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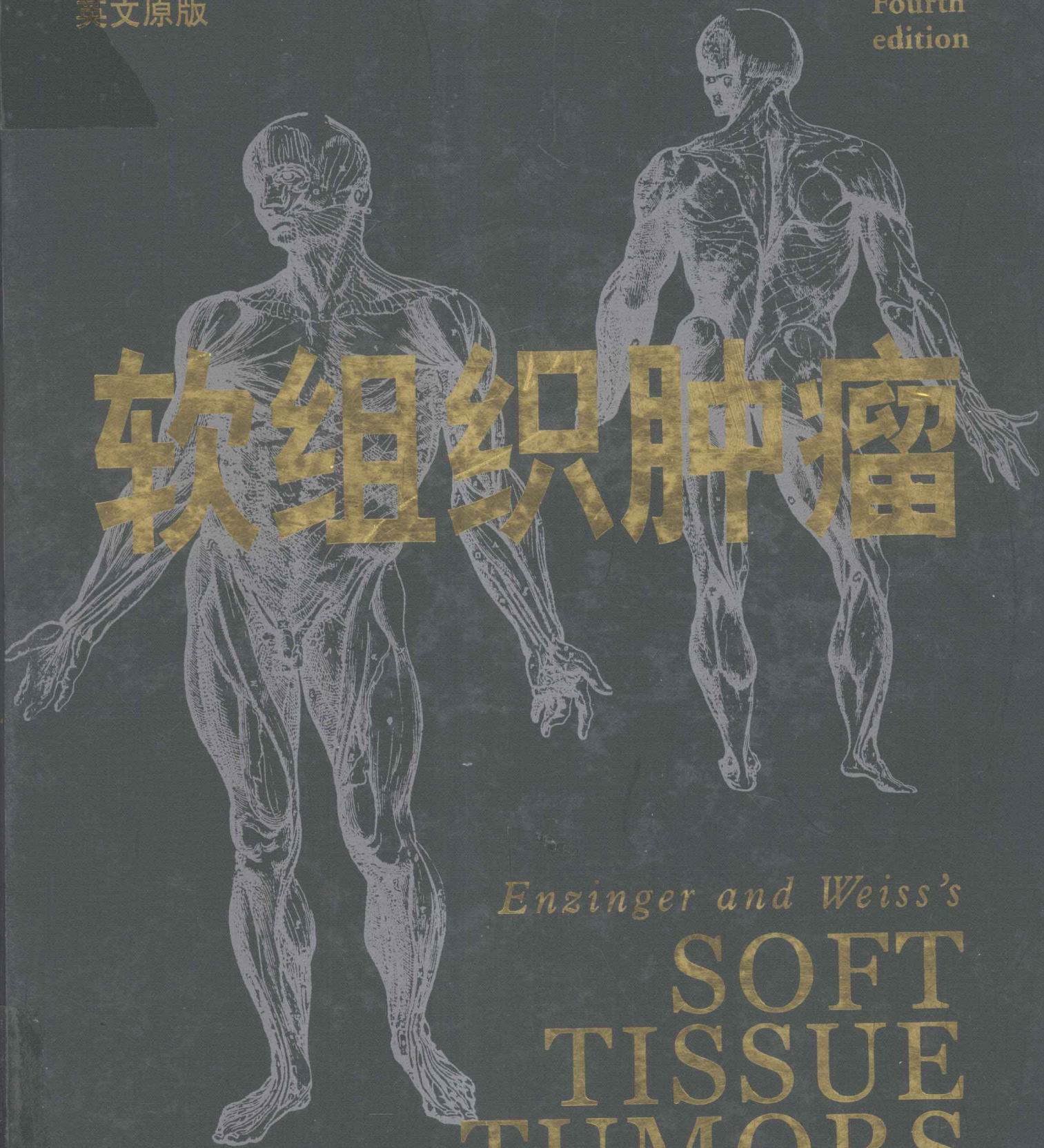

Enzinger and Weiss's

SOFT TISSUE TUMORS

Sharon W. Weiss

John R. Goldblum

人民卫生出版社

Health Science Asia, Elsevier Science

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PREFACE
to the Fourth Edition

