnosed hypothyroidism for adrenal insufficiency and to consider administering glucocorticoids in addition to thyroxine replacement during the intraoperative and postoperative periods.

B. Intraoperative and Postoperative Assessment

1. Hyperthyroidism

a. Patients with known hyperthyroidism, who have achieved a biochemically euthyroid status as a result of appropriate management, are not at increased risk for anesthetic complications. Patients with undetected or untreated thyrotoxicosis are at risk for severe complications including the precipitation of thyroid storm (15,24–30). Other thyroid-related complications of specific concern to the anesthesiologist include difficulties in endotracheal intubation and maintaining a patent airway in patients with large goiters and retrosternal extensions of the thyroid, cardiac dysfunction including tachyarrhythmias, ventilatory and respiratory compromise. Further, liver dysfunction, hypermetabolism, altered protein binding, and other effects of uncontrolled hyperthyroidism may interfere with the clearance of anesthetic drugs and must be monitored carefully with appropriate changes in dosing. Conventional doses of propofol may achieve only subtherapeutic serum levels of the drug in hyperthyroid patients due to increased volumes of distribution and clearance, and the effects of propofol may be attenuated by the use of beta-blockers. Hence, increased dosing of propofol may be required during surgery in such patients (31–33)

b. Thyroid storm is easily precipitated in the suboptimally treated or undiagnosed hyperthyroid patient due to the stress of surgery or infection (25,26,32a,34,35–37). Burch and Wartofsky have proposed a clinical score to help diagnose thyroid storm, but there is really no definitive set of signs or laboratory tests to define the condition. Thyroid storm should be suspected whenever a patient has signs, symptoms, and thyroid function test results consistent with thyrotoxicosis, together with any marked decompensation of an organ system—e.g., severe heart failure, intractable tachyarrhythmia, extreme volume loss, marked hepatic dysfunction, or acute, global central nervous system dysfunction. It has been noted to occur upon induction of anesthesia and in association with malignant hyperthermia in a patient with well-controlled Grave's disease undergoing subtotal thyroidectomy. These patients responded well to a high dose of dantrolene during the perioperative period (26,36). In another instance, thyroid storm presented as unconsciousness in a patient after emergent Caesarian section (25). Hyperthyroidism and possible thyroid storm should be suspected in any patient developing unexplained tachycardia during surgery. The principles of managing thyroid storm are as described earlier for hyperthyroidism in the setting of urgent surgery; however, the chronology of treatment is very important. When there is a reasonable possibility of thyroid storm, the first step is to administer a large dose of PTU (1–2 g) or methimazone (60–80 mg) by any enteral route, in order to inhibit thyroid hormone synthesis. After ~1 hr, this should be followed by administration of a large enteral dose of iodine, such as SSKI (3–4 drops), Lugol's iodide (8–12 drops), or sodium ipodate (1–3 g), to block the release of preformed thyroid hormone. An intravenous bolus of radiocontrast dye is also an effective way to supply

a large dose of iodine. Administering iodine before the initial dose of the antithyroid drug may actually exacerbate thyrotoxicosis, and hence the order of treatment is crucial. Both the antithyroid drug and the iodine preparation should be continued at the same or slightly lower doses for every 6–8 hr, until the patient has stabilized. Additional measures include intravenously administered beta-blocker (esmolol) for tachyarrhythmia or acute heart failure, cooling blankets for hyperthermia, normal saline to maintain blood volume, stress-dose glucocorticoids, and, in general, close monitoring and intensive support.

c. The risks, complications, and management of hyperthyroid patients undergoing nonthyroidal surgery have already been considered. Surgical removal of all or part of the thyroid gland itself, for treatment of hyperthyroidism, requires special consideration. Although in the U.S.A. surgical treatment for Graves' disease, the most common cause of hyperthyroidism, has been largely replaced by radioiodine ablation, surgery is still offered to patients unable or unwilling to undergo medical therapy. The surgical approaches to treat hyperthyroidism include subtotal thyroidectomy and total thyroidectomy. In either case, it is imperative that the patient be rendered euthyroid prior to surgery, using the methods described earlier, in order to avoid the risk of precipitating thyroid storm. With these precautions, hyperthyroidism due to Graves' disease and toxic nodular goiter may be treated successfully by surgical thyroidectomy. Amiodarone-induced thyrotoxicosis has also been treated surgically using local anesthesia because of the higher risk of complications associated with general anesthesia. A meta-analysis by Palit et al. (38). found an appreciable rate of persistent hypothyroidism among patients undergoing total thyroidectomy and a 7.9% failure rate in patients undergoing subtotal thyroidectomy. The surgical complications included permanent paralysis of the recurrent laryngeal nerve (in 0.9%) and permanent hypoparathyroidism in up to 1.6% of patients.

2. Hypothyroidism

a. Hypothyroidism has generally been considered a contraindication to surgery, but the anesthetic and surgical risks for a mildly hypothyroid patient are probably less than for a patient with hyperthyroidism. An early study by Ladenson et al. (39) examined perioperative complications in hypothyroid patients and found that intraoperative hypotension occurred frequently during noncardiac surgery, and that cardiac surgery was complicated by heart failure more often than in euthyroid patients. Postoperative complications were also found to be higher in hypothyroid patients and included gastrointestinal and neuropsychiatric complications, difficulty in weaning from ventilatory support, and hyponatremia. However, other studies have found that patients with mild hypothyroidism undergoing surgery do not appear to be at increased risk for perioperative complications (40). More recent retrospective studies on the risks of percutaneous transluminal coronary angioplasty also did not detect increased morbidity or mortality in patients with either overt or subclinical hypothyroidism who underwent this procedure (41,42). However, patients with more severe hypothyroidism (defined by TSH >90 mU/L) may have an increased risk of ventilatory complications that appear to reverse with replacement therapy (21).

b. In conclusion, patients undergoing surgery must be carefully screened and evaluated for thyroid disease. The presence of hyperthyroidism is associated with increased risk in the peri- and postoperative period and must be fully treated before proceeding with surgery. Mild hypothyroidism is not a contraindication to surgery; however, severe hypothyroidism (TSH >90 mU/L) must be treated before surgery.

IV. DISORDERS OF THE ADRENAL GLAND

A. Adrenal Insufficiency

1. Clinical Features

Overt features of adrenal cortical insufficiency include nausea and vomiting, hypotension, electrolyte abnormalities (hyponatremia, hyperkalemia, metabolic acidosis), dehydration (elevated blood urea nitrogen and creatinine), hypoglycemia, and hyperpigmentation; the latter is caused by chronic elevation of adrenocorticotrophic hormone (ACTH)-related peptides with melanocyte stimulating activity. Unfortunately, the only features that are strongly suggestive of adrenal

insufficiency are the combination of hyponatremia, hyperkaemia, and metabolic acidosis in a hypotensive patient. More commonly, in the cancer patient, there are few overt features of adrenal insufficiency and the clinician must infer the possibility of corticosteroid deficiency from certain historical and clinical features. The diagnosis should be considered in patients who have been treated with suppressive doses of corticosteroids (>7.5 mg prednisone equivalents/day or recurrent depot injections of potent corticosteroids) for a month or lower doses for a longer period of time. Metastasis of cancer to the adrenal gland is common in certain malignancies (renal cell, lung, breast, and melanoma, among others). In addition, the diagnosis should be considered in those with systemic fungal infections or tuberculosis, anticoagulated patients, and patients with hypothalamic or pituitary metastasis.

2. Diagnosis

a. Primary Adrenal Insufficiency

A high-dose cosyntropin test should be performed, as outlined in Table 7. A serum cortisol of >18 μg/dL basally or after synthetic ACTH indicates a normal response. In the context of a preoperative assessment, a lesser response should prompt intraoperative and postoperative corticosteroid replacement. Although not all patients with a lesser response will have adrenal insufficiency, a more detailed assessment may not be possible in the compressed context of a preoperative

Table 7 Testing for Adrenal Insufficiency and Stress Dose Steroids

Tests for adrenal insufficiency
If there is no time to perform diagnostic testing and the patient is critically ill, draw a baseline cortisol and ACTH before giving steroids; alternatively, give 4 mg of dexamethasone IV and perform testing within a few hours
Primary adrenal insufficiency
High-dose cosyntropin (Cortrosyn®) stimulation test
Measure a baseline serum cortisol (± ACTH), inject 250 μg of cosyntropin IV/IM, and measure serum cortisol 30 and 60 min later
Normal response is cortisol >18–20 μg/dL (500–550 nmol/L)
Central adrenal insufficiency
Low-dose cosyntropin (Cortrosyn®) stimulation test
Measure a baseline serum cortisol (± ACTH), inject 1.0 μg of cosyntropin IV, and measure serum cortisol 20 and 30 min later
Normal response is cortisol >18–20 μg/dL (500–550 nmol/L)
Overnight metyrapone (Metopirone®) test
Give metyrapone 3000 mg with food at 11–12 PM; at 8 AM the next morning, draw a serum cortisol (± ACTH) and 11-desoxycortisol (compound S)
Normal response is cortisol <5 μg/dL and 11-desoxycortisol >7 μg/dL
Insulin tolerance test
Obtain baseline cortisol (± ACTH); give 0.05–0.1 U/ kg of regular insulin IV; draw serum cortisol levels every 15 min for 1 hr; sugar should be <40 mg/dL to provide an adequate stimulus
Normal response is cortisol >18–20 μg/dL (500–550 nmol/L)
Stress steroid dosing (*should be individualized on the basis of patient's clinical history and current status*)
During minor physiologic or surgical stress
Take the usual daily steroid dose (if already on steroids)
Or
Administer 25 mg of hydrocortisone IV/IM on-call to the operating room
During moderate physiologic or surgical stress
Take triple the usual steroid dose (if already on steroids at physiologic doses)
Or
Administer 50 mg of hydrocortisone IV/IM on-call to the operating room and
Administer 25–50 mg of hydrocortisone IV q8 hr (or as continuous drip)
During major physiologic or surgical stress
Administer 50–100 mg of hydrocortisone IV/IM on-call to the operating room and
Administer 50–100 mg of hydrocortisone IV q8 hr (or as continuous drip)

evaluation. If the diagnosis of adrenal insufficiency is considered during a surgical procedure, obtaining a serum cortisol prior to the administration of corticosteroids will allow the clinician to separate adrenal insufficiency from other causes of hypotension during the postoperative period.

b. Secondary or Central Adrenal Insufficiency

Table 7 provides several testing procedures for assessing the intactness of the hypothalamic–pituitary–adrenal (HPA) axis. It will be discussed in greater detail in the following section that addresses hypopituitarism.

3. Management

a. Primary adrenal insufficiency should be managed with a combination of corticosteroid and mineralocorticoid. Hydrocortisone or cortisone acetate in doses of 20–25 mg in the morning and 10–15 mg in the evening will provide satisfactory long-term corticosteroid replacement. These steroids are generally considered more physiologic than corticosteroids with a longer half-life (prednisone 5 mg in the morning and 2.5 mg in the evening, or dexamethasone) that have been used extensively in the past. Aldosterone is replaced with fludrocortisone (Florinef™) 0.05–0.1 mg/day.
b. Corticosteroid coverage is addressed in Table 7. The duration of corticosteroid coverage should be based on the extent and length of the surgical procedure. For example, a patient with a minor surgical procedure may require supplemental corticosteroid coverage only for the procedure, returning to baseline corticosteroid coverage the following day. More complicated surgical procedures (neurosurgical, thoracic, or abdominal procedures) may require stress doses of corticosteroids for several days or longer. Stress doses of corticosteroids should be used in critically ill or infected patients until their physiologic status has returned to normal; corticosteroids should be tapered, once the patient appears to be stable, by halving the doses of corticosteroids each day until baseline replacement doses have been achieved.
c. Management of the patient with suspected adrenal insufficiency. Adrenal insufficiency may be suspected in patients with unexplained hypotension during the intraoperative or postoperative period, particularly when there is an inadequate response to pressors. It is appropriate to treat such patients with stress doses of corticosteroids (mentioned earlier); obtaining a serum cortisol immediately prior to infusion of corticosteroid is useful for determining post hoc whether a state of adrenal insufficiency existed.
d. Management of the patient who has received chronic corticosteroid therapy: There is a spectrum of risk for adrenal insufficiency associated with the usage of chronic corticosteroid. A spectrum of recommendations for adequate replacement is shown in Table 8. In general, if there is uncertainty about the dosage or duration of corticosteroid treatment (for

Table 8 Assessing the Risk of Adrenal Insufficiency in Patients on Chronic Steroids

Risk for adrenal insufficiency	Patient characteristics	Recommended action
Low	Any dose of GC for <3 weeks Daily doses of <20 mg/day of hydrocortisone or its equivalent[a] Alternate-day dosing	Continue usual steroid dose
High	Supraphysiologic dosing for >3 weeks Daily doses of >80 mg/day of hydrocortisone or its equivalent[a] Clinical Cushing's syndrome	Treat with perioperative stress steroid coverage until usual home dose can be resumed (see Table 7)
Undetermined	Daily doses between 20 and 80 mg/day of hydrocortisone or its equivalent[a] Patients on high daily doses of inhaled or topical steroids	Observe closely while continuing home dose, empirically cover with stress steroids, or test using a 1 μg ACTH stimulation test (see Table 7)

Note:[a] 20 mg Hydrocortisone = 5 mg prednisone = 4 mg methylprednisolone = 0.5 mg dexamethasone.
Abbreviations: AI, adrenal insufficiency; GC, glucocorticoid
Source: Adapted from Ref. 50.

patients on corticosteroid coverage at the time of preoperative evaluation), patients should be tested preoperatively to assess the adequacy of the HPA axis (Table 7) or placed on the appropriate stress doses of corticosteroids during the operative and postoperative periods (Table 7).

B. Glucocorticoid Excess: Cushing Syndrome

1. *Clinical Features and Perioperative Management*

   a. Features of Cushing syndrome that are of importance during the perioperative period include the presence of hypertension, hypokalemic metabolic alkalosis, diabetes mellitus, and propensity for infection. Several different mechanisms of glucocorticoid excess can be envisioned: ACTH dependent (pituitary Cushing disease caused by an ACTH producing pituitary tumor or ectopic ACTH by benign or malignant nonpituitary tumors) or production of cortisol by a benign or malignant adrenal cortical tumor. Optimally, patients with excessive production of cortisol should be pretreated with inhibitors of corticosteroid synthesis for a period of days to weeks to normalize the serum cortisol concentration and other metabolic abnormalities. Treatment with metyrapone, 2–4 g/day orally in divided doses, combined, if necessary, with ketoconazole 300–600 mg/day will normalize cortisol production and reverse most of the metabolic abnormalities over a period of days to a few weeks. It is important to treat the patient with 1–2 mg dexamethasone/day during therapy with corticosteroid synthesis inhibitors to prevent adrenal insufficiency. In patients on inhibitors of adrenal corticosteroid synthesis, stress doses of corticosteroids should be given during and after the operative period (see the section on Adrenal Insufficiency). In Cushingoid patients, where emergent or semiemergent surgery is necessary, hypertension, hyperglycemia, and hypokalemic metabolic alkalosis should be corrected by use of antihypertensive agents, insulin therapy, and replacement of potassium prior to the surgical procedure. Postoperative management of a patient with Cushing syndrome can be complicated by poor wound healing, muscle weakness, poor intestinal motility, difficult-to-manage diabetes mellitus, wound or other infections and fluid retention, resulting in prolongation of the postoperative recovery period.

   b. Once the patient has stabilized following the operative period, the goal should be to maintain the serum cortisol in the normal physiologic range of 10–20 μg/dL by titrating doses of metyrapone or ketoconazole.

C. Pheochromocytoma

1. *Clinical Features*

   a. Pheochromocytoma is a neoplastic process of the adrenal gland, rarely malignant, characterized by excessive production of catecholamines. Approximately 75% of pheochromocytomas are sporadic and therefore unilateral. In 15–25% of cases, patients may have hereditary pheochromocytoma [multiple endocrine neoplasia types 1 and 2, von Hippel Lindau syndrome, neurofibromatosis, and hereditary paraganglioma syndromes types 2 and 4], an important distinction because they may be bilateral and multicentric. Most pheochromocytomas, both nonhereditary and hereditary, produce norepinephrine, creating a clinical phenotype characterized by attacks of hypertension, headaches, palpitations, and jitteriness. These symptoms and signs may be intermittent or sustained.

   b. Measurement of plasma or urine catecholamines or metanephrines remains the mainstay for diagnosis of pheochromocytoma (43). Plasma catecholamines or metanephrine values are almost always abnormal; in rare patients with small tumors, catecholamine or metanephrine abnormalities may be intermittent, requiring measurements during an attack to make a diagnosis. Localization of a pheochromocytoma is accomplished by either CT or MRI scanning of chest and abdomen with rare pheochromocytomas in the pelvis; in most symptomatic pheochromocytomas or catecholamine-producing paragangliomas, the tumor will be localized by these imaging studies (44). Occasionally, additional radionuclide scans (utilizing radiolabeled octreotide or metaiodo-benzyl guanidine) are helpful to identify a small tumor not visualized by CT or MRI scanning (45).

   c. Preoperative management of pheochromocytoma is straightforward: either inhibit synthesis of catecholamines or interfere with their

interaction with adrenergic receptors. Treatment with alpha-methyl tyrosine (Demser™), a tyrosine hydroxylase inhibitor, inhibits synthesis of catecholamines. It should be started at a dose of 250 mg once or twice a day and titrated upward to control hypertension and other symptoms of pheochromocytoma. It is important to initiate therapy several weeks prior to a planned surgical procedure to allow time to titrate the dose of alpha-methyl tyrosine to an effective dose (usually 1–2 g/day). In addition, most patients should also be treated with a combination of alpha- and beta-adrenergic antagonists. The authors prefer to use a short acting alpha-adrenergic antagonist such as prazosin (Minipress™), starting at 1 mg once or twice a day and titrating upward; others prefer a longer-acting agent such as phenoxybenzamine (Dibenzyline™; starting dose of 10 mg/day with titration). In addition, beta-adrenergic antagonists may reduce tachycardia or ventricular arrhythmias. Therapy with an alpha-adrenergic antagonist should be initiated concomitantly or before beta-adrenergic therapy. Occasionally, initiation of adrenergic therapy is associated with hypotension, sometimes severe enough to require intravenous fluids. It is important to start pharmacologic therapy several weeks prior to a planned surgical procedure, particularly in hypertensive patients. Controlling the hypertension diminishes vasoconstriction and re-establishes normal intravascular volume, thereby eliminating the hypotension associated with rapid vasodilation following removal of a pheochromocytoma.

d. There are several challenges associated with intraoperative management of a patient with a pheochromocytoma. The first is the unsuspected pheochromocytoma, an event that occurs infrequently but must be dealt with in the context of another surgical procedure, labor and delivery, or removal of an adrenal tumor not thought to be a pheochromocytoma. In situations where the situation is unstable, it may be advisable to stop the surgical procedure and stabilize the patient prior to a reoperation. In most cases, treatment with short-acting intravenous alpha- or beta-adrenergic antagonists or nitroprusside will control blood pressure and other cardiovascular manifestations and permit continuation of the surgical procedure. In such cases, hypotension may follow removal of the pheochromocytoma, necessitating volume replacement and short-term pressor therapy. The second is the inevitable intermittent release of catecholamines associated with induction of anesthesia and manipulation of the tumor. The anesthesiologist must be prepared to manage transient episodes of hypertension or arrhythmia by a combination of intravenous nitroprusside or alpha- and beta-adrenergic antagonists.

e. Hypotension in the postoperative period is uncommon in pretreated patients. If it occurs, it should be treated with fluids and pressors.