Each new edition of a textbook bears its unmistakable marks. Ours, appearing at the dawn of a new millennium, is no exception. The familiar cover, with its adaptation of a Vesalius drawing, suggests a comforting continuity with the past, a reassurance that questions posed will still be answered, that illustrations will again serve to guide one to a particular diagnosis, and that novel ideas will be presented in a manner understandable by the practicing physicians for whom this book has always been intended. Yet there is a significant difference. The authorship has for the first time in nearly 20 years changed, and I would like to take this opportunity to acknowledge the extraordinary influence that Franz Enzinger, the senior author of previous editions, has had on this book and in soft tissue pathology in general. Franz represents one of the generation of great diagnostic pathologists, the likes of which we may never again see. Their generation was one that never fully knew the advantages of immunohistochemistry, cytogenetics, and molecular biology, and as a result their raw diagnostic skills reached heights that our trainees today can only imagine. Franz's descriptions of new lesions, epitomized by his classic paper on epithelioid sarcoma, serve as models for the power of observation and the nuances of detail. His seminal paper on liposarcoma, published with Dr. Winslow, presented a classification that today stands largely intact, firmly validated by cytogenetic and molecular findings.

The first edition of this book in many areas represented a distillate of this great man's personal observations, buttressed by the enormous treasure trove of cases accessioned at the Armed Forces Institute of Pathology. In preparing this fourth edition, we have strived to build on that extraordinary foundation, while embracing new ideas and technologies. Although I have missed Franz's wisdom and counsel in preparing this edition, I have found great personal satisfaction in working with a new colleague and former resident, Dr. John Goldblum, whose ebullience and energy have served as a mainstay in assuring the timely completion of this edition.

In addition to the change in authorship, our readers will note that this edition has been converted almost entirely to color, and a substantial number of new illustrations have been added. We are indebted to Dr. Irving Dardick, who is responsible for the outstanding color renditions in this book. New chapters have been written on the topics of "Fine Needle Aspiration Biopsies of Soft Tissue Tumors" by Drs. Geisinger and Fadi-Karim and "Immunohistochemistry for Analysis of Soft Tissue Tumors" by Drs. Folpe and Gown. Drs. Jonathan Fletcher and Paul Meltzer have again provided superlative updates in the fast-moving fields of cytogenetics and molecular biology of soft tissue tumors, while Drs. Sondak and Chang and Moser and Parrish have expanded their respective clinical and radiologic chap-

ters. All of our authors are preeminent authorities who have graciously taken time from their busy lives to share their expertise. We thank them very much.

We are indebted to our publisher and their outstanding staff who have facilitated our work on this edition. These include Marc Strauss, Lynne Gery, Joan Sinclair, and Berta Steiner. We deeply appreciate the help of our secretaries, Susan Raven, Kathleen Ranney, and Sandy Swanson, and the residents and fellows who performed the proofreading: Drs. Steve Billings, Edward Garcia, Jessica Leiden, and Jessica Sigel. Finally, without the love and support of our families—Bernie, Francine, Asmita, Andrew, Ryan, Janavi, and Raedan, we doubt any of this would have been possible. We could tell them this book is also theirs, but we suspect in their hearts they know this already.

Sharon W. Weiss, M.D.
Atlanta, 2001

PREFACE
to the First Edition

Since the publication of the *AFIP Fascicle on Soft Tissue Tumors* by A.P. Stout in 1957 and the revised edition by A.P. Stout and R. Lattes in 1967, there have been numerous advances and changes both in the diagnosis and treatment of soft tissue tumors. This book combines traditional views, which have stood the test of time, and newer concepts and observations accrued over the past 20 years. Because a precise diagnosis is essential for planning of treatment and assessment of prognosis, emphasis has been placed throughout the book on clear and concise descriptions and differential diagnoses of the tumors discussed. Each chapter has been freely illustrated, and comprehensive references have been added with emphasis on recent publications.

The WHO Classification of Soft Tissue Tumors provided the basis for the classification in this book. However, since its publication in 1969 several modifications have become necessary. Fibrohistiocytic and extraskeletal cartilaginous and osseous tumors have been included as separate groups, and a number of changes have been made, especially in the classification of fibrous, vascular, and neural tumors. The role of histochemistry, electron microscopy, and immunohistochemistry has been noted when applicable. Relatively less emphasis, however, has been placed on the specifics of therapy because of the rapidly changing nature of this discipline. It is our hope that this blending of old and new will make this book valuable not only as a reference book for those specifically interested in soft tissue tumors but also as a diagnostic aid for the practicing general pathologist.