V. HYPERCALCEMIA AND HYPOCALCEMIA

A. Hypercalcemia

1. Malignancy-related hypercalcemia is the most common cause of hypercalcemia in the context of a cancer hospital. The differential diagnosis includes humoral hypercalcemia of malignancy, most commonly caused by overproduction of parathyroid hormone-related protein (PTHrp) by a malignant tumor, bone metastasis, increased production of 1,25-dihydroxyvitamin D3 in lymphoma or associated with fungal infection or tuberculosis. Multiple myeloma may cause hypercalcemia through increased bone resorption. Hyperparathyroidism occurs with an incidence of 1 in 1000 in the general population and should be considered in hypercalcemic patients with or without cancer. Finally, hyperthyroidism and Addison disease can rarely cause hypercalcemia.
2. Measurement of the immunoreactive serum intact parathyroid hormone concentration is central to the evaluation process. Patients with hyperparathyroidism will have elevated serum ionized or total calcium and intact PTH measurements and a normal or elevated serum 1,25-dihydroxyvitamin D_3. Patients with all other types of hypercalcemia will have a suppressed intact PTH value. It is possible to separate hyperparathyroidism from other causes in most cases using this approach. There are rare patients, particularly in the context of oncology, who may have more than one cause for their hypercalcemia (lymphoma and 1° hyperparathyroidism or breast cancer and 1° hyperparathyroidism). The routine evaluation of a patient with hypercalcemia in the context of cancer should include a serum ionized or total

calcium, intact PTH and PTHrp measurements, serum and urine protein electrophoresis and immunoelectrophoresis, thyroid hormone levels, and serum 1,25-dihydroxyvitamin D_3 and 25-hydroxyvitamin D_3 measurements. If there are clinical signs suggestive of adrenal insufficiency, a cosyntropin test should be performed (Table 7).

3. Hypercalcemia associated with an elevated intact PTH should be further evaluated by obtaining a sestamibi scan and an ultrasound of the neck to identify a parathyroid adenoma. If the diagnosis is confirmed the parathyroid adenoma should be surgically removed. In patients who have hypercalcemia caused by cancer, an attempt should be made to differentiate between humoral hypercalcemia of malignancy (PTHrp-mediated or myeloma) and 1,25-dihydroxyvitamin D_3-mediated hypercalcemia (lymphoma and fungal or tuberculous infections). Humoral hypercalcemia of malignancy will respond to intravenous pamidronate [60–90 mg intravenously over 2 hr or zoledronic acid 4 mg intravenously over 30 min], whereas 1,25-dihydroxyvitamin D_3-mediated hypercalcemia will respond to corticosteroids (10–20 mg prednisone/day). Hydration (half-normal saline at 100–200 cc/hr) will reverse dehydration and hasten the clearance of calcium. Lowering of the serum calcium concentration may require 48–72 hr following initiation of therapy. Complete removal of a tumor producing PTHrp will lead to normalization of the serum calcium concentration.
4. It is inadvisable to perform surgery on a hypercalcemic patient; the surgical procedure should be delayed until the serum calcium is normalized or lowered <11 mg/dL. The one exception to this may be a patient with a parathyroid adenoma, in whom normalization of the serum calcium can be expected to occur rapidly following removal of a parathyroid adenoma.

B. Hypocalcemia

1. Hypocalcemia is uncommon in the oncologic setting, although a low total serum calcium may occur as a result of hypoalbuminemia, a common occurrence in cancer patients. The total serum calcium concentration can be corrected for a low albumin concentration by adding the value obtained by multiplying 0.8 mg/dL times the difference between a normal albumin value (4 gm/dL) and the observed value. For example, the corrected serum calcium concentration in a patient with an observed serum calcium concentration of 7.5 mg/dL and a serum albumin concentration of 2 gm/dL is given by 7.5 mg/dL + 0.8 (4 – 2 gm/dL) which is equal to a corrected calcium concentration of 9.1 mg/dL, a normal value. Alternatively, one could obtain an ionized calcisum measurement.
2. The differential diagnosis includes vitamin D deficiency caused by malabsorption or defects in synthesis of vitamin D, hypoparathyroidism [autoimmune, genetic (pseudohypoparathyroidism) or acquired during head and neck surgery for squamous cell or thyroid carcinoma] or severe magnesium (Mg^{++}) deficiency. Preoperative identification of hypocalcemia should lead to a detailed evaluation of calcium metabolism to exclude parathyroid hormone deficiency or resistance (pseudohypoparathyroidism) or vitamin D deficiency. The serum calcium concentration should be normalized prior to anesthesia and surgery. This is best accomplished emergently by a calcium infusion or by a combined replacement with oral calcium supplementation and vitamin D therapy over a 3–5 day period.
3. Hypocalcemia following head and neck surgery is always caused by a transient or permanent hypoparathyroidism. The serum calcium should be checked in the night after surgery. Symptomatic hypocalcemia (perioral numbness or tetany) can be treated with a continuous infusion of calcium gluconate (3 g/L) with an infusion rate of 100 cc/hr. This can be tapered as an oral calcium or calcitriol effect is manifested. If the serum calcium is between 7.5 and 8.5 mg/dL, the oral calcium should be initiated at 1–2 g of elemental calcium twice daily; a serum calcium <7.5 mg/dL should be treated with 2–3 g of elemental calcium orally twice daily and calcitriol of 0.5–1 μg/day. It is preferable to initiate calcitriol therapy early in the course of hypocalcemia; 2–3 days may be required before the serum calcium is normalized. If parathyroid function returns to normal (usually occurs within the first 24–48 hr, if it is to occur), the calcitriol can be stopped.
4. After initiating calcium and vitamin D analog therapy, it is important to continue to monitor the serum calcium concentration weekly for several weeks, monthly for 6 months, and

then every 3–6 months, once a stable dose of calcium and vitamin D has been established.

VI. PERIOPERATIVE MANAGEMENT OF THE PATIENT WITH PITUITARY DISEASE

A. General Concepts

1. Patients with disorders of the anterior and/or posterior pituitary pose a unique challenge to the clinician. Because there are multiple hormones to consider, the perioperative and intensive care management of the pituitary patient require a systematic approach, so that each patient can be optimally managed based on his/her unique underlying hormonal status.
2. The most important pituitary hormones to assess in the surgical patient are TSH, ACTH, and arginine vasopressin (AVP). Although clinically relevant to the outpatient management of pituitary patients, disorders of GH, gonadotropins (LH or FSH), prolactin (PRL), and oxytocin secretion do not generally need to be addressed in the perioperative period, unless the surgical procedure directly addresses a disorder of one of these hormones. Next, in a patient with pituitary dysfunction, the most common deficiencies are GH and the gonadotropins (LH and FSH) (46), followed by TSH and ACTH when there is more extensive pituitary involvement. This hierarchy of pituitary hormone loss is helpful to the clinician; for example, a patient is unlikely to have ACTH (and subsequent cortisol) deficiency, if all other anterior pituitary function is normal. Likewise, a patient with GH, gonadotropin, and TSH deficiencies is at very high risk for having concomitant ACTH deficiency.
3. Other clinical ''pearls'' to consider in the evaluation of pituitary function include: (i) levothyroxine replacement in the patient with ACTH deficiency can unmask adrenal insufficiency and precipitate an adrenal crisis; therefore, every effort should be made to clarify the patient's adrenal status, if one is going to treat central hypothyroidism (defined as hypothyroidism with a low TSH concentration) and (ii) the treatment of cortisol deficiency can unmask AVP deficiency; therefore patients with central adrenal insufficiency should be alerted to look for signs of DI when starting glucocorticoid replacement.

B. Patient with Previously Diagnosed Hypopituitarism

1. Prior to elective surgery, the patient with pre-existing hypopituitarism should be evaluated for the adequacy of thyroid, corticosteroid, and vasopressin replacement. Measurements of thyroid hormone and electrolytes should be made. Although the clinical signs and symptoms of pituitary hormone deficiencies are more subtle and less severe than those that accompany diseases affecting the end organ, adequate hormone replacement is important for a smooth operative course.
2. Hypothyroid patients are at increased operative risk, and an attempt should always be made to render the patient euthyroid, documented by a normal free T4 concentration preoperatively, to ensure an uneventful operation and recovery. A low TSH value is expected in central hypothyroidism; measurement is unnecessary and a low value may confuse the clinician unaware of the pituitary disorder, leading to cessation of thyroid replacement. An individual discovered to have a mildly low free T4 (20% below normal) secondary to TSH deficiency can be cleared for surgery. However, more profound thyroid hormone deficiency should be corrected (with an ultimate levothyroxine dose of 1.6 μg/kg per day) prior to any elective surgery. This can typically be accomplished in a few weeks, but it may take longer in those individuals with coronary artery disease or congestive heart failure where rapid thyroid replacement could lead to myocardial ischemia or arrhythmias.
3. In the hypothyroid patient who requires emergency surgery, lower anesthetic doses should be administered, necessitating inclusion of the anesthesiologist in the preoperative discussions. Recovery from anesthesia, which may be prolonged, must be carefully monitored, and the indiscriminate use of narcotics and sedatives should be avoided (47). Finally, hypothyroid patients have a decreased ability to excrete free water, and their fluid and electrolyte management should be closely managed, particularly if the patient has a coexistent disorder of vasopressin secretion.
4. Levothyroxine, the most commonly used preparation to treat hypothyroidism, has a half-life of 6–7 days. Therefore, in the patient on chronic therapy, it can be held for a few days without any clinical consequence. However, if a postoperative patient is able to take oral medications, the

preoperative dose of thyroid replacement should be administered. For the ICU patient or patient on prolonged bowel rest after surgery, levothyroxine can be administered intravenously once daily, typically at 50% of the oral dose.

5. Surgery is a significant physiologic stress that activates the HPA axis. Plasma ACTH and cortisol levels normally increase at the time of incision and are secreted continuously during surgery, with the greatest production of these hormones during reversal of anesthesia and the immediate postoperative recovery period (48). Serum ACTH and cortisol concentrations typically return to baseline values within 1–2 days (49). The adrenal glands produce about 50 mg/day of cortisol during minor surgery and 75–150 mg/day with major surgery (49); although cortisol secretion rates can reach 200–500 mg/day in severe stress, it would be unusual to see similar secretion rates after surgery (50,51). Therefore, if the patient has preexisting ACTH/cortisol deficiency, it is imperative to cover the patient with stress dose steroids during the surgery and recovery period (Table 7). If a patient has multiple anterior pituitary hormone deficiencies (e.g., GH, gonadotropin, and TSH deficiencies) and is not on corticoid replacement, the patient should be assessed for adrenal insufficiency prior to surgery (Table 7). If this is not feasible, the patient should be empirically covered during the perioperative period so as to ensure that symptomatic adrenal insufficiency does not occur. Any patient with known pituitary disease, who develops hypotension after surgery and who is not on steroids, should also be treated with stress steroids after appropriate testing is obtained (Table 7). Of note, unlike primary adrenal insufficiency, those persons with ACTH deficiency do not gene rally require treatment with a mineralocorticoid (i.e., fludrocortisone), because the renin–angiotensin–aldosterone axis is intact in these individuals.
6. In the patient already on corticosteroid replacement, hydrocortisone can be administered immediately prior to surgery and then every 8 hr. Alternatively, a continuous hydrocortisone infusion can be utilized. The exact dosing of perioperative steroid coverage should be tailored to the patient's medical history, preoperative steroid dose, and the amount of stress anticipated by the given surgical procedure (Table 7). Once the patient is taking adequate liquids and medications by mouth, oral steroids should be substituted. For the first 1–2 postoperative days (in cases of moderate to major stress), an increased dose of corticosteroid is administered. If the patient continues to do well and is without fever or other complications, normal maintenance doses can be resumed.
7. The replacement of GH and sex steroids is not necessary in the acute inpatient management of the patient with pituitary disease. In the critically ill patient, anabolic agents such as GH and androgens have previously been used to counteract the catabolic response (52). These studies have had limited success and in one report, the use of high dose GH actually increased morbidity and mortality (53). Of note, these studies were not conducted in patients with hypopituitarism. There is currently no compelling evidence to support the continuation of sex steroids and GH in patients during the perioperative period. In addition, the risk of venous thrombosis is sufficiently great in the postoperative patient to warrant withholding estrogen therapy in the hypogonadal female patient. Finally, in the patient taking a dopamine agonist to treat hyperprolactinemia, therapy can typically be withheld briefly and restarted once the patient is discharged from the hospital.

C. Patient with a Sellar or Suprasellar Mass Whose Pituitary Status Is Unknown

1. The neurosurgical patient who has a mass within or in the region of the sella turcica requires special consideration during the preoperative and postoperative periods. These patients should be evaluated by an endocrinologist prior to elective surgery. In cases where there is rapid visual loss, cranial nerve palsy, hydrocephalus, or pituitary apoplexy, urgent surgery usually precludes a detailed evaluation. A complete endocrinologic evaluation assures the identification of hypopituitarism and syndromes of endocrine hormone excess. A history and physical exam and the following screening labs should be performed: an 8 AM fasting IGF-1, prolactin, electrolytes, LH, FSH, testosterone or estradiol, TSH, free T4, ACTH, and cortisol. For pituitary tumors, the risk of preoperative hypopituitarism correlates directly with the size of the tumor; the patient with a pituitary microadenoma ($\leq$1 cm) is unlikely to have compromised pituitary functioning, whereas approximately 70–90% of patients with

macroadenomas (>1 cm) will have deficiencies of one or more hormones (54). A caveat: DI is rarely seen in pituitary adenomas, regardless of size, but is more likely to be present in the patient with other tumors (craniopharyngioma, germinomas) or infiltrative diseases (Langerhans' cell histiocytosis, sarcoidosis) (55).

2. Postoperative care should address both endocrine and nonendocrine issues. CSF leakage, meningitis, worsening of vision, and CNS hemorrhage are uncommon events and will generally be addressed by the neurosurgeon (54). The postoperative endocrine issues include the management of fluid balance and the assessment of long-term hormone requirements.
3. In patients undergoing neurosurgery for a sellar/suprasellar mass, there are two main perioperative issues to consider: the management of postoperative fluid/sodium balance and the determination of postoperative hormone therapy. The most immediate endocrine sequela of neurological surgery is the development of either central DI or the syndrome of inappropriate antidiuretic hormone (SIADH). Hyponatremia (caused by excessive or unregulated secretion of AVP) may occur in up to 25% of patients 7 days postsurgery and DI (deficiency of AVP) occurs in ~20% of patients (54,56). The detailed management of these disorders is described in subsequent sections. Typically, if a patient exhibits hypopituitarism before surgery, postoperative hypopituitarism is likely, although ~6% of patients with preoperative pituitary deficiencies will experience some recovery of pituitary function after surgery (55). Hormone replacement in this setting is generally the same as those for patients with previously diagnosed hypopituitarism. In all patients who have undergone pituitary surgery, hypopituitarism should be considered a possibility and specific testing should be performed. Clinical features that can assist the clinician in identifying the patients at highest risk for long-term pituitary dysfunction include the size and type of tumor, the extent of surgery, the presence or absence of post-op DI, and the amount of normal pituitary tissue removed (as identified by histopathological evaluation of the surgical specimen).
4. A thorough evaluation and treatment plan is often not relevant during the immediate post-op period because of edema and healing. Typically, the need for long-term hormone therapy is determined 6–8 weeks after surgery. However, the clinician must decide whether or not to discharge these patients on corticosteroid replacement. Two approaches are used. First, one can empirically discharge every patient on maintenance doses of hydrocortisone and reassess adequacy of cortisol production, as described in Table 1, following cessation of corticosteroids at least 24 hr earlier. An alternative is to give stress steroids perioperatively and then discontinue hydrocortisone in the hospital, once the patient is stable, assessing an AM cortisol level 24 hr later; patients with cortisol levels >15 μg/dL can be discharged without corticoid replacement, although they should be educated about the signs and symptoms of adrenal insufficiency. Those patients with values <15 μg/dL can be sent home on hydrocortisone with plans for reassessing 6–8 weeks after surgery.
5. Each patient with permanent hypopituitarism should be provided specific instructions on the use of "stress" doses of corticosteroids and should also be offered a "MedicAlert" or similar bracelet, available from http://www.medicalert.org.

D. Unique Situations

1. Pituitary Apoplexy

a. Pituitary apoplexy refers to the potentially life-threatening clinical syndrome that results from an acute hemorrhage into or infarction of a pituitary adenoma or rarely from these same events in an otherwise normal pituitary gland. The classical presentation is one of an abrupt onset of severe headache, visual defects, typically with ophthalmoplegia, and/or alteration of mental status. A high clinical suspicion is warranted in these cases, as prompt treatment with glucocorticoids and neurosurgical intervention is often necessary to preserve vision and life (57,58). It appears that the risk for pituitary apoplexy may be higher in those patients who are anticoagulated (59) or who undergo combined pituitary stimulation tests prior to surgery (60). Therefore, the benefit of such interventions should be weighed against the theoretical risks in patients known to have pituitary adenomas.

b. It is important for the anesthesiologist and neurosurgeon to recognize the possibility of hypopituitarism and initiate "stress" doses of corticosteroid replacement (Table 7).

2. *Cushing Syndrome*

   a. The preoperative assessment of the Cushing patient is geared towards optimizing treatment of the multiple medical morbidities that coexist with hypercortisolism, including diabetes mellitus, cardiac failure, infection, hypertension, and electrolyte abnormalities (hypokalemic metabolic alkalosis). Severe cortisol excess can transiently suppress normal anterior pituitary hormone production (61); therefore, these patients may need hormone replacement initially but may spontaneously recover after successful treatment of the underlying disorder causing Cushing syndrome. In severely affected patients, medical therapy to decrease cortisol production may be of value to reduce postoperative complications (see section on Glucorticoid Excess: Cushing syndrome).
   b. Patients with Cushing disease have excessive corticosteroid production and do not need perioperative steroid administration. Furthermore, adequate treatment, i.e. successful removal of the pituitary adenoma, will result in secondary adrenal insufficiency because of long-term suppression of the HPA axis. Some centers treat Cushing patients with glucocorticoids perioperatively (54), whereas other centers do not (55). It is reasonable to withhold steroids after surgery to assess whether or not the hypercortisolism is cured. Some centers even recommend performance of a low dose dexamethasone test at this time (62). In those patients who are successfully treated, the cortisol level (obtained at least 24 hr after surgery and 24 hr after the last dose of hydrocortisone) will be $< 3\,\mu g/dL$ and the patient will have symptoms of adrenal insufficiency, such as anorexia, weakness, nausea, etc. If the patient does not develop symptoms or signs of adrenal insufficiency postoperatively, pituitary tumor treatment failure is suggested. Those with low postoperative cortisol values have a higher probability of long-term remission (62a). These general comments are also relevant for Cushing syndrome caused by ectopic ACTH production (bronchial carcinoids) or cortisol production by adrenal tumors (benign or malignant adrenal cortical tumors).
   c. Patients with chronic glucocorticoid excess may have poor tissue healing, prolonged ileus following abdominal surgery, a higher risk for infection, hypercoagulability, and venous thromboembolism (63), and appropriate steps should be taken to address each of these problems.

3. *Acromegaly*

   a. Patients with acromegaly are at increased risk for cardiovascular/cerebrovascular disease and should have the appropriate medical clearance prior to surgery. Whether acromegalics should receive specific therapy to lower GH and IGF-1 levels prior to surgery is not clear (64).
   b. Long-term effects of GH excess on soft tissues may cause macroglossia; obstructive sleep apnea is common, and intubation in these patients may be more difficult (65). Furthermore, acromegalic patients may have more difficulty breathing with the nasal packs after trans-sphenoidal surgery (55).
   c. The anesthesiologist should also be aware that anesthetic requirements may be altered in acromegalic patients (65).
   d. Diabetes mellitus is identified in about a quarter of acromegalic patients, and the blood glucose concentration should be normalized in the preoperative period. This can be either accomplished with oral diabetes agents or with insulin (see the section on Perioperative Management of Diabetes Mellitus). Successful removal of a pituitary adenoma will often result in reversal of diabetes mellitus in the postoperative period.
   e. After successful tumor resection, GH levels drop within a few hours; therefore, measurement of GH in the postoperative period may be useful in determining the likelihood of cure. The success rate of surgery is highest in those patients with the smallest tumors. IGF-1 levels should not be measured immediately after surgery because of the longer half-life of this molecule. Surgical cure may result in a significant mobilization of tissue fluid and diuresis, easily confused with acquired DI (54).

4. *Prolactinomas*

Most prolactinomas are treated medically with a dopamine agonist. In the rare patient who has surgery for a prolactin-secreting tumor (serum prolactin usually $> 200\,ng/mL$), the management issues are similar to those for other pituitary tumors.

5. Patient on Chronic Corticosteroid Therapy: 2° Adrenal Insufficiency

a. The chronic use of exogenous glucocorticoids may suppress the HPA axis. Even patients who are no longer taking these agents, but who were on prolonged treatment with supraphysiologic doses within the preceding year, may be at risk for secondary adrenal insufficiency. Although clinically relevant adrenal insufficiency is unlikely to occur in this setting and there is good evidence that stress steroid coverage may not always be needed (66,67), each of these patients should be considered individually.

b. Surgeons and anesthesiologists should be aware that there are well-documented examples of HPA axis suppression caused by oral, inhaled, or topical steroids. If it is not possible to perform an adequate preoperative evaluation, consideration should be given to "stress" dose coverage or initiation of corticosteroid replacement intraoperatively at the first sign of adrenal insufficiency (usually hypotension during the intraoperative period). In the preoperative assessment of these patients, the main issue to address is whether or not the patient's dose and duration of steroid therapy have predisposed them to clinically relevant adrenal insufficiency (Table 8). Other important aspects to consider in patients on chronic corticosteroids are the impaired wound healing and other postoperative complications that may be secondary to that treatment (50).

c. The exact dose at which suppression of the HPA axis occurs in a given individual is unknown, and previous studies have demonstrated the difficulty in predicting suppression on the basis of the dose or extent of therapy (49,50,68). Nevertheless, if one approaches this question physiologically, it may be possible to predict for a given individual. The typical physiologic replacement dose of hydrocortisone in an average adult (1.73 m^2) would be 20 mg of hydrocortisone per day. Doses >20 mg taken for more than 3 weeks may place the patient at risk for adrenal insufficiency (see Refs. 49,69,70 for a discussion). Table 7 offers some general guidelines.

E. Patient with a Disorder of Sodium and Water Balance

1. General

It is not uncommon for the clinician to encounter disorders of fluid and sodium balance, particularly in hospitalized patients and those with cancer (47,71). There are a multitude of etiologies that contribute to such processes, and a complete review of hyponatremia and hypernatremia is beyond the scope of this chapter. Therefore, the following discussion will center on the management of disorders of AVP excess (SIADH) and deficiency (DI), common problems in the perioperative period.

2. Syndrome of Inappropriate Antidiuretic Hormone Secretion

a. SIADH refers to the abnormal production or action of AVP, resulting in an excess of total body free water relative to sodium. Excess secretion of antidiuretic hormone is manifested by hyponatremia (serum Na <135 mEq/L) and by definition, the urine is inappropriately concentrated (urine osmolality >100 mOsm/kg, usually >300 mOsm/kg)in the presence of low serum osmolality (<289 mOsm/kg), euvolemia, and normal liver, kidney, and adrenal function. In SIADH, there is decreased aldosterone production and possibly increased secretion of natriuretic peptides (72). This results in increased renal sodium excretion (>20 mEq/L, usually >40 mEq/L). This helps to distinguish SIADH from hypovolemic and hypervolemic hyponatremia, where the urine sodium is typically <20 mEq/L unless there is an underlying process contributing to renal salt wasting (e.g., those patients on diuretics). Inappropriate secretion of antidiuretic hormone is a diagnosis of exclusion; other processes that can cause euvolemic hyponatremia, including adrenal insufficiency and profound hypothyroidism, should be excluded. The hemodilution associated with SIADH commonly lowers hematocrit and serum concentrations of uric acid and BUN (73). Measurement of AVP and water loading tests to differentiate SIADH from other conditions are rarely helpful (47).

b. The causes of SIADH are outlined in Table 9. The perioperative management of hyponatremia should focus on understanding cause and implementing therapy. Critically ill or

Table 9 Causes of SIADH

Tumor related
Extrapulmonary small cell carcinoma
Lymphoma
Meningeal carcinomatosis
Metastatic brain tumors
Olfactory neuroblastoma (esthesioneuroblastoma)
Pancreatic carcinoma
Primary brain tumors
Prostate carcinoma
Small cell lung carcinoma and other pulmonary tumors
Thymic tumors
Nonmalignant conditions
Acute psychosis
Acute respiratory failure/positive pressure ventilation
AIDS
Encephalitis
Hydrocephalus
Idiopathic, particular in the elderly
Meningitis
Nausea and pain
Pneumonia
Postoperative state (major abdominal or thoracic surgery; pituitary surgery)
Stroke
Subarachnoid hemorrhage and other intracranial hemorrhages
Traumatic brain injury
Drugs
First generation sulfonylureas (Chlorpropamide)
Carbamazepine
Cisplatin
Cyclophosphamide
Desmopressin/Vasopressin
Melphalan
Methylenedioxymethamphetamine (“ecstasy”)
Nonsteroidal anti-inflammatory agents
Opiates
Oxytocin
Phenothiazines
Prostaglandin-synthesis inhibitors
Selective serotonin reuptake inhibitors (SSRIs)
Tricyclic antidepressants
Vinblastine
Vincristine

postoperative patients may have several processes contributing to hyponatremia, necessitating a thorough evaluation. Early clinical findings of hyponatremia include malaise, anorexia, muscle cramps, nausea, vomiting, confusion, lethargy, and headache; this can progress to cerebral edema and severe neurologic manifestations such as seizures, respiratory arrest, coma, and death. In the patient with a gradual onset of hyponatremia, the brain can adapt to the hypotonic state, and these symptoms do not typically occur unless the serum sodium is < 120 mEq/L. However, these same neurologic findings may occur at higher sodium levels, particularly if there is a rapid descent of the serum sodium concentration. Although SIADH may spontaneously improve after treatment of the underlying disease or withdrawal of the offending medication, medical therapy is frequently instituted to prevent a further fall in serum tonicity and attendant neurologic sequelae.

c. In the patient with significant neurologic manifestations or profound hyponatremia, the sodium should be increased 1–2 mEq/hr (see the following for discussion of complications of increasing the serum sodium too quickly) using hypertonic saline (3% NaCl) (Table 10), preferably in an ICU setting. Initial therapy is aimed at improving neurologic symptoms, and frequently, even a minimal rise in the sodium levels will improve the clinical situation. Once the patient’s

Table 10 Management of SIADH and Hyponatremia

Demeclocycline (Declomycin®)
Produces reversible nephrogenic DI
300–600 mg BID
Lithium carbonate
Produces reversible nephrogenic DI
600–1800 mg/day in divided doses
Narrow therapeutic window
Fludrocortisone (Florinef®)
Increased renal sodium retention
0.1–0.3 mg/day
High salt diet and/or oral NaCl
Increased solute intake helps to augment water loss
Start 1–3 gm/day
Urea
Increased solute intake helps to augment water loss
30 gm/day
Vasopressin 2 receptor antagonists
Inhibit ADH action at the V2 receptor
In clinical trials
Hypertonic saline (formula derived from Ref. 74)
Can use with a loop diuretic (enhances free water clearance)
Total amount of 3% NaCl to infuse (mL) = Desired change in serum Na $\times$ 1000 / ΔNa
[a]ΔNa (change in serum sodium per liter infused) = 513[a]-Serum sodium / Total body water (L)[b] + 1

[a] Amount of sodium (mmol) in 1 L of 3% NaCl.

[b] TBW (L)= Weight (kg)$\times$ 0.6 (children, nonelderly men); 0.5 (nonelderly women, elderly men); or 0.45 (elderly women).

symptoms have improved, the rate of infusion should be slowed with a gradual rise toward the range of 125–130 mEq/L, combining hypertonic saline with a loop diuretic such as furosemide to limit treatment-induced expansion of extracellular fluid volume and to promote electrolyte-free water excretion (74). Normal saline should not be used in the acute management of hyponatremia (74).

d. In the asymptomatic patient, SIADH is initially treated with fluid restriction (500–1000 mL daily in adults; 1 L/m^2 per day or two-thirds maintenance in children). Intake and output should be monitored closely to ensure compliance with fluid restriction and to maintain an oral intake of at least 500 mL/day below the average urine volume (in adults). If unsuccessful, other strategies can be employed (Table 10). The most commonly used agent is the tetracycline antibiotic, demeclocycline, which interferes with the effect of AVP at the level of the renal tubule. A period of $\geq$5 days may be required for a maximal effect (47).

e. The rapid correction of hyponatremia by any means can cause central pontine myelinolysis or osmotic demyelination syndrome. It is characterized by severe and often irreversible neurologic sequelae such as dysarthria, dysphagia, psychiatric disturbances, spastic paraplegia or quadriplegia, seizures, pseudobulbar palsy, and altered mental status (75). Therefore, in the patient with chronic hyponatremia, the goal of treatment should be not to increase the serum sodium levels by >0.5 mEq/L per hour (or 12 mEq/L per day) (76). However, some experts recommended an even more conservative therapeutic goal of an increase of no more than 8 mEq/L per day (74).

3. *Cerebral Salt Wasting*

Although it remains controversial and incompletely understood, the cerebral salt wasting (CSW) syndrome is a clinical entity characterized by hyponatremia and volume depletion in patients with intracranial disorders, particularly neurosurgical patients. Cerebral salt wasting is defined as significant renal salt wasting as a consequence of intracranial disease. This combination causes hyponatremia and decreased extracellular fluid volume (77). It is differentiated from SIADH by the presence of volume depletion (clinical signs of dehydration or low central venous or pulmonary wedge pressure). In SIADH, there will be evidence of hemodilution and lower than normal uric acid and blood urea nitrogen measurements, whereas these are likely to be increased in CSW. This differentiation is important, because CSW requires volume replacement. It is believed that CSW results from the primary overproduction of natriuretic peptides (78).

4. *Diabetes Insipidus*

a. Diabetes insipidus is characterized by the excessive production of a dilute urine (polyuria) with a compensatory increase in thirst (polydipsia). The diagnosis of DI should be considered only in those individuals with daily urinary volumes >3 L/day (in children $>1.5\,L/m^2$ per day) who also complain of extreme thirst. Thirst and polyuria that persist throughout normal sleeping hours are particularly compelling evidence for DI. It is generally caused by inadequate production of AVP (central DI) or a defect of AVP action on the renal tubular cell (nephrogenic DI) (Table 11). Patients with DI who have an intact thirst mechanism and free access to water should not develop derangements in serum sodium or osmolality. On the other hand, when an individual with DI is fasted, has an altered thirst mechanism, or develops an altered mental status that precludes adequate fluid intake, there is a risk for development of hypernatremia and hyperosmolality.

b. The diagnosis of DI should be considered in any patient with polyuria accompanied by significant polydipsia, particularly those with a sellar/suprasellar mass or who have had recent surgery affecting the hypothalamic–pituitary region. However, DI is but one cause of frequent urination or excessive thirst. For example, DI may be difficult to distinguish from primary polydipsia, in which AVP secretion is appropriately decreased by excessive free water intake. In the patient who has had a trans-sphenoidal pituitary adenoma resection and who is an obligate mouth breather due to the nasal packings, polyuria result from the excessive fluid intake used to alleviate symptoms of a dry mouth. Furthermore, postoperative patients will often have postoperative diuresis secondary to intraoperative fluid expansion.

c. In the outpatient setting, the diagnosis of DI can be established by the measurement of paired urine and serum electrolytes and

Table 11 Causes of DI

- *Central DI*
  - Autoimmune
  - Congenital
    - DIDMOAD/Wolfram syndrome
    - Familial autosomal dominant
    - Septo-optic dysplasia
    - Cytomegalovirus infection
  - Granulomatous diseases
    - Sarcoidosis
    - Mycobacterial infection
  - Idiopathic
  - Neoplastic
    - Germinoma
    - Langerhans cell histiocytosis
    - Metastatic tumors
      - Lung and breast
    - Craniopharyngioma
    - Leukemia/myelodysplastic syndrome
    - Other suprasellar tumors
  - Pituitary ischemia
    - Shock
    - Brain death
  - Postsurgical
  - Trauma
- *Nephrogenic DI*
  - Congenital
    - X-linked
      - V_2 receptor mutations
    - Autosomal recessive
      - Aquaporin-2 mutations
  - Drugs
    - Amphotericin B
    - Demeclocycline
    - Lithium
    - Methoxyflurane
    - Vincristine
  - Electrolyte disorders
    - Hypercalcemia
    - Hypokalemia
  - Renal disease
    - Amyloidosis
    - Medullary sponge kidney
    - Obstructive uropathy
    - Polycystic kidney disease
    - Sickle cell disease
- *Other*
  - Pregnancy-increased vasopressinase

osmolality in the morning following an overnight fast. A normal serum sodium concentration and osmolality in the presence of a urine osmolality >300 mOsm/kg excludes significant DI. The higher the urine osmolality after an overnight fast, the lower the likelihood of DI is. Individuals with significant symptoms of polydipsia and polyuria, particularly during the night, may be at risk for development of volume depletion from a prolonged fast. In these situations, it may be necessary to hospitalize the patient or to conduct the fast under controlled conditions in the outpatient setting. The water deprivation test, performed with frequent monitoring of laboratory parameters, urine output, vital signs, and weight, remains the gold standard for the diagnosis of DI. Once the urine osmolality has reached a plateau (a rise in urine osmolality <50 mOsm/kg over two successive hourly collections), the patient is given aqueous vasopressin to separate central from nephrogenic DI. A rise in the urine osmolality of >50% following vasopressin administration indicates a central deficiency of AVP. Measurement of an AVP level just prior to the administration of vasopressin may also be helpful; a low AVP concentration in this context is indicative of central DI.

d. In outpatients, the treatment should focus on alleviation of symptoms of polyuria and polydipsia. In most cases, serum tonicity will be maintained in those with access to fluids. In

Table 12 Management of DI and Hypernatremia

- *Aqueous vasopressin (Pitressin®)*
  - 20 U/mL
  - 5–10 U SQ/IM q4–6 hr
  - Shorter duration of action (4–6 hr)
  - Can be used as a continuous drip to a maximum of 0.01 U/kg per hour (significant pressor activity when used intravenously)
- *Desmopressin acetate (DDAVP®)*
  - Duration of action 8–12 hr
  - Synthetic analog of AVP
  - Intranasal rhinal tube (10 μg/0.1 mL)
  - 0.05–0.4 mL (5–40 μg) divided one to two times per day
  - Nasal spray (one spray = 10 μg = 0.1 mL)
  - One to four sprays (10–40 μg) divided one to two times per day
  - For injection: 4 μg/mL
  - 2–4 μg SQ/IM divided one to two times per day
  - Tablets (0.1 and 0.2 mg)
  - 0.2–1.2 mg divided two to three times per day
- *Hypotonic fluids (formula derived from Ref. 74)*:
  - Total amount of D5W to infuse (mL) = Desired change in serum Na × 1000 / [a]ΔNa
  - [a]ΔNa (change in serum sodium per liter infused) = 0[a]- Serum sodium / Total body water (L)[b] + 1

[a] Amount of sodium (mmol) in 1 L of D5W (may substitute 77 for 0.45% NS, etc.).

[b] TBW (L)= Weight (kg) × 0.6 (children, nonelderly men); 0.5 (nonelderly women, elderly men); or 0.45 (elderly women).

the hospitalized patient with DI, fluid intake and output must be closely monitored. Central DI is treated by the administration of desmopressin, a synthetic analog of AVP (79) (Table 12). Oral and intranasal routes of administration are available, and the dose and frequency of administration are adjusted so that symptoms are alleviated and breakthrough urination occurs prior to the next scheduled dose, the latter eliminating the risk of excessive water retention that can result in hyponatremia. In hospitalized patients, additional parenteral compounds are available for routine use (Table 12). In the intensive care unit, a vasopressin drip may also be used to maintain antidiuresis.

e. Patients who develop DI after a neurosurgical procedure may show a typical triphasic response: DI followed by SIADH followed by recurrence of DI (79). Severe hyponatremia may occur during the second phase (highest risk about 1 week after surgery), and caution should be used when treating central DI immediately after surgery. Patients with DI in this setting should be advised to drink fluids only to quench their thirst lest they develop hyponatremia. This is a particular concern in the neurosurgical patient with a nasal pack. In the rare individual with hypodipsia, scheduled free water intake may be required to maintain serum sodium levels and osmolality.

f. Nephrogenic DI can be a difficult problem in the hospitalized patient. Treatment includes adequate fluid intake, diuretics, salt restriction, and nonsteroidal anti-inflammatory drugs (79). Severe or symptomatic hypernatremia should be treated with the replacement of the free water deficit using hypotonic fluid administration (Table 12). Rapid correction of prolonged hypernatremia and hyperosmolality in this context can result in cerebral edema and, therefore, hypotonic fluids should be infused at a rate designed to reduce the serum sodium concentration to a maximum of 0.5 mEq/L per hour (74).

REFERENCES

1. Zimmet P, Alberti KG, Shaw J. Global and societal implications of the diabetes epidemic. Nature 2001; 414:782–787.
2. Pandit MK, Burke J, Gustafson AB, Minocha A, Peiris AN. Drug-induced disorders of glucose tolerance. Ann Intern Med 1993; 118:529–539.
3. Rosenberg CS. Wound healing in the patient with diabetes mellitus. Nurs Clin North Am 1990; 25:247–261.
4. McMahon MM, Bistrian BR. Host defenses and susceptibility to infection in patients with diabetes mellitus. Infect Dis Clin North Am 1995; 9:1–9.
5. Tomas E, Lin YS, Dagher Z, Saha A, Luo Z, Ido Y, Ruderman NB. Hyperglycemia and insulin resistance: possible mechanisms. Ann N Y Acad Sci 2002; 967:43–51.
6. Tayek J. A review of cancer cachexia and abnormal glucose metabolism in humans with cancer. J Am Coll Nutr 1992; 11:445–456.
7. Poulson J. The management of diabetes in patients with advanced cancer. J Pain Symptom Manage 1997; 13:339–346.
8. Malmberg K. Prospective randomised study of intensive insulin treatment on long term survival after acute myocardial infarction in patients with diabetes mellitus. DIGAMI (Diabetes Mellitus, Insulin Glucose Infusion in Acute Myocardial Infarction) Study Group. Br Med J 1997; 314:1512–1515.
9. Malmberg K, Norhammar A, Ryden L. Insulin treatment post myocardial infarction: the DIGAMI study. Adv Exp Med Biol 2001; 498:279–284.
10. Diaz R, Paolasso EA, Piegas LS, Tajer CD, Moreno MG, Corvalan R, Isea JE, Romero G. Metabolic modulation of acute myocardial infarction. The ECLA (Estudios Cardiologicos Latinoamerica) Collaborative Group. Circulation 1998; 98:2227–2234.
11. van den Berghe G, Wouters P, Weekers F, Verwaest C, Bruyninckx F, Schetz M, Vlasselaers D, Ferdinande P, Lauwers P, Bouillon R. Intensive insulin therapy in the surgical intensive care unit. N Engl J Med 2001; 345:1359–1367.
12. Levetan CS, Magee MF. Hospital management of diabetes. Endocrinol Metab Clin North Am 2000; 29:745–770.
13. Kanaya AM, Harris F, Volpato S, Perez-Stable EJ, Harris T, Bauer DC. Association between thyroid dysfunction and total cholesterol level in an older biracial population: the health, aging and body composition study. Arch Intern Med 2002; 162:773–779.
14. Mya MM, Aronow WS. Subclinical hypothyroidism is associated with coronary artery disease in older persons. J Gerontol A Biol Sci Med Sci 2002; 57: M658–M659.
15. Murkin JM. Anesthesia and hypothyroidism: a review of thyroxine physiology, pharmacology, and anesthetic implications. Anesth Analg 1982; 61:371–383.
16. Duntas LH. Thyroid disease and lipids. Thyroid 2002; 12:287–293.
17. Villabona C, Sahun M, Roca M, Mora J, Gomez N, Gomez JM, Puchal R, Soler J. Blood volumes and renal function in overt and subclinical primary hypothyroidism. Am J Med Sci 1999; 318:277–280.
18. Sarich TC, Wright JM. Hypothyroxinemia and phenytoin toxicity: a vicious circle. Drug Metabol Drug Interact 1996; 13:155–160.