In many areas the contents of this book reflect our personal experience derived from approximately 5000 cases reviewed annually in the Department of Soft Tissue Pathology of the Armed Forces Institute of Pathology. The large number of cases has afforded us a unique opportunity for which we are extremely grateful.

We also wish to express our appreciation and gratitude to the many contributing pathologists who not only shared their interesting and problematic cases with us but also provided additional teaching material in the form of photographs, roentgenograms, and electron micrographs. We also owe thanks to our professional colleagues for their advice and support in this endeavor, to the photographic staff of the Institute, especially Mr. C. Edwards and Mr. B. Allen, for their skill and assistance in preparing the photographs, and to Mrs. P. Diaz and Mrs. J. Kozlay for typing the manuscript. We are also greatly indebted to our publishers for their cooperation and help throughout the production of this book. We are particularly indebted to our families for their patience and tolerance.

Franz M. Enzinger
Sharon W. Weiss

CONTENTS

CHAPTER 1

GENERAL CONSIDERATIONS

Soft tissue can be defined as nonepithelial extraskeletal tissue of the body exclusive of the reticuloendothelial system, glia, and supporting tissue of various parenchymal organs. It is represented by the voluntary muscles, fat, and fibrous tissue, along with the vessels serving these tissues. By convention it also includes the peripheral nervous system because tumors arising from nerves present as soft tissue masses and pose similar problems in differential diagnosis and therapy. Embryologically, soft tissue is derived principally from mesoderm, with some contribution from neuroectoderm.

Soft tissue tumors are a highly heterogeneous group of tumors that are classified on a histogenetic basis according to the adult tissue they resemble. Lipomas and liposarcomas, for example, are tumors that recapitulate to a varying degree normal fatty tissue; and hemangiomas and angiosarcomas contain cells resembling vascular endothelium. Within the various histogenetic categories, soft tissue tumors are usually divided into benign and malignant forms.

Benign tumors, which more closely resemble normal tissue, have a limited capacity for autonomous growth. They exhibit little tendency to invade locally and are attended by a low rate of local recurrence following conservative therapy.

Malignant tumors, or *sarcomas,* in contrast, are locally aggressive and are capable of invasive or destructive growth, recurrence, and distant metastasis. Radical surgery is required to ensure total removal of these tumors. Unfortunately, the term sarcoma does not indicate the likelihood or rapidity of metastasis. Some sarcomas, such as dermatofibrosarcoma protuberans, rarely metastasize, whereas others, such as malignant fibrous histiocytoma, do so with alacrity. For these reasons it is important to qualify the term sarcoma with a statement concerning the degree of differentiation or the histologic grade. "Well differentiated" and "poorly differentiated" are qualitative, and hence subjective, terms used to indicate the relative maturity of the tumor with respect to normal adult tissue. Histologic grade is a means of quantitating the degree of differentiation by applying a set of histologic criteria. Usually well differentiated sarcomas are low grade lesions, whereas poorly differentiated sarcomas are high grade neoplasms. There are also borderline lesions for which it is difficult to determine the malignant potential, and there are benign neoplastic and nonneoplastic lesions that morphologically appear to be malignant but follow a benign clinical course (*pseudosarcomas*).

INCIDENCE

The incidence of soft tissue tumors, especially the frequency of benign tumors relative to malignant ones, is nearly impossible to determine accurately. Benign soft tissue tumors outnumber malignant tumors by a margin of about 100:1 in a hospital population, and their annual incidence is approximately 300 per 100,000 population.[100,101] The fact that many benign tumors, such as lipomas and hemangiomas, do not undergo biopsy makes direct application of data from most hospital series invalid for the general population, however.

Malignant soft tissue tumors, on the other hand, ultimately come to medical attention. Soft tissue sarcomas, compared with carcinomas and other neoplasms, are relatively rare and constitute fewer than 1% of all cancers.[86] Based on data from the American Cancer Society, it was estimated that 8100 new soft tissue sarcomas would develop during 2000 in the United States (Table 1–1). The incidence varies among age groups; it also depends on the definition

TABLE 1–1 ESTIMATED NEW CASES OF CANCER BY SITE (UNITED STATES, 2000)

Site	No. of Cases
Lung	164,000
Colon and rectum	130,200
Breast	184,200
Central nervous system	16,500
Soft tissue	8,100
Bone	2,500

Data from Cancer Statistics, 2000. CA Cancer J Clin 50:12, 2000.