19. O'Connor P, Feely J. Clinical pharmacokinetics and endocrine disorders. Therapeutic implications. Clin Pharmacokinet 1987; 13:345–364.
20. Muller B, Tsakiris DA, Roth CB, Guglielmetti M, Staub JJ, Marbet GA. Haemostatic profile in hypothyroidism as potential risk factor for vascular or thrombotic disease. Eur J Clin Invest 2001; 31: 131–137.
21. Ladenson PW, Goldenheim PD, Ridgway EC. Prediction and reversal of blunted ventilatory responsiveness in patients with hypothyroidism. Am J Med 1988; 84: 877–883.
22. Hiasa Y, Ishida T, Aihara T, Bando M, Nakai Y, Kataoka Y, Mori H. Acute myocardial infarction due to coronary spasm associated with L-thyroxine therapy. Clin Cardiol 1989; 12:161–163.
23. Arlot S, Debussche X, Lalau JD, Mesmacque A, Tolani M, Quichaud J, Fournier A. Myxoedema coma: response of thyroid hormones with oral and intravenous high-dose L-thyroxine treatment. Intensive Care Med 1991; 17:16–18.
24. Wolfson B, Smith K. Cardiac arrest following minor surgery in unrecognized thyrotoxicosis: a case report. Anesth Analg 1968; 47:672–676.
25. Pugh S, Lalwani K, Awal A. Thyroid storm as a cause of loss of consciousness following anaesthesia for emergency caesarean section. Anaesthesia 1994; 49:35–37.
26. Bennett MH, Wainwright AP. Acute thyroid crisis on induction of anaesthesia. Anaesthesia 1989; 44:28–30.
27. Robson NJ. Emergency surgery complicated by thyrotoxicosis and thyrotoxic periodic paralysis. Anaesthesia 1985; 40:27–31.
28. Ragaller M, Quintel M, Bender HJ, Albrecht DM. [Myxedema coma as a rare postoperative complication]. Anaesthesist 1993; 42:179–183.
29. Sherry KM, Hutchinson IL. Postoperative myxoedema. A report of coma and upper airway obstruction. Anaesthesia 1984; 39:1112–1114.
30. Mizuno J, Nakayama Y, Dohi T, Tokioka H. [A case of hypothyroidism found by delayed awakening after the operation]. Masui 2000; 49:305–308.
31. Tsubokawa T, Yamamoto K, Kobayashi T. Propofol clearance and distribution volume increase in patients with hyperthyroidism. Anesth Analg 1998; 87:195–199.
32. Matsumoto S, Unoshima M, Takeshima N, Yamamoto H, Yoshitake S, Noguchi T. [Hemodynamic effects of propofol as an anesthesia induction agent in hyperthyroidism patients on chronic beta-blocker]. Masui 2000; 49:976–980.
32a. Burch HB, Wartofsky L. Life-threatening thyrotoxicosis. Thyroid strom. Endocrinol Metab Clin North Am 1993; 22:263–277.
33. Nishio W, Takahata O, Yamamoto Y, Mamiya K, Iwasaki H. [Perioperative management using propofol in a patient with uncontrolled preoperative hyperthyroidism]. Masui 2001; 50:655–657.
34. Yoshida D. Thyroid storm precipitated by trauma. J Emerg Med 1996; 14:697–701.
35. Burger AG, Philippe J. Thyroid emergencies. Baillieres Clin Endocrinol Metab 1992; 6:77–93.
36. Nishiyama K, Kitahara A, Natsume H, Matsushita A, Nakano K, Sasaki S, Genma R, Yamamoto Y, Nakamura H. Malignant hyperthermia in a patient with Graves' disease during subtotal thyroidectomy. Endocr J 2001; 48:227–232.
37. So PC. Unmasking of thyrotoxicosis during anaesthesia. Hong Kong Med J 2001; 7:311–314.
38. Palit TK, Miller CC III, Miltenburg DM. The efficacy of thyroidectomy for Graves' disease: a meta-analysis. J Surg Res 2000; 90:161–165.
39. Ladenson PW, Levin AA, Ridgway EC, Daniels GH. Complications of surgery in hypothyroid patients. Am J Med 1984; 77:261–266.
40. Weinberg AD, Brennan MD, Gorman CA, Marsh HM, O'Fallon WM. Outcome of anesthesia and surgery in hypothyroid patients. Arch Intern Med 1983; 143:893–897.
41. Sherman SI, Ladenson PW. Percutaneous transluminal coronary angioplasty in hypothyroidism. Am J Med 1991; 90:367–370.
42. Mantzoros CS, Evagelopoulou K, Moses AC. Outcome of percutaneous transluminal coronary angioplasty in patients with subclinical hypothyroidism. Thyroid 1995; 5:383–387.
43. Lenders JW, Keiser HR, Goldstein DS, Willemsen JJ, Friberg P, Jacobs MC, Kloppenborg PW, Thien T, Eisenhofer G. Plasma metanephrines in the diagnosis of pheochromocytoma. Ann Intern Med 1995; 123: 101–109.
44. Laursen K, Damgaard-Pedersen K. CT for pheochromocytoma diagnosis. Am J Roentgenol 1979; 134: 277–280.
45. Fujita A, Hyodoh H, Kawamura Y, Kanegae K, Furuse M, Kanazawa K. Use of fusion images of I-131 metaiodobenzylguanidine, SPECT, and magnetic resonance studies to identify a malignant pheochromocytoma. Clin Nucl Med 2000; 25:440–442.
46. Kelly DF, Gonzalo IT, Cohan P, Berman N, Swerdloff R, Wang C. Hypopituitarism following traumatic brain injury and aneurysmal subarachnoid hemorrhage: a preliminary report. J Neurosurg 2000; 93: 743–752.
47. McGlynn T, Simons R. Endocrine disorders. Kammerer W, Gross RMedical Consultation; The Internist on Surgical, Obstetric, and Psychiatric Services. 2nd ed. Philadelphia: Lippincott, Williams & Wilkins, 1990: 275–309.
48. Udelsman R, Norton JA, Jelenich SE, Goldstein DS, Linehan WM, Loriaux DL, Chrousos GP. Responses of the hypothalamic–pituitary–adrenal and renin–angiotensin axes and the sympathetic system during controlled surgical and anesthetic stress. J Clin Endocrinol Metab 1987; 64:986–994.

49. Lamberts SW, Bruining HA, de Jong FH. Corticosteroid therapy in severe illness. N Engl J Med 1997; 337:1285–1292.
50. Welsh GA, Manzullo E, Orth DN. The surgical patient taking corticosteroids. In: Rose BD, ed. UpToDate. Online 11.2 ed. Wellesley, MA: UpToDate, 2003.
51. Salem M, Tainsh RE, Jr, Bromberg J, Loriaux DL, Chernow B. Perioperative glucocorticoid coverage. A reassessment 42 years after emergence of a problem. Ann Surg 1994; 219:416–425.
52. Hadley JS, Hinds CJ. Anabolic strategies in critical illness. Curr Opin Pharmacol 2002; 2:700–707.
53. Takala J, Ruokonen E, Webster NR, Nielsen MS, Zandstra DF, Vundelinckx G, Hinds CJ. Increased mortality associated with growth hormone treatment in critically ill adults. N Engl J Med 1999; 341:785–792.
54. Singer PA, Sevilla LJ. Postoperative endocrine management of pituitary tumors. Neurosurg Clin N Am 2003; 14:123–138.
55. Vance ML. Perioperative management of patients undergoing pituitary surgery. Endocrinol Metab Clin North Am 2003; 32:355–365.
56. Olson BR, Gumowski J, Rubino D, Oldfield EH. Pathophysiology of hyponatremia after transsphenoidal pituitary surgery. J Neurosurg 1997; 87:499–507.
57. Rolih CA, Ober KP. Pituitary apoplexy. Endocrinol Metab Clin North Am 1993; 22:291–302.
58. da Motta LA, de Mello PA, de Lacerda CM, Neto AP, da Motta LD, Filho MF. Pituitary apoplexy. Clinical course, endocrine evaluations and treatment analysis. J Neurosurg Sci 1999; 43:25–36.
59. Fuchs S, Beeri R, Hasin Y, Weiss AT, Gotsman MS, Zahger D. Pituitary apoplexy as a first manifestation of pituitary adenomas following intensive thrombolytic and antithrombotic therapy. Am J Cardiol 1998; 81:110–111.
60. Otsuka F, Kageyama J, Ogura T, Makino H. Pituitary apoplexy induced by a combined anterior pituitary test: case report and literature review. Endocr J 1998; 45:393–398.
61. Watanabe K, Adachi A, Nakamura R. Reversible panhypopituitarism due to Cushing's syndrome. Arch Intern Med 1988; 148:1358–1360.
62. Chen JC, Amar AP, Choi S, Singer P, Couldwell WT, Weiss MH. Transsphenoidal microsurgical treatment of Cushing disease: postoperative assessment of surgical efficacy by application of an overnight low-dose dexamethasone suppression test. J Neurosurg 2003; 98: 967–973.

62a. Bochicchio D, Losa M, Buchfelder M, Institute of Endocrine Sciences OMIMI. Factors influencing the immediate and late outcome of Cushing's disease treated by transsphenoidal surgery: a retrospective study by the European Cushing's Disease Survey Group. J Clin Endocrinol Metab 1995; 80(11):3114–3120.

63. Jackson JA, Trowbridge A, Smigiel M. Fatal pulmonary thromboembolism after successful transsphenoidal hypophysectomy for Cushing's disease. South Med J 1990; 83:960–962.
64. Ben-Shlomo A, Melmed S. Clinical review 154: the role of pharmacotherapy in perioperative management of patients with acromegaly. J Clin Endocrinol Metab 2003; 88:963–968.
65. Seidman PA, Kofke WA, Policare R, Young M. Anaesthetic complications of acromegaly. Br J Anaesth 2000; 84:179–182.
66. Glowniak JV, Loriaux DL. A double-blind study of perioperative steroid requirements in secondary adrenal insufficiency. Surgery 1997; 121:123–129.
67. Bromberg JS, Alfrey EJ, Barker CF, Chavin KD, Dafoe DC, Holland T, Naji A, Perloff LJ, Zellers LA, Grossman RA. Adrenal suppression and steroid supplementation in renal transplant recipients. Transplantation 1991; 51:385–390.
68. Schlaghecke R, Kornely E, Santen RT, Ridderskamp P. The effect of long-term glucocorticoid therapy on pituitary–adrenal responses to exogenous corticotropin–releasing hormone. N Engl J Med 1992; 326: 226–230.
69. Esteban NV, Loughlin T, Yergey AL, Zawadzki JK, Booth JD, Winterer JC, Loriaux DL. Daily cortisol production rate in man determined by stable isotope dilution/mass spectrometry. J Clin Endocrinol Metab 1991; 72:39–45.
70. Kerrigan JR, Veldhuis JD, Leyo SA, Iranmanesh A, Rogol AD. Estimation of daily cortisol production and clearance rates in normal pubertal males by deconvolution analysis. J Clin Endocrinol Metab 1993; 76:1505–1510.
71. Yeung SJ, Lazo-Diaz G, Gagel RF. Metabolic and endocrine emergencies. In: Yeung SJ, Escalante CP eds. Oncologic Emergencies. 1st ed. Hamilton, Ontario: BC Decker Inc, 2002:103–144.
72. Kamoi K, Ebe T, Kobayashi O, Ishida M, Sato F, Arai O, Tamura T, Takagi A, Yamada A, Ishibashi M, et al. Atrial natriuretic peptide in patients with the syndrome of inappropriate antidiuretic hormone secretion and with diabetes insipidus. J Clin Endocrinol Metab 1990; 70:1385–1390.
73. Miller M. Syndromes of excess antidiuretic hormone release. Crit Care Clin 2001; 17:11–23.
74. Adrogue HJ, Madias NE. Hyponatremia. N Engl J Med 2000; 342:1581–1589.
75. Lampl C, Yazdi K. Central pontine myelinolysis. Eur Neurol 2002; 47:3–10.
76. Sterns RH. The management of symptomatic hyponatremia. Semin Nephrol 1990; 10:503–514.
77. Harrigan MR. Cerebral salt wasting syndrome. Crit Care Clin 2001; 17:125–138.
78. Betjes MG. Hyponatremia in acute brain disease: the cerebral salt wasting syndrome. Eur J Int Med 2002; 13:9–14.
79. Singer I, Oster JR, Fishman LM. The management of diabetes insipidus in adults. Arch Intern Med 1997; 157:1293–1301.

6

Principles of Bioimmunotherapy: Interferon, Interleukins, Growth Factors, Monoclonal Antibodies, Antisense

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I. INTRODUCTION

The evolving field of biotherapy represents the fourth modality of cancer care. Biotherapy has represented one of the first attempts to target cancer therapies more specifically toward the cancerous cell (1). The understanding of cancer as a multifactorial disease that results from mutations in specific classes of genes controlling the cell's life cycle will ultimately lead to ever newer and more specific forms of cancer therapy in the future. Categories of agents included under the umbrella of biotherapy are the interferons (IFNs), interleukins (ILs), hematopoietic growth factors, monoclonal antibodies, vaccines, and antisense technology.

The roots of biotherapy used therapies based on stimulation of the immune system. The use of immunotherapy as treatment for malignant disease can be traced back to the 19th century and even earlier. Immunotherapy, defined broadly, is a form of therapy that uses the immune system, its cells, and molecules, which serve as messengers among cells involved in immune responses to battle disease. The mission to understand and control the relationship between the immune system and cancer is linked to three observations that have withstood the test of time: spontaneous remissions in patients with cancer, the increased incidence of cancer in immunosuppressed patients, and the presence of lymphoid infiltrates in solid tumors (2).

In the 1980s, scientific advancement in the way biological agents were identified, isolated, produced, and used improved tumor responses to biotherapy and positioned it as a viable cancer-treatment modality. Advances in four areas were critical in establishing biotherapy as a promising treatment entity: (1) an

increased understanding of the intricate complexities of the immune system, (2) refinement of recombinant deoxyribonucleic acid (DNA) and hybridoma technology, (3) laboratory methods to produce large quantities of immune effector cells in culture, and (4) isolation and purification of new biologic products aided by advances in computer hardware and software.

II. DEFINITION AND CLASSIFICATION OF BIOTHERAPY

Biotherapy encompasses the use of agents derived from biological sources or of agents that affect biological responses (3). Primarily, these are products derived from the mammalian genome. In 1983, the National Cancer Institute, Division of Cancer Treatment Subcommittee on Biologic Response Modifiers, defined biological response modifiers (BRMs) as "agents or approaches that modify the relationship between tumor and host by modifying the host's biologic response to tumor cells with a resultant therapeutic effect" (4). This term distinguishes a class of agents composed of native and altered endogenous proteins that result in a specific desired cellular response. Most BRMs are either lymphokines or cytokines (5). The terms used to describe these agents and approaches have changed as scientific advances have increased our understanding of them. Historically, the term "immunotherapy" was used because the major focus of this therapeutic approach was modulation of the immune response. Although modulation of the immune response remains a major focus, the terms "biotherapy" or "biological therapy" have replaced "immunotherapy" because the scope of the field has widened to include "gene therapy." In actuality, most BRMs are a form of "gene therapy" since they are produced using recombinant DNA technology. Biological response modifiers, or more commonly biological agents—the agents used in this therapeutic modality—have pleiotropic effects, that is, they possess multiple actions. They are capable of producing immunologic actions, other biological effects, or a combination of these activities. Biotherapy is generally used as a global term to refer to all of these activities.

The specific categories of BRMs are described below in the order of their discovery and clinical uses. In addition, a summary of the most common side effects of each BRM is presented. This latter information should be of use to both anesthesiologists and critical care physicians.

A. Interferons

In the early 1930s, it was a known fact that cells infected with viruses were capable of protecting other cells from viral infection. In 1957, Isaacs and Lindemann (6) discovered the protein that partly explained this phenomenon and named it IFN because of its ability to "interfere" with viral replication. Within a few years, researchers began to identify the unique biological properties of this molecule (e.g., its antiproliferative and immunomodulatory cellular effects). As of 2003, five major species of IFN are known: alpha (α), beta (β), gamma (γ), omega (ω), and tau (τ) (7). Interferon-ω and interferon-τ remain in the early stages of study and not yet approved for therapeutic use in humans (7,8).

Cantell et al. (9) in Finland developed techniques for purifying IFN-α from donated human blood. This method proved to be costly as well as time and resource intensive and resulted in an impure product. However, it did provide the opportunity to begin to test this molecule as an antitumor agent in the late 1970s and early 1980s. The development of recombinant DNA technology in 1980 and the birth of the biotechnology industry led to the production of highly purified IFN molecules through recombinant technology. In 1981, the first human trials with recombinant IFN-α began in the United States (U.S.). Since then, research has led to the U.S. Food and Drug Administration (FDA) approval of IFN-α as treatment for multiple diseases and approval of IFN-β and IFN-γ as treatment for one disease each (see Table 1) (10,11).

The IFN family comprises a very complex set of proteins and glycoproteins. To date, two types and five species of IFNs have been described: Type I, which includes IFN-α, -β, -ω, and -τ and Type II, which includes IFN-γ. Interferons are termed pleiotropic cytokines, meaning they have multiple biological effects. Type I IFNs differ from Type II IFNs in their structure and their interaction with cell-surface receptors. Type I IFNs are more effective in inducing an antiviral state in cells, whereas type II IFNs are linked to the proper functioning of the immune system. Additionally, Type I IFNs share a common ligand-binding site, induce common biological effects, and are generally defined by the cell that produces them. Both IFN-α and IFN-ω are derived primarily from leukocytes, and IFN-β is derived from fibroblasts. Interferon-τ is derived from trophoblasts. Interferon-γ is secreted by CD8+ T cells and some CD4+ T cells. These cells secrete IFN-γ only when activated by IL-2 and IL-12 (7,8).

For IFN-α, the type principally used in treating patients with cancer, these effects can be summarized as antiviral, antitumor effects, immuomodulatory, and antiangiogenic activity. Virally infected cells synthesize and release IFN into the extracellular space. Interferon then binds to receptors on other cells and is internalized. The IFN-induced cells then produce several enzymes that can regulate the process of viral

Table 1 Type I and II Interferons in Clinical Use

Species	Subtype	Trade name	Manufacturer	FDA-approved indications
Alpha (α)	Recombinant alpha-A (IFN-α2a)	Roferon-A®	Hoffmann-LaRoche	Hairy-cell leukemia AIDS-related Kaposi's sarcoma Chronic myelogenous leukemia Chronic hepatitis C
	Recombinant alpha-2 (IFN-α2b)	INTRON-A®	Schering-Plough	High-risk melanoma Non-Hodgkins Lymphoma Hairy-cell leukemia AIDS-related Kaposi's sarcoma Condylomata acuminata Chronic hepatitis C Chronic hepatitis B (adult and pedi)
	Lymphoblastoid (IFN-αN1)	Wellferon®	Wellcome Foundation	Not commercially available in the United States – Approved for hepatitis C in patients 18 year
	Human leukocyte derived (IFN-αN3)	Alferon®	Interferon Sciences	Condylomata acuminata
	Recombinant consensus (IFN-Con_1)	Infergen®	Amgen	Chronic hepatitis C
Beta (β)	Recombinant beta-1a (IFN-β1a)	Avonex®	Biogen	Multiple sclerosis
	Recombinant beta-1a	Rebif®	Serono	Multiple sclerosis
	Recombinant beta-1b (IFN-β1b)	Betaseron®	Chiron/Berlex	Multiple sclerosis
Gamma (γ)	Interferon gamma-1b (IFN-γ1b)	Actimmune®	Intermune	Chronic granulomatous disease

[a] Denotes common side effects.

protein synthesis. Among the IFN-induced proteins important in the antiviral actions of IFNs are the RNA-dependent protein kinase (PKR), the 2′, 5′-oligoadenylate synthetase (OAS) and RNase L, and the Mx protein GTPases. Indirectly, the IFNs may mediate antiviral effects by stimulating cytotoxic T lymphocytes (CTLs) to lyse virally infected cells (12).

The alpha IFNs also exhibit antitumor or direct effects though cytostatic (i.e., prolongation of the cell cycle) effects on tumor cells which is thought to be achieved by modulation of OAS or cellular oncogenes. Interferon-α may also act synergistically with IFN-γ to promote cell lysis (8). Recently, research has demonstrated that IFN-α has proapoptotic effects in human tumor cells lines (13). Lastly, IFN-α exherts indirect antitumor effects through upregulation of Class I histocompatibility antigens (i.e., making cells more recognizable by the immune system) and through the stimulation of other immune cells such as natural killer cells, cytotoxic T cells and activation of macrophages (7,8).

Angiogenesis or neovascularization is now known to play a significant role in tumor metastasis. In addition to enabling the metastatic spread of tumor cells, the process of angiogenesis is also believed to reduce the tumor's accessibility to chemotherapeutic drugs (14). Endogenous IFN is one of the many negative regulators of angiogenesis. Of clinical note, IFN-α has demonstrated efficacy in the treatment of hemangiomas (15).

The IFNs have been referred to as the "prototype" biological agent and have undergone extensive molecular, preclinical, and investigational scrutiny. Interferon-α therapy now has an established role in the treatment of several advanced malignancies. For reviews of the use of IFN as cancer therapy, see Refs. 7, 8, 16, 17. Numerous phase II and phase III trials have demonstrated its efficacy as a single agent. Additional studies have shown its ability to induce responses in refractory neoplasms and to modify chromosomal disorders in disease such as chronic myelogenous leukemia (CML).

In 1986, just a few years after its introduction as an anticancer agent, the first IFN-α was approved by the FDA for its significant role in the treatment of hairy cell leukemia (HCL). Although there are now more effective treatments for HCL (e.g., cladrabine), it represents an important milestone as the first disease for which a biological agent received regulatory approval (11).

Shortly thereafter, in 1989, IFN-α received its second FDA approval for the treatment of acquired immunodeficiency syndrome (AIDS)-related Kaposi's

sarcoma (KS). It has been useful in patients with predominantly mucocutaneous disease. It is most effective in patients with limited lymphadenopathy, no history of opportunistic infections, absence of B symptoms (fever, night sweats, cachexia, and diarrhea), and an intact immune system (CD4 count greater than $200/mm^3$). Although initially approved as high-dose therapy [36 million international units (MIU) daily as induction therapy], current research is focusing on the use of lower doses and IFN in combination with antiviral agents (18,19).

Additional oncology indications in the United States for IFN-α include treatment of CML, as adjuvant therapy for melanoma, and for non-Hodgkin's lymphoma (NHL) (10,11). During the last four decades, the optimal first-line treatment for CML in chronic (stable) phase has progressed from alkylating agents, to hydroxyurea (HU), and then to IFN-α which was first approved for this indication in the late 1980s. Allogeneic stem-cell transplantation, which offers the chance of prolonged leukemia-free survival to about 20% of all CML patients, is the only certain approach to cure. Recently, the FDA approved imitimab, a new inhibitor specific for tyrosine kinase of the Bcr–Abl oncoprotein as frontline therapy for CML. Research will continue to investigate the role of IFN, both alone and in combination, in context with new and emerging therapies (20).

Melanoma, diagnosed and treated at its earliest stages, can be cured by surgery alone. However, when metastatic beyond the regional nodes, it is almost uniformly fatal. Adjuvant therapy targeted toward the treatment of microscopic residual disease after surgical resection has been the focus of numerous clinical investigations because this is the stage at which it is possible to have the greatest impact on disease-free and overall survival. Based on response rates in the range of 15% for patients with metastatic melanoma, many studies have centered on the use of IFN in the adjuvant setting. The reader is referred to Refs. 7, 8, 21, 22 for a review of these studies. In 1995, based on the results of an Eastern Cooperative Group (ECOG) trial, IFN-α2b was approved at high doses for the adjuvant treatment of melanoma. Since then, numerous studies worldwide have continued to evaluate the role of IFN in different doses, schedules, and as combination therapy. Overall, it appears that high-dose IFN increases disease-free survival, but does not prolong overall survival. Data continue to indicate that high-dose IFN-α2b should be offered to appropriately select intermediate- and high-risk patients with melanoma not involved in an experimental protocol (21).

In the past 15–20 years, IFN-α has been shown to be effective in the treatment of non-Hodgkin's lymphoma, with response rates of 40–50%. These encouraging single-agent results have led to the incorporation of these agents into combination programs. Interferon-α2b was approved by the FDA in 1997 for use with CHOP-like regimens in patients with advanced low-grade follicular NHL. The approval was based on research by the French co-operative group, Groupe d'Etude des Lymphomes Folliculaires (GELF) (23). Interferon has been incorporated into combination chemotherapy programs either as a maintenance strategy or as concurrent therapy. Most studies have shown a favorable impact of IFN on failure-free survival but not on overall survival. Some studies have shown no impact at all. A major barrier has been management of IFN-associated side effects. Many practitioners feel that the modest favorable impact of IFN is offset by the fatigue and other side effects of the drug, even though a quality-of-life analysis has concluded that the incorporation of IFN is worthwhile (24). In a variety of malignancies (e.g., multiple myeloma, T-cell malignancies, renal cell cancer, bladder cancer, and squamous carcinomas of the skin and cervix in combination with the retinoids), the use of IFN remains experimental (7).

Interferon has efficacy in a variety of other diseases as well. In viral diseases, IFN-α has clinical applications for the treatment of hepatitis B, hepatitis C (7,25), and condylomata acuminata. Chronic granulomatous disease (CGD) is an inherited abnormality of certain cells of the immune system that "ingest" bacteria and kill them (phagocytic cells). The abnormality results in chronic infection by certain types of bacteria that result in severe, recurrent infections of the skin, lymph nodes, liver, lungs, and bone. Because treatment with IFN-γ led to a 70% reduction of serious infections in patients with this disease, this agent was approved in 1990 (7,26). In 1993, IFN-β was approved for the treatment of relapsing-remitting (RR)-multiple sclerosis (MS). Interferon therapy provides hope for an effective treatment for MS since the disease was first described in 1868 (10,11,27,28).

The toxicity profile of IFN-α is dependent on the dose, the route of administration, and the treatment schedule (7,29). The majority of side effects associated with IFN are constitutional. They include fatigue, fever, chills, myalgias, headache, and anorexia. This constellation of side effects is often referred to as flu-like symptoms. They are reported almost universally following initial administration of treatment. The appearance of subsequent tachyphylaxis or tolerance depends on the dose, the route, and the schedule of administration. The chronic side effect of fatigue can be the most clinically challenging and patients often report a negative impact on quality of life (30).

In summary, IFN-α was the first pure human protein found to be effective in the treatment of cancer. The most important future direction for research on IFNs and possibly their greatest value will be in prolonging the disease-free interval and, ultimately, survival. Numerous studies have demonstrated improvement in these areas. The hope remains that as biotherapy with IFN becomes applied to earlier-stage disease, greater gains in survival and disease-free interval may be sustained. The challenge remains to maximize the use of this drug while reducing the patient's experience of side effects.

B. Interleukins

The ILs are a family of cytokines that represent a major communication network in living organisms. Interleukins are proteins that exist as natural components of the human immune system and they are produced by monocytes, endothelial cells, astrocytes/glial cells, fibroblasts, bone marrow stromal cells, and thymocytes as well as lymphocytes. The primary function of ILs is the immunomodulation and immunoregulation of leukocytes; however, most ILs are capable of inducing multiple biological activities in a variety of target cells (31).

The term ''interleukin'' was originally used to define substances produced by leukocytes that had activity on other leukocytes. However, this early definition fails to adequately describe the production and range of activities now attributed to the family of ILs. As a result, of the many ILs described in early research, each had several names, each of which describes a different function. In 1986, the Sixth International Congress of Immunology decided that new cytokines would be named according to their biological properties but that, on identification of the amino-acid sequence, a sequential IL number would be assigned (32). To qualify as an IL, the cytokine must be documented to have a unique amino-acid sequence and functional activity involving leukocytes. The evidence is evaluated by the Nomenclature and Standardization Committee of the International Cytokine Society and the Union of Immunological Societies, which then make a recommendation to the World Health Organization (33). There is no ranking in terms of importance or specific activity.

Over 25 ILs have so far been identified and isolated as of June 2003 and are undergoing either preclinical or clinical evaluation (34,35). Only IL-2 and IL-11 have been approved by the FDA for use in patients with cancer. Interleukin-2 is indicated for treatment of metastatic renal cell cancer (metastatic RCC) and metastatic melanoma. Interleukin-11 has been approved for use in preventing severe thrombocytopenia and in decreasing the need for platelet transfusions following myelosuppressive therapy (10,11).

Various ILs may produce autocrine, paracrine, or endocrine actions within the body. Autocrine action refers to the binding and activation of the same cell that produced the IL. Paracrine action describes the binding and activation of nearby cells. Endocrine action occurs when ILs are secreted and bind to distant cells in the body (31). Primarily, the ILs affect local or regional cells rather than distant cells as seen in endocrine actions.

The complex balance between cellular activation and immunoregulation is orchestrated by the secretion of ILs and the resultant effects of the immune system on cells. Actions produced by the ILs may by redundant, synergistic, or antagonistic. Redundant actions are similar actions that may be produced by different ILs. Synergistic activity occurs when more than one IL is essential to produce activity in a particular target cell. Antagonistic effects occur when an IL inhibits the target-cell activity induced by another cytokine (36).

Interleukin-2 is a lymphokine first described in 1976 as a T-cell growth factor (37). Produced primarily by activated T-helper (T_h) cells, IL-2 is a messenger-regulatory molecule that has profound immunomodulatory effects in the body. The regulation of IL-2 production is dependent on the activation of T cells by antigens. Its biologic effects are numerous and include stimulation of the growth and maturation of subpopulations of T cells, including cytotoxic T cells (killer T cells), and the proliferation of natural killer cells. It is capable of enhancing humoral immune responses and stimulates the production of other immune messenger molecules as well. Its potent stimulation of immune responses led to clinical investigation in a variety of diseases; however, the majority of clinical successes thus far have been seen in patients with renal cell cancer and melanoma. It is the first agent available for the treatment of metastatic cancer that functions solely through stimulation of the immune system.

Initial clinical trials with IL-2 were high-dose bolus regimens, and often included the administration of immune effector cells. Although some complete responses were achieved, the side effects were substantial and the regimen was not easily replicated in the community setting. Interleukin-2 first received regulatory approval for the treatment of adults with metastatic RCC in 1992 based on combined data from randomized clinical trials. Two hundred and fifty-five patients with metastatic RCC were treated with single-agent IL-2 in seven clinical studies conducted at 21 institutions. In 1998, IL-2 was approved for the treatment of metastatic melanoma based on studies involving 270 patients with

metastatic melanoma treated with single-agent IL-2 in eight clinical studies conducted at 22 institutions. In these clinical trials, IL-2 was given by 15 min intravenous (IV) infusion every 8 hr for up to 5 days (maximum of 14 doses). No treatment was given on days 6–14 and then dosing was repeated for up to 5 days on days 15–19 (maximum of 14 doses). These two cycles constituted one course of therapy. Patients could receive a maximum of 28 doses during a course of therapy. In practice >90% of patients had doses withheld. Metastatic RCC patients received a median of 20 of 28 scheduled doses of IL-2. Metastatic melanoma patients received a median of 18 of 28 scheduled doses of IL-2 during the first course of therapy (38).

Because of the significant toxicity associated with high-dose regimens, current research has focused on regimens using subcutaneous administration of IL-2 in the ambulatory setting or infusion by an ambulatory pump both in renal cancer and melanoma, the goal being to decrease toxicity and maintain clinical responses. With these regimens, IL-2 doses are lower, generally in the range of 3–10 MIU/m^2, given 3–5 days/week over several weeks. Patients may also receive concomitant therapy with IFN-α and/or chemotherapy. Low-dose IL-2 therapy has produced disappointing clinical response rates in melanoma. Although the response rates to low-dose IL-2 have been better in renal cell carcinoma, the quality of these responses relative to those seen with high-dose IL-2 therapy remains a concern. The addition of IL-2 to chemotherapeutic regimens (biochemotherapy) has been associated with overall response rates (ORRs) of up to 60% in patients with metastatic melanoma, but this has yet to be translated into a confirmed improvement in survival. Clinical trials have not demonstrated superiority for combinations of IL-2 and IFN-α than high-dose IL-2 alone. It remains to be determined whether further modifications of IL-2-based regimens or the addition of newer agents to IL-2 will produce better tumor response and survival (39,40).

The side effects profile for patients who receive IL-2 therapy differs depending on the dose, route, and schedule of IL-2 given. In general, high-dose IL-2 therapy produces more severe toxic effects which have the potential to involve nearly every major organ system. Patients who are to be treated with IL-2 should have normal cardiac, pulmonary, hepatic, and CNS function at the start of therapy. For a summary of toxicities, see Table 2 at the end of this chapter.

In summary, IL-2 has demonstrated efficacy in two very difficult-to-treat diseases, RCC and metastatic melanoma. Future investigations of IL-2 will involve combination regimens that include other cytokines, activated lymphocytes, vaccines, and chemotherapeutic agents for these two malignancies and a variety of malignancies and other diseases. Doses, routes of administration, and schedules will be altered to attempt to achieve greater efficacy with less toxic effects. In some patients who have received therapy with IL-2 or RCC or metastatic melanoma, startling and durable complete remissions have been seen. However, the percentage of patients achieving this response is low. In the future, new technologies, such as microarray technology, may help clinicians determine, which subset of patients will best respond to therapy with IL-2.

C. Hematopoietic Growth Factors

Myelosuppression is a common dose-limiting factor for many cancer patients receiving cytotoxic treatment, and contributes to the need for hospitalization, IV antibiotic administration, transfusion of blood products, dose reduction, and treatment delays. In addition, it may have significant negative effects on patient's quality of life or even response to treatment. Over the past several years, a great deal of progress has been made in understanding the process of hematopoiesis by which mature cellular elements of blood are formed (41). Hematopoietic growth factors are a family of regulatory molecules that play important roles in the growth, survival, and differentiation of blood progenitor cells, as well as in the functional activation of mature cells. In the last decade, several hematopoietic growth factors have become available for attenuating hematologic toxicity of chemotherapy. Table 3 lists the recombinant human hematopoietic growth factors that have been approved by the FDA for clinical use: granulocyte colony-stimulating factor [G-CSF, filgrastim (Neupogen)], yeast-derived granulocyte–macrophage colony-stimulating factor [GM-CSF, sargramostim (Leukine)], erythropoietin [EPO (Epogen, Procrit)], and interleukin-11 [IL-11, oprelvekin (Neumega)]. More recently, two new growth factors of second generation, pegfilgrastim and darbepoetin alfa with a long serum half-life, have received FDA approval in oncology setting. In addition, several other hematopoietic cytokines are under clinical development (34,42).

Granulocyte colony-stimulating factor is lineage specific for the production of functionally active neutrophils. It has been extensively evaluated in several clinical scenarios. It was first approved in 1991 for clinical use to reduce the incidence of febrile neutropenia in cancer patients receiving myelosuppressive chemotherapy. This broad initial indication has since been expanded even further to include many other areas of oncologic practice, such as mobilization of progenitor

Table 2 Side Effects of Biologic Agents

System	Interferons	Interleukin-2	Hematopoietic growth factors	Monoclonal antibodies	Vaccines	Antisense-oligos
Central nervous system	Impaired concentration, headache, lethargy, confusion, depression	Impaired concentration, headache, lethargy, confusion, anxiety, psychoses, depression	Rare	Rare	Rare	Rare
General	Constitutional symptoms,[a] fatigue[a]	Constitutional symptoms,[a] fatigue,[a] weight gain during therapy, followed by weight loss[a]	Mild constitutional symptoms, fatigue (mostly with GM-CSF)	Constitutional symptoms, allergic reactions, rare anaphylaxis	Constitutional symptoms,[a] chills, fatigue[a]	Fever,[a] malaise
Cardiovascular	Hypotension, tachycardia, arrhythmias, rare myocardial ischemia	Hypotension,[a] edema,[a] ascites arrhythmias, decreased systemic vasculoresistance[a]	Rare hypertension with epoetin alfa	Hypotension, chest pain	Rare	Rare
Pulmonary	Rare	Dyspnea, pulmonary edema	Rare occurrence of dyspnea with first dose of GM-CSF	Dyspnea, wheezing	Rare	Rare
Renal/hepatic	Proteinuria, elevated liver enzymes[a]	Oliguria,[a] increased BUN, creatinine,[a] proteinuria, azotemia, increased bilirubin, SGOT, SGPT, LDH	Rare elevation of LDH, alkaline phosphatase with G-CSF	Rare	Rare	Elevation of liver enzymes
Gastro-intestinal	Nausea/vomiting, diarrhea, anorexia[a]	Nausea/vomiting,[a] diarrhea,[a] anorexia,[a] mucositis	Rare	Nausea/vomiting	Rare	Nausea and vomiting,[a] mucositis,[a] diarrhea
Genitourinary	Impotence, decreased libido	Decreased libido	Rare	Rare	Rare	Rare
Integumentary	Alopecia, rash	Rash,[a] dry desquamation,[a] erythema,[a] pruritus,[a] inflammatory reaction at injection sites[a]	GM-CSF/G-CSF: inflammation at injection site, rare occurrence of rash	Urticaria, rash, pruritus	Pruritus, inflammatory reaction at injection sites	Rare
Hematologic	Leukopenia,[a] anemia, thrombocytopenia	Anemia,[a] thrombocytopenia, lymphopenia,[a] eosinophilia[a]	Leukocytosis,[a] eosinophilia (GM-CSF).[a] Note—expected biologic effect of HGF used	In hematologic malignancies, leukopenia	Rare	Platelet aggregation,[a] thrombocytopenia bleeding[a]
Musculo-skeletal	Myalgias,[a] arthralgias[a]	Myalgias, arthralgias	Bone pain[a] with GM- and G-CSF	Rare arthralgias	Myalgias	Bone pain,[a] myalgias,[a] arthralgias[a]

[a] Denotes common side effects.
Source: From Ref. 41a.