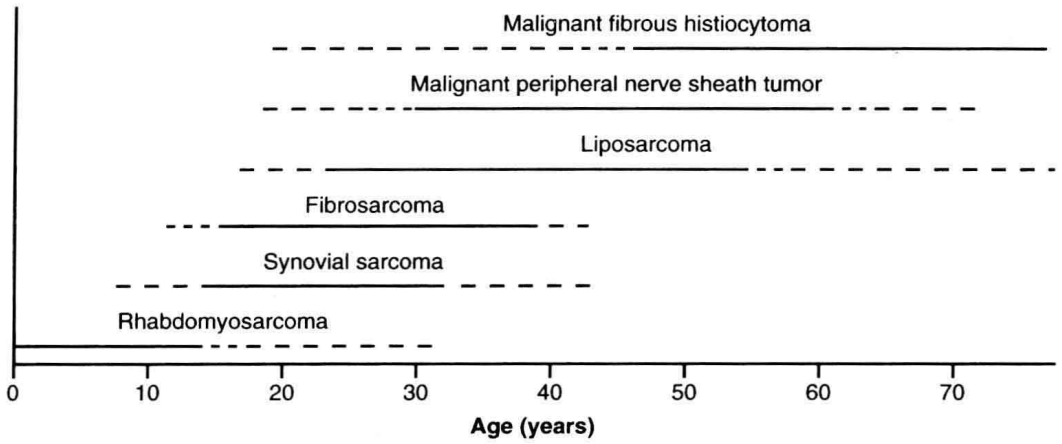

FIGURE 1–1. Approximate relation of age to incidence of various types of sarcoma. Continuous line indicates peak incidence of tumor. Dotted line indicates reduced incidence of tumor.

of soft tissue sarcomas and the types of neoplasm included among these tumors. For example, in one study of sarcomas of the locomotor system,[101] the overall annual incidence rate was 1.4 per 100,000, whereas the age-specific incidence for patients 80 years or older was 8.0 per 100,000. Moreover, in the National Cancer Survey,[21] retroperitoneal, mesenteric, and omental sarcomas are counted among the neoplasms of the digestive system, and pleural sarcomas (malignant mesotheliomas) are included among the tumors of the respiratory tract.

There seems to be an upward trend in the incidence of soft tissue sarcomas, but it is not clear whether this represents a true increase or reflects better diagnostic capabilities and greater interest in this type of tumor. According to Ross et al.,[97] with data from the National Cancer Institute's Surveillance, Epidemiology, and End Results Program (SEER), there was a marked increase in the age-adjusted incidence of soft tissue sarcomas between 1981 to 1987. However, when patients with Kaposi's sarcoma were eliminated from this analysis, the rates remained relatively unchanged throughout that time period. Judging from the available data, the incidence and distribution of soft tissue sarcomas seem to be similar in different regions of the world. Soft tissue sarcomas may occur anywhere in the body, but most arise from the large muscles of the extremities, the chest wall, the mediastinum, and the retroperitoneum. They occur at any age and, like carcinomas, are more common in older patients; about 15% affect persons younger than 15 years, and about 40% affect persons 55 years or older.

Soft tissue sarcomas occur more commonly in males, but gender and age-related incidences vary among the histologic types (Fig. 1–1). For instance, embryonal rhabdomyosarcoma occurs almost exclusively in young individuals, whereas malignant fibrous histiocytoma is predominantly a tumor of old age and is rare in children younger than 10 years. There is also no proven racial variation, even though the annual age-adjusted incidence rates have been reported to be higher for Blacks than Whites in the United States.[90]

PATHOGENESIS

As with other malignant neoplasms, the pathogenesis of most soft tissue tumors is still unknown. Recognized causes include various physical and chemical factors, exposure to ionizing radiation, and inherited or acquired immunologic defects. Evaluation of the exact cause is often difficult because of the long latent period between the time of exposure and the development of sarcoma, as well as the possible effect of multiple environmental and hereditary factors during the induction period. Origin of sarcomas from benign soft tissue tumors is rare, except for malignant peripheral nerve sheath tumors arising in neurofibromas, which are nearly always in patients with the manifestations of type 1 neurofibromatosis (von Recklinghausen's disease).