Table 3 FDA-Approved Hematopoietic Growth Factors/Cytokines

Cell lineage	Growth factor/cytokine	Trade name	Approval date	Manufacturer/distributor
Myeloid lineage	G-CSF (filgrastim)	Neupogen	1991	Amgen
	GM-CSF (sargramostim)	Leukine	1991	Immunex/Berlex
	Pegfilgrastim	Neulasta	2002	Amgen
Erythroid lineage	Epoetin alfa	Epogen	1989 (Nephrology)	Amgen
		Procrit	1993 (Oncology)	OrthoBiotech
	Darbepoetin alfa	Aranesp	2001 (Nephrology) 2002 (Oncology)	Amgen
Megakaryocytic lineage	Interleukin-11 (oprelvekin)	Neumega	1997	Genetics Institute/Wyeth

cells, stimulation of neutrophil recovery following high-dose chemotherapy with stem-cell support. In addition, G-CSF is indicated to increase neutrophil production in endogenous myeloid disorders, such as congenital neutropenic states. The recommended dose of recombinant human G-CSF (Neupogen) is 5 μg/kg/day. Granulocyte colony-stimulating factor is used at a higher dose (10 μg/kg/day) for mobilization of progenitor cells and following bone marrow transplantation (BMT). Outside of the context of stem-cell mobilization and transplantation, however, there is no data indicating that doses in excess of 5 μg/kg/day are ever required.

Myeloid growth factors have been remarkably well tolerated based on extensive clinical experience with these cytokines over the past decade. The predominant side effect observed with the use of G-CSF is mild-to-moderate bone pain, which is usually seen at the initiation of G-CSF therapy or at the very beginning of neutrophil recovery. Occasionally, the pain can be severe with vigorous marrow response to CSF stimulation, and may require analgesics for control (41,42).

Granulocyte–macrophage colony-stimulating factor, primarily a myeloid-lineage-specific growth factor, stimulates the production of neutrophils, monocytes, and eosinophils. It received a more narrow FDA approval in 1991 for clinical use in patients with nonmyeloid malignancies undergoing autologous BMT. Since that initial indication, GM-CSF has also been approved for an expanded range of conditions, such as mitigation of myelotoxicity in patients with leukemia who are undergoing induction chemotherapy. To date, no large-scale randomized trials have compared the efficacy of the two CSFs in the same clinical setting. Future comparative trials may help determine the optimal clinical utility of these CSFs in different clinical situations.

The recommended dose of yeast-derived GM-CSF following autologous BMT is 250 $\mu g/m^2$/day given by a 2-hr IV infusion. In phase I and II studies in the chemotherapy setting, activity has been observed at doses ranging from 250 to 750 $\mu g/m^2$/day. In patients with MDS, neutrophil responses have been seen at much lower doses. Yeast-derived GM-CSF (sargramostim) is generally well tolerated at recommended doses. In the transplant setting, no excessive toxicity is seen in patients treated with this form of GM-CSF, as compared with controls. In other settings, the most commonly reported side effects of GM-CSF have included constitutional symptoms, such as fever, bone pain, myalgia, headaches, and chills. These side effects are seen more frequently when GM-CSF is administered at higher doses and by continuous IV infusion than when given at recommended doses by the SC route. In patients with MDS, the dose can be titrated to the smallest effective level to avoid untoward side effects (41,42).

Erythropoietin was the first hematopoietic growth factor to become commercially available for clinical use in the United States. Recombinant human EPO has been approved for the treatment of anemia of chronic renal failure in predialysis or dialysis patients, anemia associated with zidovudine (Retrovir) therapy in patients infected with human immunodeficiency virus (HIV), anemia in cancer patients receiving chemotherapy, and anemia in patients scheduled for elective, noncardiac, and nonvascular surgery.

The anemia caused by chemotherapy is due mainly to drug effects on bone marrow precursor cells and is proportional to chemotherapy dose intensity. In addition, with platinum agents, anemia may be related to renal effects on these drugs on EPO production. Several trials, both randomized and nonrandomized, support the finding that EPO can significantly reduce transfusion requirements and improve patient's reported quality of life (41,43). Overall, about 60% of cancer patients receiving chemotherapy respond to EPO treatment. Therefore, patient selection is important to ensure the cost effectiveness of EPO therapy. Available data suggest that patients with baseline anemia or a fall in hemoglobin value >2 g/dL after the first cycle of chemotherapy are more likely to need

blood transfusions. The best predictors of a clinical response to EPO therapy are an early rise in hemoglobin values and an increase in reticulocyte counts. The current FDA approved initial dose of EPO in cancer patients is 150 U/kg SC three times a week, which can be increased to 300 U/kg three times weekly if an adequate response does not occur after 4 weeks of therapy. However, a more common practice, based on data from several clinical trials, is to administer EPO at a dose of 40,000 units SC once weekly to be increased to 60,000 units weekly in nonresponders. Patients who do not respond after 8 weeks of EPO therapy (despite a dose increase) are unlikely to respond to higher doses. Erythropoietin has been well tolerated in cancer patients receiving chemotherapy. Hypertension associated with a significant rise in hemoglobin has been observed rarely in cancer patients receiving EPO therapy. Occasionally, seizures have been observed in patients with underlying CNS disease and in the context of a significant rise in blood pressure (41,43).

Severe thrombocytopenia requiring platelet transfusions is an uncommon acute problem with standard dose chemotherapy; however, it can represent a cumulative problem with the many chemotherapeutic regimens especially in heavily pretreated patients. Several hematopoietic cytokines with thrombopoietic activity have been evaluated in clinical trials. These include IL-l, IL-3, IL-6, IL-11, thrombopoietin (TPO), megakaryocyte growth and development factor (MGDF), and PIXY 321. Most of these cytokines have shown modest thrombopoietic activity and mediate a multitude of biological effects, including some undesirable effects. To date, IL-11 is the only thrombopoietic cytokine that has received FDA approval for clinical use (41,44).

Interleukin-11 is a pleiotropic cytokine which acts synergistically with other hematopoietic growth factors, such as TPO, IL-3, and stem cell factor (c-kit ligand), to promote the proliferation of hematopoietic progenitor cells and to induce maturation of megakaryocytes. It was approved by the FDA to prevent severe thrombocytopenia and to reduce the need for platelet transfusions following myelosuppressive chemotherapy in patients with nonmyeloid malignancies who are at risk of severe thrombocytopenia (45). The recommended dose of IL-11 in adults is 50 μg/kg SC once daily and is continued until the postnadir platelet count is $\geq 50{,}000/mm^3$. Dosing beyond 21 days per treatment cycle is not recommended. Patients treated with IL-11 commonly experience mild-to-moderate fluid retention, as manifested by peripheral edema and/or dyspnea. In some patients, pre-existing pleural effusions have increased during IL-11 administration. In addition, moderate decreases in hemoglobin values (thought to be related to dilutional anemia) have also been observed. Interleukin-11 should be used with caution in patients with a history of cardiac arrhythmias, since palpitations, tachycardia, and atrial arrhythmias have been reported in some patients receiving this agent (44,45).

Thrombopoietin is a lineage-dominant hematopoietic cytokine that regulates proliferation and maturation of cells of the megakaryocyte/platelet lineage. Results of initial clinical trials using truncated or full-length forms of the TPO molecule indicate that TPO is a powerful stimulus for the production of megakaryocytes and normal platelets in humans and that it enhances platelet recovery following chemotherapy (46–48). However, clinical development of MGDF, a truncated version of TPO, was halted due to the occurrence of neutralizing antibodies directed against TPO. However, similar antibodies have not been detected with the full-length version of recombinant human TPO. Recombinant human thrombopoietin (rhTPO) is a full-length molecule that is glycosylated. This carbohydrate moiety, although, not required for thrombopoietic activity, it contributes to a long circulating half-life to the molecule (18–32 hr). Thus, a single dose of rhTPO results in a platelet increase that is sustained for long time, with a peak response around day 12 and return of the counts close to a baseline at 3 weeks. This delayed peak response has contributed in part to a complexity in development of this molecule (49,50). With the regimens that cause late nadir (e.g., carboplatin), rhTPO-administered postchemotherapy has been shown to be effective in attenuating the severity of thrombocytopenia and the need for platelet transfusions (48). However, with the regimens that cause early nadir, rhTPO-administered postchemotherapy has not shown consistent effect. Recently, it has been shown that administration of rhTPO both before and after chemotherapy reduced the severity of thrombocytopenia (51). Thus, future trials will need to optimize the dose/schedule of this agent in chemotherapy and other settings where severe thrombocytopenia is problematic. Recent studies have also shown utility of this growth factor in increasing plateletpheresis yield in normal donors and in cancer patients for cryopreservation and autologous platelet transfusions to support during chemotherapy-induced severe thrombocytopenia (52,53). This strategy may be quite useful in the management and, in certain high-risk patients, in the prevention of alloimmunization and platelet refractoriness.

Recently, longer-acting hematopoietic growth factors, pegfilgrastim (Neulasta) and darbepoetin alfa (Aranesp) have been developed. Both these molecules were created to provide therapeutic agents with a long

half-life to reduce the frequency of administration (54–60).

Pegfilgrastim is manufactured by the conjugation of a 20-kDa polyethylene glycol (PEG) moiety to the amino terminal residue of filgrastim. Pegfilgrastim's mechanism of action is similar to filgrastim (54). Filgrastim is cleared from the circulation by a combination of renal and neutrophil-mediated clearance. Pegylation of filgrastim makes its molecular size greater and thus reduces its renal clearance, which then results in a greater dependence on neutrophil-mediated clearance. Elimination half-life of filgrastim is approximately 3.5 hr, whereas, plasma half-life of pegfilgrastim is approximately 46–62 hr in healthy volunteers. However, in cancer patients receiving chemotherapy, clearance is directly related to neutrophil recovery which supports the rationale for administering pegfilgrastim once per cycle of chemotherapy (55–57). In the phase III trials, pegfilgrastim administered once per cycle at a dose of 6 mg fixed dose or 100 mcg/kg provided neutrophil support similar to that with filgrastim administered daily. Pegfilgrastim is FDA approved for the indication of prevention of infections, as manifested by febrile neutropenia, in patients with nonmyeloid malignancy receiving myelosuppressive chemotherapy.

Darbepoetin alfa has a half-life approximately three times longer than that of epoetin alfa (58). Early observations indicated that increasing the sialic acid content of epoetin alfa would increase its biological activity. Darbepoetin alfa was created by using site-directed mutagenesis to allow for the attachment of two additional sialic-acid-containing carbohydrate chains. Despite the structural differences, darbepoetin alfa binds to the same receptor as endogenous erythropoietin and exerts the same receptor-mediated erythropoietic action. Darbepoetin alfa has been approved for the treatment of anemia in patients with renal failure and in patients with nonmyeloid malignancies with chemotherapy-related anemia. Clinical trials in cancer patients receiving chemotherapy have shown that darbepoetin is safe and effective when administered at every 1-, 2-, or 3-week intervals (59,60). The results of these trials have shown that darbepoetin alfa administered at every 2 weeks has similar efficacy to epoetin alfa administered every week. The randomized comparative trials are ongoing.

In conclusion, the availability of hematopoietic regulatory molecules have reduced hematologic toxicity and related complications in cancer patients receiving cytotoxic treatment. Although this first generation of growth factors has been widely used, the necessity of frequent administration has posed an inconvenience and compliance issues for some patients. The recent introduction of the new molecules with a longer serum half-life would simplify patient management. The future directions with the growth factors would likely involve use of the new agents designed with the need for infrequent dosing, less potential for immunogenicity and toxicity, and expanding role in improving overall treatment outcome.

D. Monoclonal Antibodies and Immunoconjugates

In the early 1900s, Paul Ehrlich envisioned that antibodies could be used as "magic bullets" to deliver drugs and toxins to tumor cells. This dream was not realized until 1975 when Köhler and Milstein (61) published a seminal article describing a method to produce large quantities of antibodies recognizing a single antigen (Ag). The technique involved fusing B-lymphocytes from mice immunized with tumor cells or cell lysates to an "immortal" murine plasma cell resulting in a "hybridoma" capable of secreting unlimited quantities of pure "monoclonal" antibodies (Mab). Following selection in "HAT-free" medium hybridomas could be grown continuously in cell culture or as mouse ascites; supernatants were then screened for the Mab(s) of choice.

Monoclonal antibodies can mediate antitumor effect either directly or indirectly (Table 4). They may lyse tumors through interaction of the Fc end with human complement or immune effector cells resulting in antibody-dependent cell-mediated cytotoxicity (ADCC). Several Mab have been capable of regulating cell growth through receptor–ligand interactions, or as anti-idiotype vaccines. Indirect mechanisms include the use of immunoconjugates consisting of Mab coupled to radionuclides, drugs, toxins, or cytokines to target tumors (62).

The advent of hybridoma technology resulted in large quantities of pure Mab specific for tumor-

Table 4 Strategies for In Vivo Use of Monoclonal Antibodies as Anticancer Therapy

Antibody alone
Complement mediated cytotoxicity (CMC)
Antibody-dependent cell-mediated cytotoxicity
ADCC
Regulatory (ligand/receptor) interactions
Anti-idiotype vaccine
Immunoconjugates
Radiolabeled antibodies
Immunotoxins
Chemotherapy-antibody conjugates
Cytokine immunoconjugates
Cellular immunoconjugates

Source: From Ref. 62.

associated Ag. In the early 1980s and 1990s, a number of clinical trials were performed in cancer patients (reviewed in Refs. 63, 64). Although toxicity was minimal, unmodified murine Mab were largely unsuccessful in mediating antitumor effects. This was due to several problems which could be categorized under the following headings (Table 5): (1) properties of the tumor Ag, (2) properties of the target cell, (3) properties of the Mab themselves, and (4) immunologic mechanisms. With respect to (1), Ag shedding and/or low levels of expression on tumors resulted in inadequate Mab binding to tumor, formation of immune complexes, and rapid clearance from the circulation. Binding of Mab to tumors often resulted in internalization of the Mab/Ag complex with failure of re-expression of Ag (termed "modulation"). The majority of Mab upon binding to tumors were unable by themselves to initiate downstream intracellular events which resulted in tumor lysis or apoptosis. With respect to problems (3) and (4), murine Mab were extremely immunogenic in humans resulting in the formation of human antimouse antibodies (HAMA) (65), or were unable to mediate immune effector functions such as ADCC or complement-mediated lysis.

Several major innovations occurred which addressed each of the above issues (66): (1) recombinant DNA techniques such as phage libraries resulting in the ability to produce mouse–human "chimeric" or "humanized" Mab were developed (Fig. 1). By insertion of the mouse variable region genes along with the human constant region genes into an expression vector, "chimeric" Mab could be produced containing the mouse variable region and human constant region of light and heavy chains, respectively. Similarly, the insertion of complementarity-determining (CD) regions [i.e., the sections of variable light (V_L) chain which interact with Ag] into the human variable/constant region framework resulted in the production of "humanized" Mab. Recently, completely human Mab have been made using transgenic mice containing human immunoglobulin genes (67). Chimeric and humanized Mab are much less immunogenic and are more capable of mediating effector functions, (2) humanized Mab were produced against growth factor receptors such as the epidermal growth factor receptor (EGFr) family, which upon binding to receptor could inhibit ligand binding and subsequent intracellular signaling events, eventually leading to apoptosis or cell death (Fig. 2), and () stable, more potent immunoconjugates—Mab bound to radioisotopes, drugs, or toxins—were developed. These innovations resulted in a number of newer Mab/immunoconjugates which mediated more potent antitumor effects and were less able to induce antihuman antibodies.

The first Mab to be approved and licensed by the FDA for treatment of cancer was rituximab

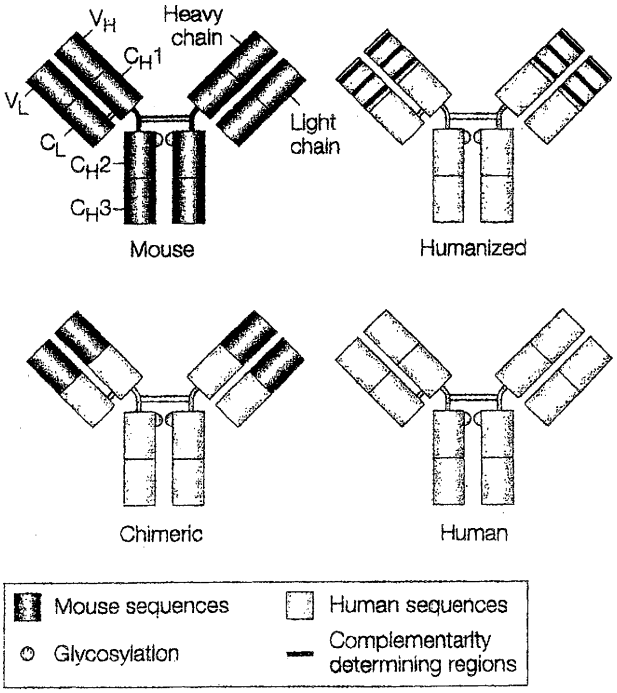

Figure 1 Types of Mab: *Murine Mab*: Derived by hybridoma technology. *Chimeric Mab*: Obtained by joining the antigen-binding variable domains (V_L, V_H) of a mouse Mab to human constant domains (C_L, C_H). *Humanized Mab*: Grafting antigen-binding loops, or complementary determining (CD) regions from a moise Mab into a human IgG. *Human Man*: Obtained from very large, single-chain variable fragments (scFvs), Fab phage display libraries, or transgenic mice that contain human Ig genes. *Source*: Adapted from Ref. 66.

Table 5 Barriers to Effective Therapy with Unmodified Monoclonal Antibodies

Properties of antigen	*Properties of monoclonal antibodies*
Secretion/shedding of antigen	Immunogenicity
Low-level expression	Correct isotype
Modulation	Ability to trigger apoptosis
Permissive for lysis/apoptosis	Accessibility to tumor masses
	Effector mechanisms
Properties of target cell	Quantity
Cellular defense mechanisms	Activation
	Recruitment to tumor sites

Source: Adapted from Ref. 69a.

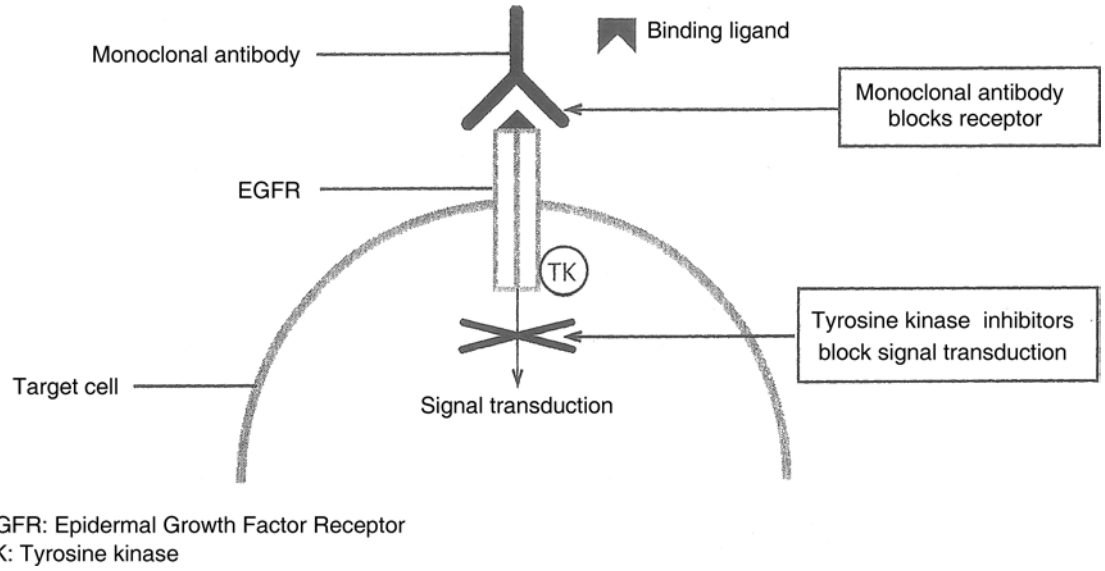

Figure 2 Mechanisms of anti-EGFr Mab inhibition: Mab binding to receptor blocks ligand interactions which results in inhibition of tyrosine kinase activation along with several proliferative signaling pathways that are associated with antiapoptotic, pro-proliferative signaling processes. *Source*: Adapted from Bristol-Myers Squibb Oncology.

(Rituxan^{TM}). Rituximab is a chimeric Mab which binds to the CD20 Ag, a differentiation Ag found on developing and mature B cells. Over 90% of non-Hodgkin's lymphomas express CD20 (68).

In a pivotal phase II trial, McLaughlin et al. (69) treated low-grade NHL patients refractory to chemotherapy with weekly infusions of rituximab for a duration of 4 weeks. The ORR was 48%. More importantly, durable responses occurred as late as 6 months after treatment and lasted for a median of 11 months. Side effects were mild and included minor allergic-type reactions. Ten percent of patients had grade 3–4 toxicity including neutropenia, thrombocytopenia, hypotension, bronchospasm, angioedema, and recurrence of pre-existing cardiac conditions. Ninety-seven percent completed all four infusions.

Since FDA approved rituximab has had potential in combination with chemotherapy (70), resulting in higher initial response rates and more prolonged time to progression (TTP). Rituximab has also shown promise in other hematologic malignancies and autoimmune diseases such as chronic lymphocytic leukemia (71), immune thrombocytopenic purpura (72), and autoimmune hemolytic anemia (73). A presumptive mechanism for its efficacy in the latter two diseases is prolonged B-cell lymphopenia with decrease in auto-antibody formation.

Trastuzumab (Herceptin^{TM}) is a humanized Mab which has been recently approved for the treatment of metastatic breast cancer. Trastuzumab binds to the HER2/neu oncoprotein receptor, a member of the EGFr family (74). The receptor is expressed in 30% of breast cancers and is associated with a poor prognosis (75). By binding to the EGFr receptor, the Mab inhibits ligand binding and subsequent downstream signaling pathways involved in tumor mitogenesis, motility, and invasion (Fig. 2).

Cobleigh et al. (76) performed a phase II trial of trastuzumab in which patients received a loading dose of 4 mg/kg i.v. followed by 2 mg/kg weekly. Toxicity was minimal and the ORR was 15%. Based on preclinical data that demonstrated that trastuzumab had additive or synergistic effects on tumors when combined with chemotherapy (77), a randomized, multicenter phase III trial was performed in which response rate, TTP, and overall survival (OS) were compared for patients who received adriamycin/cytoxan (AC) or taxol (T) alone at the time of first relapse for metastatic disease to a combination of either AC + Herceptin (H) or T + H. The ORR, TTP, and OS were significantly better for both AC + H and T + H compared to either drug alone (78). A downside to treatment with the combination of AC + H, however, was an increased incidence of cardiac toxicity. Additional trials of other chemotherapy drugs including platinum compounds and Herceptin appear promising and Mab/drug combinations are being compared to chemotherapy alone in the adjuvant situation. Another Mab from the EGFr receptor family which has been shown to synergize with chemotherapy and/or radiation is cetuximab, an IgG1 chimeric Mab which binds to the EGFr. Cetuximab has recently shown promise when combined with chemotherapy for the treatment of head and neck cancer and pancreatic cancer (79,80).

Several other Mab have been approved for cancer treatment especially for hematological malignancies. For a review, see Ref. 81.

Mab have also shown promise when conjugated to radionuclides, drugs, or toxins. Ibritumomab tiuxetan (Zevalin™), an anti-CD20 murine Mab chelated to the radioactive isotope yttrium-90 (^{90}Y), was shown to induce significant tumor responses in low-grade NHL patients in phase I/II trials (82). A randomized phase III trial comparing Zevalin to rituximab demonstrated a superior ORR (80% vs. 56%) and CR rate (30% vs. 16%) for Zevalin. The TTP for each agent was similar at 11 months (83). In combined studies of Zevalin (84), toxicity was primarily hematologic and consisted of grade 4 reversible neutropenia, thrombocytopenia, and anemia in 30%, 10%, and 3% of patients, respectively. Based on these encouraging results, Zevalin has been recently approved for the treatment of recurrent/refractory low-grade follicular NHL. Similar results have been observed with anti-CD20 murine Mab coupled to iodine-131 (Bexxar™) (85). Clinical trials of high-dose radioimmunotherapy with ^{131}I-labeled anti-CD20 Mab followed by peripheral blood stem-cell reconstitution have been impressive, with complete response rates close to 80% and the majority of NHL patients surviving beyond 5 years free of recurrent disease (86). Additional trials combining Zevalin or Bexxar with standard or high-dose chemotherapy are in progress.

A number of preclinical and clinical studies have evaluated the effect of plant [i.e., ricin (R) and gelonin (G)] or bacterial [i.e., diphtheria (DT) and pseudomonas exotoxin (PE)] toxins coupled to Mab for their effects on inhibition of tumor growth (reviewed in Ref. 87). The majority of toxin molecules consist of an alpha (α) chain, which upon internalization into the cell inhibits protein synthesis, and a beta (β) chain, which binds to galactose residues on the cell and assists entry of the α chain. Immunotoxins have been constructed by coupling the Mab to the α chain or the whole molecule along with a "blocking" sugar residue to inhibit nonspecific binding of the β chain to cells. Fewer toxin conjugates have been approved to date due to their modest antitumor effects along with significant toxicities, including a "vascular leak" phenomenon and liver abnormalities. Despite these problems, one toxin, DAB-IL-2 (Ontak™), has been approved for the treatment of hairy-cell leukemia. Ontak is not actually a whole Mab but consists of recombinant DNA resulting from a fusion of genes for IL-2 and PE.

Several Mab conjugated to drugs such as adriamycin or oligomycin (88,89) have been tested in the clinic. Mylotarg™, consisting of an anti-CD33 Mab (gemtuzumab) which binds to an acute leukemia Ag conjugated to oligomycin has been approved for the treatment of acute myelogenous leukemia (90).

Mab have also been evaluated as anti-idiotype vaccines (reviewed in Ref. 90) or for other nonmalignant conditions, including prevention and treatment of transplant rejection (91), respiratory syncytial virus (RSV) infections (92), rheumatoid arthritis (93), and septic shock (94).

In summary, the use of Mab for cancer treatment and other conditions appears extremely promising. Future directions include the development of "bifunctional" Mab (Fig. 3). Identification of novel targets such as vascular endothelial growth factor (VEGF) (95), along with novel routes of Mab administration [i.e., intraperitoneal (96,97) and intracranial (98)], should solidify Mab/immunoconjugates along with IFN, IL-2, and growth factors as the fourth major modality of cancer treatment.

E. Vaccines

Tumor vaccines refer to a means of active immunization against tumors in contrast to adoptive immunotherapy where immune cells or products are given, either for secondary prevention of tumor recurrence, or induction of tumor regression. Therapeutic anticancer vaccines differ from traditional vaccines against viruses and bacteria for primary prevention of infection. Furthermore, traditional vaccines are mostly designed to induce antibody stimulation by B cells while tumor vaccines are designed to stimulate T-cell responses.

Antitumor immunity is mostly mediated by T lymphocytes. CD8+ CTLs, and to lesser degree CD4+ T cells ("helper" cells), have been found to mediate most of the antitumor effects in animal models (99). In humans, the most convincing evidence of endogenous immune responses against cancer has been observed in melanoma and CML. In CML patients, antiproteinase 3 CD8 cells are found only in patients with sustained remission after IFN treatment and bone marrow transplantation, modalities to stimulate T-cell responses, but not in patients who are not in remission and who were treated with chemotherapy (100). For melanoma, CD4 and CD8 lymphocytes have been detected infiltrating tumor sites, circulating in the peripheral blood and residing in lymph nodes of melanoma patients (101,102). In recent years, many antigens recognized by these T cells (tumor-associated antigens, TAAs) have been molecularly cloned from cDNA expression libraries of the tumor cells. They can be divided into three categories: differentiation antigens that are expressed in malignant cells as well as in normal counterparts (such as Mart-1/Melan A, tyrosinase,

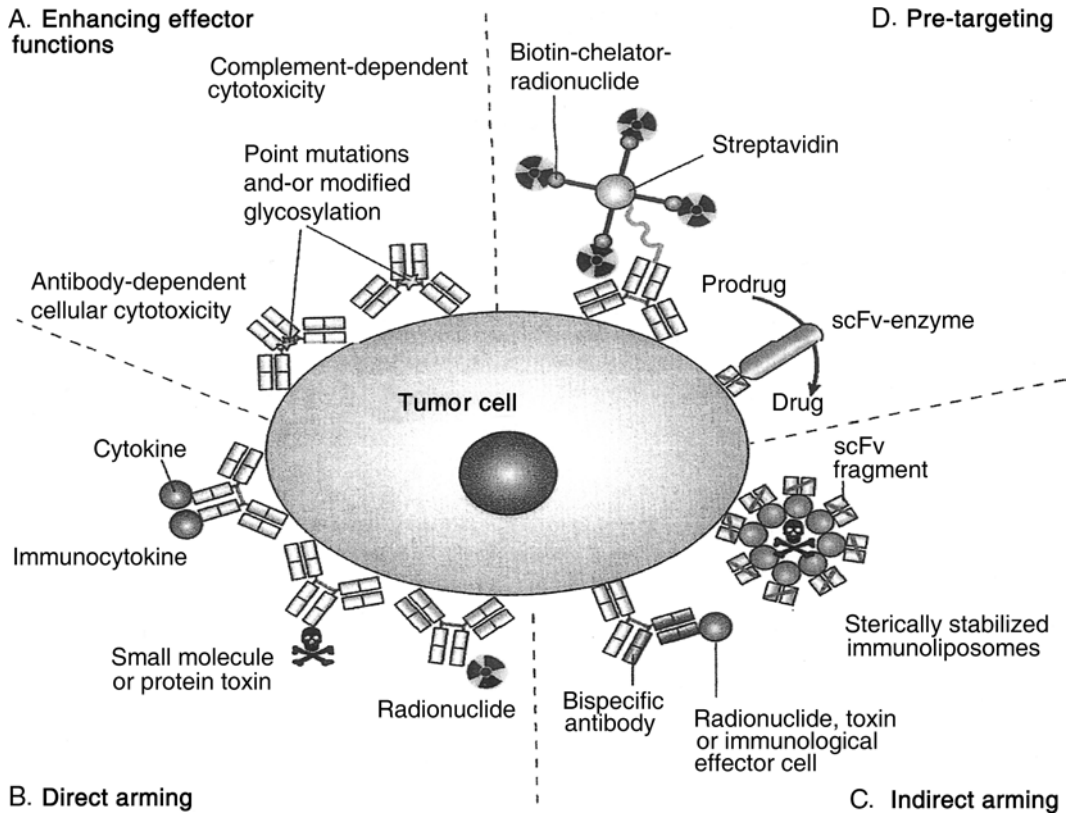

Figure 3 Strategies for enhancing the potency of antitumor antibodies: (A) Enhancing effector function by point mutations in the Fc region. (B) Direct arming with drugs, radionuclides, toxins, and cytokins. (C) Indirect arming by bifunctional Mab or attaching Ab fragment to drug-loaded liposomes. (D) Pretargeting enzyme-linked Mab to tumor followed by enzyme activation (prodrug approach). *Source*: Adapted from Ref. 66.

gp100, and proteinase 3), cancer testis antigens that are expressed in testis and cancer cells, but not in any normal somatic cells (such as Mage antigens), and cancer-specific antigens that are the consequence of mutations of a particular protein in the tumor (103).

Most of the TAAs are intracellular proteins. In order for the T cells to recognize the antigens, the antigen proteins are processed by the cells into short peptides (epitopes) and presented on tumor cells and antigen-presenting cells in association with the major histocompatibility complex (MHC). T cells then recognize the peptide–MHC complexes in an HLA restricted fashion. The most potent cells that can stimulate CTLs are dendritic cells (DCs) that are capable of capturing large amounts of antigen and expressing high level of peptide–MHC and costimulatory molecules to stimulate CTLs. Identification of TAAs, their HLA restricted epitopes, techniques to procure and manipulate CTLs and DCs have provided unprecedented opportunities to treat some cancers immunologically.

The clinical success of immunotherapy has long been evidenced in the setting of bone marrow transplantation pioneered by Dr. E. Donnal Thomas of the Fred Hutchinson Cancer Research Center, who found allogeneic immune response to be crucial in curing leukemia (104). Infusion of antigen-specific CTLs led to regression of tumor nodules bearing the target antigens (105). Although these treatments served to prove the principle of immunotherapy, they carry high degree of toxicity or complexity in preparing the cells. The study of tumor immunology revealed an interesting relationship among the tumor cells and immune cells, in that patients can mount CTL response against tumor antigens through cross-presentation of TAAs by DCs to CD8 T cells (Fig. 4). However, the natural CTL response is not sufficient to eradicate tumors and many such CTLs are incapable of tumor killing (102). Vaccination through DCs is believed to be an attractive intervention point to change the relationship between T cells and tumor cells without much toxicity and complexity of CTL preparation.

There are two different vaccination approaches: direct delivery of antigens to the subjects, where the antigens are picked up by DCs in vivo and presented

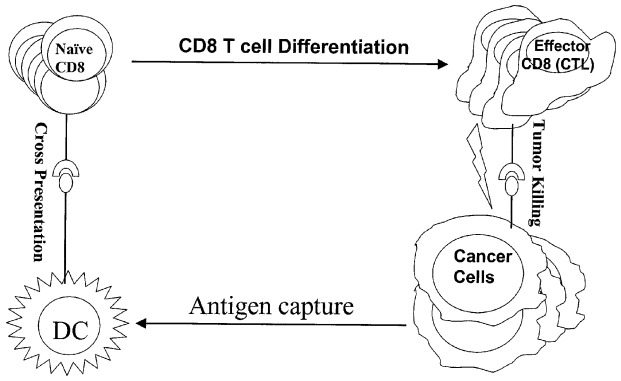

Figure 4 Relationship among tumor cells, dendritic cells and CD8+ T cells. DCs pagocytose apoptosing or necrotic tumor cells, crosspresent the TAAs to naïve CD8 T cells and stimulate them to become CTLs. In patients, such stimulated CTLs may not function well, so tumor cells continue to grow. Vaccination with DCs loaded with TAAs is aimed to CD8 response and tumor regression.

to T cells, and a cell therapy approach, where antigen loaded-DCs are prepared ex vivo and injected into the subject. Peptides and plasmid DNA can be delivered in the former approach, whereas the latter approach can deliver antigens in the forms of peptide, DNA, RNA, apoptotic tumor cells, necrotic tumor cells, cell lysate, and tumor–DC hybrid cells.

The direct delivery approach has the advantage of ease of administration. Peptides can be injected alone or with adjuvants such as incomplete Freud adjuvant, QS-21, or GM-CSF, to subcutaneous tissue. The injected peptides are picked up by DCs and presented to T cells. T-cell stimulations have been observed with this approach and even tumor nodule regressions have been observed on patients (106). Since peptides are HLA restricted, delivery of whole antigen would bypass this limitation. A novel approach employs delivery of attenuated intracellular bacteria such as *Salmonella*, *Shigella*, and *Listeria* species that are transformed with the tumor antigen. After the bacteria are given orally, they transmigrate across mucosa and are phagocytosed by DCs. The DCs can then crosspresent the antigens to T cells (Fig. 4) (107). Such an approach has been shown to stimulate T-cell responses in animals. Clinical trials are planned and it would be very interesting to observe whether this technique is efficacious in cancer patients.

Most clinical trials have taken the form of cell therapy although there is no clear evidence for its superiority to the direct delivery approach. There are two functional states of DCs, immature and mature. Dendritic cells residing in the subcutaneous tissues or submucosa are immature DCs capable of antigen capture. They become capable of T-cell stimulation only when they become mature DCs after stimulation with inflammatory signals (108). How to mature the DCs seems critical in T-cell stimulation and in the breaking of ''immune tolerance,'' particularly for antigens expressed on normal tissues. The cell therapy approach may render a better ex vivo manipulation on this process than the direct delivery approach. An example of such an advantage is illustrated in the case of HLA-A1 restricted MAGE-A3 peptide vaccination, where the cell therapy approach generated polyclonal T-cell stimulation while the direct injection approach only gave rise to monoclonal stimulation (109). Table 6 lists clinical trial results using both approaches.

In the cell therapy approach, it seems that the effectiveness of the vaccine is mostly governed by maturation status of DCs and how antigens are loaded onto the DCs. For an antigen whose gene has been isolated and immunogenic epitopes have been identified, the choice of antigen forms may include peptide, protein, DNA, or RNA encoding the antigen. Peptides are suitable for mass production and easy to load onto DC. Clinical trials of peptide vaccines have resulted in the stimulation of cytotoxic T cells with regression of some tumor nodules (Table 6). However, peptides tend to stimulate CTLs with low TCR avidity, and it is difficult to pulse DCs with multiple peptides covering most of Class I and Class II alleles. This problem can be bypassed by loading the DC with protein, DNA, or RNA encoding the whole antigen protein. Although proteins are difficult to prepare, DNA and RNA can be easily obtained in large quantity, and be molecularly engineered to stimulate both $CD4^+$ and $CD8^+$ T cells. Most of techniques to introduce DNA rely on viral vectors that may be complicated with issues such as safety and immunogenicity against the vector. Recently, adenovirus vector- and alpha virus-based vaccines have been tested in animals and they seem promising. In addition, nonviral DNA transfection techniques are being developed utilizing electroporation, lipid, or polymer. It would be interesting to see how efficient any of these techniques will be in eliciting T-cell responses against tumor. RNA-transfected DCs have many advantages because expression of antigens from mRNAs is transient and is not dependent on promoters or vectors, as compared with DNA-vector-based vaccines, therefore eliminating vector immunogenicity and potential insertional mutagenesis and oncogenesis due to persistent expression of prooncogenic tumor antigens, such as E7 of HPV. In addition, RNA-transfected DCs have been shown to be more potent in stimulating CTL activity than DNA transfected DC (119) and peptide pulsed DCs (X. Liao,

Table 6 Examples of Tumor Vaccine Clinical Trials

Antigen used	Adjuvant	No. of points	T cell response	Clinical response	Ref.
MAGE-A3.A1 peptide	None	25	Monoclonal	4 PR, 3 CR	106,109
Tyrosinase A2 peptide	QS-21	9	2	0	110
NY-ESO-1 A2 peptide	No	9	7	1 Nodule PR 4 Nodules CR	111
Gp100 A2 peptide	No	7	7	0	112
Melanoma peptides	DC	16	11	2 CR, 3 PR	113
MAGE-3 A1 peptide	DC	11	8	8 PR	114
MART-1 A2 peptide	DC	7	1	1 PR	115
Melanoma peptides	DC	14	5	2 PR	116
PSA RNA	DC	13	13	6 SD	117
Renal Ca cells	DC hybrid	17		4 CR, 2 PR	118

Abbreviations: CR, complete response; PR, partial response; SD, stable disease; DC, dentritic cell.

submitted for publication). Clinical trials using RNA-transfected DCs in prostate cancer and colon cancer showed little toxicity and some efficacy in clearing the circulating cancer cells (117). For suspected antigens that are not identified, one can load the DCs with whole cellular content, either DCs pulsed with tumor cell lysate (120) or whole cellular RNA (121,122), or in the form of tumor cell–DC fusion (118).

In summary, there is no doubt that T cells play a critical role in regression of some cancers, and DCs are the most effective way to stimulate them. Although the principle of tumor vaccine has been proven, it is very important to note that tumor vaccine development is still in its infancy. Successful development of tumor vaccines as a part of cancer treatment regimen has to await the resolution of some important issues, such as tumor heterogeneity, and efficient T-cell expansion after immunization. Other important areas for research include testing of sufficient adjuvants, the use of costimulatory molecules to boost CD4 T-cell responses, and methods to overcome host tolerance and enhance CD8 T-cell proliferation and function at the tumor site. Attention to these details should hopefully make vaccines an important part of the biotherapy armamentarium.

F. Gene Therapy: Antisense Oligodeoxynucleotides

The notion of synthesizing short single-stranded DNA segments to inhibit the expression of specific genes was suggested for more than two decades ago. The earliest attempt to inhibit gene expression using antisense oligodeoxynucleotides (oligos) was reported in 1978 (123).

Antisense oligos are short sequences of DNA that selectively bind target mRNA molecules by Watson–Crick base pairing, which results in the inhibition of mRNA processing or translation. This inhibition occurs through various mechanisms including prevention of mRNA transport, splicing, and translational arrest (Fig. 5) (124). If that protein is essential for the survival of the cell, then blocking its production should bring about the death of the cell (125). Several genes known to be important for the regulation of apoptosis, cell growth, metastasis, and angiogenesis have been identified as potential targets for cancer therapy.

Antisense technology is attractive for several reasons. First, antisense drugs have the potential to offer affinity and specificity many orders of magnitude higher than the traditional chemotherapy drugs. Second, these drugs have the potential to target any mRNA molecule. This is because natural phosphodiester oligos are rapidly hydrolyzed in vivo by nucleases (126,127). The majority of experimental work and all the clinical trials have been performed using phosphorothioate oligos (128). In contrast, the phosphorothioate oligo analogs (in which sulfur substitutes one of the nonbridging oxygen atoms in the phosphate backbone) are more stable because they are more resistant to endo- and exonucleases (129,130).

By inhibiting the target gene expression, antisense oligos can induce sequence-dependent toxicity. However, antisense oligos have also been found to induce sequence independent toxicity. Antisense oligos may inadvertently inhibit the expression of a gene that is not the initial target because of its sequence homology to the original target. Furthermore, the first generation of phosphorothioate oligos can produce anticoagulant effects (131,132) and complement activation. Neither of these toxicities has contributed to major clinical problems, and can be managed by maintaining peak plasma concentrations below threshold concentrations

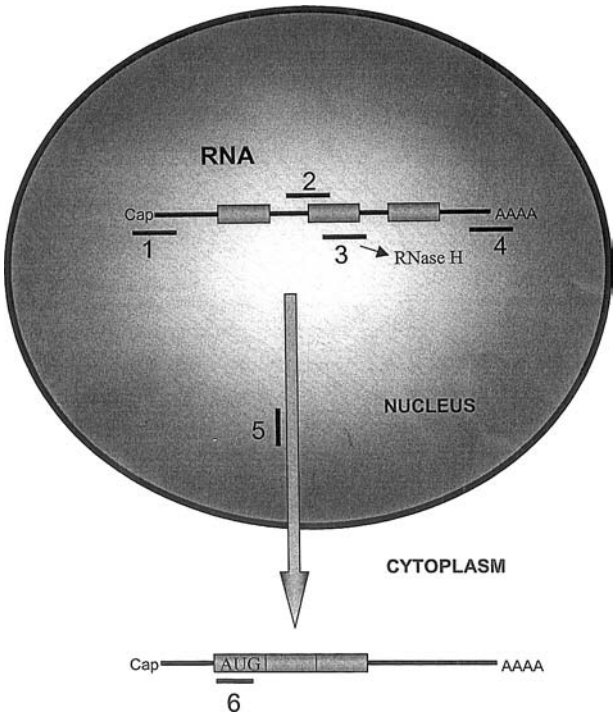

Figure 5 Mechanisms by which antisense oligonucleotides inhibit protein expression: **1**, inhibiting 5′-Cap formation; **2**, inhibiting RNA splicing; **3**, activating RNase H; **4**, inhibiting mRNA polyadenilation; **5**, inhibiting mRNA transport, **6**, inhibiting protein translation.

(133). But this may prevent administration of sufficient doses for the antisense oligos to induce significant tumor inhibition.

It is possible that a new antisense will produce a surprising toxicity not previously seen with other antisense oligos (134). With proper planning, the toxicity studies can be initiated before completion of the preclinical pharmacology studies so that the toxicology studies do not cause delays in getting the new antisense drug into clinical trials.

The application of antisense oligos as therapeutic agents in oncology has been proposed for more than two decades. Several oncogene products, most notably *bcl-2*, *c-raf-1*, protein kinase C-[alpha], and *H-ras*, have been evaluated as targets for therapeutic inhibition, and oligos designed to inhibit the expression of these gene have been studied extensively in phase I and II clinical trials. Inhibition of target expression in tumor (non-Hodgkin's lymphoma) and surrogate tissues has been demonstrated in several of these trials (135,136). Continuous infusion over 2–3 weeks appears preferable to weekly administration for toxicity and downregulation of target gene expression.

The first antisense oligo to be evaluated in clinical trials was targeted to the tumor suppressor gene *p53* and was administered to patients with acute myelogenous leukemia and myelodysplastic syndrome (137). Antisense oligos against the *bcl-2* oncogene (G3139; Genta Inc., San Diego, CA) were next evaluated in a phase I study with 11 patients who had prostate cancer. The serine/threonine kinase *c-raf* has been the subject of three phase I trials using distinct treatment schedules; five cases of grade 3 anemia were found in a thrice-weekly regimen of *c-raf* antisense (ISIS 5132; Isis Pharmaceuticals, Inc., Carlsbad, CA) (138). Antisense oligos targeted to protein kinase C-[alpha] # ISIS 3521, have been studied extensively in phase I and II clinical trials, as a continuous intravenous infusion in 21 patients with different cancers (139). Also, an antisense inhibitor of *H-ras* translation (ISIS 2503; Isis Pharmaceuticals, Inc.) has been evaluated alone and in combination with conventional chemotherapy in three phase I trials.

The efficacy data available suggest that antisense therapy alone could limit disease progression in some patients, but rarely induces major tumor responses. The specificity and tolerability of these oligos prompted the investigation of combining antisense oligos with chemotherapy, and early combination studies have yielded results of interest. Antisense oligos against *bcl-2*, *c-raf-1*, and protein kinase C-[alpha] continue to be the major focus of ongoing clinical trials.

In summary, there is increasing evidence that antisense can work in a sequence-specific manner in patients and finally live up to their promise. Antisense strategies which aim at restoration of apoptosis signaling, alteration of signaling pathways involved in cell proliferation, or targeting to the tumor's microvasculature may prove particularly useful in combination with conventional cancer therapeutic agents. By lowering the apoptotic threshold of cancer cells, antisense oligos could prove to be a very attractive strategy to overcome chemotherapy and radiation resistance. Currently much effort is devoted to making second generation of antisense oligo analogues that have higher antisense activity but reduced nonspecific toxicity.

III. BIOTHERAPY-RELATED SIDE EFFECTS

Select characteristics of biotherapy-related side effects differ from those associated with chemotherapy. As with chemotherapy, most biotherapy-related toxic effects are dose related; that is, the intensity of the toxic effects increases as the dose is elevated. However, different from some chemotherapeutic agents such as

doxorubicin, biotherapy-related toxic effects are typically noncumulative, in that there is not a ceiling dose beyond which a patient can receive no further therapy. Furthermore, most biotherapy-related side effects, myelosuppression included, are readily reversed on cessation of therapy. The timing of side effects also may differ from that of chemotherapy. For example, certain side effects may occur early in therapy and are often termed "acute." Others are manifested late in therapy and are classified as "chronic." Although most side effects are not life threatening, they often have a tremendous impact on the patient's quality of life. The chief side effects associated with each biological agent are shown below (Table 2).

IV. CONCLUSIONS

Advances in molecular biology have essentially made the human genome available as a source of potentially therapeutic biological agents (3,140). Constant discovery of new agents and the refinement of molecules through genetic-engineering techniques will continue to provide new therapeutic avenues. The "molecularization of medicine" has led to a more thorough understanding of the molecular basis of disease and disease pathogenesis. This has led in turn to the development of recombinant proteins for the treatment of disease. Within this context, a more complete understanding of the biology of cancer will lead to increasingly selective therapy and ultimately to repair of underlying cellular defects. Gene therapy is one aspect of this potential that continues to grow, with the number of new strategies and protocols increasing at an exponential rate.

The next 20 years will represent one of the most exciting eras in the management of cancer. The ability to determine the cellular defect for a given cancer and then to design effective therapy may one day become reality. Biotherapy has the potential to be a part of this revolution. Doctors caring for patients receiving biotherapy will be continually challenged to remain abreast of changes in a rapidly expanding field and to chart new territory in developing strategies of care for these patients through clinical practice and research.

REFERENCES

1. Rieger PT. Biotherapy: an overview. In: Rieger PT, ed. Biotherapy: A Comprehensive Overview. 2nd ed. Sudbury: Jones & Bartlett Publishers, 2001:3–37.
2. Oettgen H, Old L. The history of cancer immunotherapy. In: DeVita V, Hellman S, Rosenberg S, eds. Biologic Therapy of Cancer. Philadelphia: W.B. Saunders, 1991:87–119.
3. Oldhan R. Cancer biotherapy: general principles. In: Oldham R, ed. Principles of Cancer Biotherapy. 3rd ed. Dordrecht, The Netherlands: Kluwer Academic Press, 1998:1–15.
4. Mihich E, Fefer A. ed. Biological Response Modifiers: Subcommittee Report National Cancer Institute Monograph. Washington: National Cancer Institute, 1983:63.
5. Mazanet R, Morstyn G, Foote M. Development of biological agents. In: Schilsky R, Milano G, Ratain M, eds. Principles of Antineoplastic Drug Development and Pharmacology. New York: Marcel Dekker Inc, 1996:55–73.
6. Isaacs A, Lindemann J. Virus interference I. The interferon. Proc R Soc Serv 1957; B147:258–267.
7. Cuaron L, Thompson J. The interferons. In: Rieger PT, ed. Biotherapy: A Comprehensive Overview. 2nd ed. Sudbury: Jones & Bartlett, 2001:125–191.
8. Decatris M, Santhanam S, O'Byrne K. Potential of interferon-α in solid tumours part 1. Biodrugs 2002; 16(4):261–281.
9. Cantell KS, Hirvonen S, Kauppinen HL. Production and partial purification of human immune interferon. Methods Enzymol 1986; 119:54–63.
10. Food and Drug Information—Center for Biologics Evaluation and Research. Product Information. Accessed Dec 5, 2003 http://www.fda.gov/cber/index.html.
11. Medical Economics Staff, ed. Physicians' Desk Reference 2003. Medical Economics Company Inc.: Montvale, NJ.
12. Samuel CE. Antiviral actions of interferons. Clin Microbiol Rev 2001; 4:778–809.
13. Barber GN. The interferons and cell death; guardians of the cell or accomplices of apoptosis. Semin Cancer Biol 2000; 10(20):103–111.
14. Folkman J. Role of angiogenesis in tumor growth and metastasis. Semin Oncol 2002; 29(6 suppl 16):15–18.
15. Ezekowitz RAB, Mulliken JB, Folkman J. Interferon alpha-2a therapy for life-threatening hemangiomas of infancy. N Engl J Med 1992; 326(22):1455–1463.
16. Kirkwood J. Cancer immunotherapy: the interferon-alpha experience. Semin Oncol 2002; 29(3 suppl 7):18–26.
17. Jonasch E, Haluska FG. Interferon in oncological practice: review of interferon biology, clinical applications, and toxicities. Oncologist 2001; 6(1):34–55.
18. Morris AK, Valley AW. Overview of the management of AIDS-related Kaposi's sarcoma. Ann Pharmacother 1996; 30(10):1150–1163.
19. Krown SE, Li P, Von Roenn JH, Paredes J, Huang J, Testa MA. Efficacy of low-dose interferon with antiretroviral therapy in Kaposi's sarcoma: a randomized phase II AIDS clinical trials group study. J Interferon Cytokine Res 2002; 22(3):295–303.
20. Goldman JM. Therapeutic strategies for chronic myeloid leukemia in the chronic (stable) phase. Semin Hematol 2003; 40(1 suppl 2):10–17.
21. Terando A, Sabel MS, Sondak VK. Melanoma: adjuvant therapy and other treatment options. Curr Treat Options Oncol 2003; 4(3):187–199.

22. Kirkwood J. Adjuvant IFNα2 therapy of melanoma. Lancet 1998; 351:1901–1903.
23. Solal-Celigny, Lepage PE, Brousse N, Tendler CL, Brice P, Haioun C, Gabarre J, Pignon B, Tertian G, Bouabdallah R, Rossi JF, Doyen C, Coiffier B. Doxorubicin-containing regimen with or without interferon alpha-2b for advanced follicular lymphomas: final analysis of survival of toxicity in the Groupe d'Etude des Lymphomes Folliculaires 86 trial. J Clin Oncol 1998; 16(7):2332–2338.
24. McLaughlin P. Progress and promise in the treatment of indolent lymphomas. Oncologist 2002; 7(3): 217–225.
25. McHutchison JG, Fried MW. Current therapy for hepatitis C: pegylated interferon and ribavirin. Clin Liver Dis 2003; 7(1):149–161.
26. Interimmune. Actimmune–Gamma Interferon 1b (Package Insert). Brisbane: InterMune, Inc., 2001.
27. Rudick RA. Contemporary immunomodulatory therapy for multiple sclerosis. J Neuroophthalmol 2001; 21(4):284–291.
28. Filippini G, Munari L, Incorvaia B, Ebers GC, Polman C, D'Amico R, Rice GP. Interferons in relapsing remitting multiple sclerosis: a systematic review. Lancet 2003; 361(9357):545–552.
29. Kirkwood JM, Bender C, Agarwala S, Tarhini A, Shipe-Spotloe J, Smelko B, Donnelly S, Stover L. Mechanisms and management of toxicities associate with high-dose interferon alpha-2g therapy. J Clin Oncol 2002; 20(17):3703–3718.
30. Dean G. Fatigue. In: Rieger PT ed. Biotherapy: A Comprehensive Overview. 2nd ed. Sudbury: Jones & Bartlett, 2001:547–575.
31. Abbas AK, Pober JS, Lichtman AH. Cellular and Molecular Immunology. 5th ed. Philadelphia: W.B. Saunders, 2003.
32. Dinarello C, Mier J. Current concepts: lymphokines. N Engl J Med 1987; 317(15):940–945.
33. Oppenheim J. Forward. In: Thomson A, ed. The Cytokine Handbook. 3rd ed. San Diego, CA: Academic Press, 1998:xviii–xxii.
34. Hurst SD, Muchamuel T, Gorman DM, Gilbert JM, Clifford T, Kwan S, Menon S, Seymour B, Jackson C, Kung TT, Brieland JK, Zurawski SM, Chapman RW, Zurawski G, Coffman RL. New IL-17 family members promote Th1 or Th2 responses in the lung: in vivo function of the novel cytokine IL-25. J Immunol 2002; 169(1):443–453.
35. Fickenscher H, Hor S, Kupers H, Knappe A, Wittmann S, Sticht H. The interleukin-10 family of cytokines. Trends Immunol 2002; 23(2):89–96.
36. Goldsby RA, Kindt TJ, Osborne BA. Kuby immunology. Cytokines [Chap. 12]. 4th ed. New York: W.H. Freeman, 2000.
37. Morgan D, Ruscetti F, Gallo R. Selective in vitro growth of T lymphocytes from normal human bone marrows. Science 1976; 193(4257):1007–1008.
38. Chiron. Package insert. PROLEUKIN® (aldesleukin), recombinant human interleukin-2 (rhIL-2). Emeryville, CA.
39. Atkins MB. Interleukin-2: clinical applications. Semin Oncol 2002; 29(suppl 7):12–17.
40. Mier JW, Atkins MB. Interleukin-2. In: DeVita VT Jr, Hellamn S, Rosenberg SA, ed. Cancer Principles and Practice of Oncology: 6th ed. Philadelphia: Lippincott–Williams & Wilkins, 2001:471–478.
41. Demetri GD, Vadhan-Raj S. Hematopoietic Growth Factors. Cancer Management: A Multidisciplinary Approach. 4th ed. 2000; 38:747–761.

41a. Rieger PT. Biotherapy: The fourth modality of therapy. In: Barton-Burke, M, ed. Cancer Chemotherapy: A Nursing Process Approach. Boston: Jones & Bartlett Publishers, 1996.

42. Anderson JR, Anderson PN, Armitage JO, Beckhardt S, Bennett CL, Bodey GP, Crawford J, Davidson NE, Demetri GD, Hamm JT, Hillner B, Kardinal CG, Levine MN, Miller JA, Ochs JJ, Santana VM, Schiffer CA, Shea TC, Smith TJ, Vadhan-Raj S, Wade JL III, Weeks JC, Winn RJ. Recommendation for the use of hematopoietic colony-stimulating factors: evidence-based, clinical practice guidelines. J Clin Oncol 1994; 14(6):2471–2508.
43. Rizzo JD, Lichtin AE, Woolf SH, Seidenfeld J, Bennett CL, Cella D, Djulbegovic B, Goode MJ, Jakubowski AA, Lee SJ, Miller CB, Rarick MU, Regan DH, Browman GP, Gordon MS. Use of epoetin in patients with cancer: evidence-based clinical practice guidelines of the American Society of Clinical Oncology and the American Society of Hematology. J Clin Oncol 2002; 20(19):4083–4107.
44. Vadhan-Raj S. IL-11: is there evidence to evaluate risks, benefits, and impact on patient outcomes? Oncology 1999; 13(11A).
45. Tepler I, Elias S, Smith JW II, Hussein M, Rosen G, Chang AY, Moore JO, Gordon MS, Kuca B, Beach KJ, Loewy JW, Garnick MB, Kaye JA. A randomized placebo-controlled trial of recombinant human IL-11 in cancer patients with severe thrombocytopenia due to chemotherapy. Blood 1996; 87(9):3607–3614.
46. Vadhan-Raj S, Murray LJ, Bueso-Ramos C, Patel SR, Reddy SP, Hoots WK, Johnston T, Papadopolous NE, Hittelman WN, Johnston DA, Yang TA, Paton VE, Cohen RL, Hellman SD, Benjamin RS, Broxmeyer HE. Stimulation of megakaryocyte and platelet production by a single dose of recombinant human thrombopoietin in patients with cancer. Ann Intern Med 1997; 126(9):673–681.
47. Basser RL, Rasko JE, Clarke K, Cebon J, Green MD, Grigg AP, Zalcberg J, Cohen B, O'Bryne J, Menchaca DM, Fox RM, Begley CG. Randomized, blinded, placebo-controlled phase I trial of pegylated recombinant human megakaryocyte growth and development factor with filgrastim after dose-intensive chemotherapy in patients with advanced cancer. Blood 1997; 89: 3118–3128.