Environmental Factors

Trauma or *past injury* is frequently implicated in the development of sarcomas. Many of these reports are anecdotal, however, and the integrity of the injured part was not clearly established before injury. Consequently, trauma often seems to be an event that merely calls attention to the underlying neoplasm. Occasionally there is reasonable evidence to suggest a causal relation. Rare soft tissue sarcomas have been reported as arising in scar tissue following surgical procedures or thermal or acid burns, at fracture sites, and in the vicinity of plastic or metal implants, usually after a latent period of several years.[13,84] We reviewed material from a patient who developed flexion contractures and extensive heterotopic ossification after electrical injury to the arm followed 9 years later by an osteosarcoma.[1] The temporal sequence provided strong circumstantial evidence that the sarcoma

had arisen at a preexisting site of severe tissue injury. More recently, Kirkpatrick et al.[54] studied the histologic features in capsules surrounding the implantation site of a variety of biomaterials. Interestingly, these authors noted a spectrum of change, from focal proliferative lesions through preneoplastic proliferations to incipient sarcomas and suggested a model of multistage tumorigenesis akin to the adenoma–carcinoma sequence.

Environmental carcinogens have been related to the development of sarcomas, but their role is largely unexplored, and only a few substances have been identified as playing a role in the induction of sarcomas in humans. A variety of animal models exist to induce sarcomas, including the subcutaneous implantation of methylcholanthrene-induced sarcoma in Fischer rats[129] and the induction of angiosarcomas in mice using dimethylhydrazine.[66]

Asbestos, a hydrated silicate, is the most important known environmental carcinogen. Exposure to this substance, principally in the form of crocidolite or chrysotile, occurs in asbestos miners and industrial workers who process, install, or repair electrical and thermal insulation, brake linings, cement tiles, or pipes. Inhaled as a microscopic particle, asbestos ultimately reaches the pulmonary parenchyma and pleural surface, where after many years it may be associated with the development of pleural and peritoneal mesotheliomas or pulmonary carcinomas. Important risk factors are the intensity and duration of asbestos exposure, the type of asbestos, and the submicroscopic fiber diameter.[72] The risk is greatest with crocidolite, the blue asbestos mined in South Africa; the risk is much less with chrysotile, the white asbestos chiefly found in Canada and Russia, which amounts to more than 95% of the asbestos used commercially[6,57] (see Chapter 29).

Phenoxyacetic acid herbicides, chlorophenols, and their contaminants such as 2,3,7,8-tetrachlorodibenzo-para-dioxin (dioxin) have been linked to sarcoma genesis.[11,34,36,109] A series of case–control studies from Sweden from 1979 to 1990 reported an up to a sixfold increased risk of soft tissue sarcoma associated with exposure to phenoxyacetic acids or chlorophenols in individuals exposed to these herbicides in agricultural or forestry work.[30,31,39,40,128] Similar reports of an increased risk of sarcoma associated with these herbicides were reported from Italy,[103,122] Great Britian,[7] and New Zealand.[104] Although a study by Leiss and Savitz[62] linked use of phenoxyacetic acid lawn pesticides with soft tissue sarcomas in children, several other studies with more detailed exposure histories did not show this to be the case.[131] These inconsistencies may be due in part to the predominant phenoxyacetic herbicide used in different locations. In the United States 2,4-dichlorophenoxyacetic acid is the primary phenoxyacetic herbicide used, whereas in Sweden the main herbicides contain 2,4,5-trichlorophenoxyacetic acid and 2-methyl-4-chlorophenoxyacetic acid, both of which are more likely contaminated with dioxin.[131] High levels of dioxin exposure due to accidental environmental contamination near Seveso from an explosion at a chemical factory was followed by a threefold increased risk of soft tissue sarcomas reported among individuals living near this factory.[10,19] In addition, the possibility of an increased incidence of sarcomas was claimed for some of the 2 million soldiers stationed in Vietnam between 1965 and 1970 who were exposed to Agent Orange, a defoliant that contained dioxin as a contaminant.[55,102] However, in several case–control and proportional mortality studies, no excess risk of soft tissue sarcoma was reported among those Vietnam veterans who were directly involved with the spraying of Agent Orange.[43,131]

Vinyl chloride exposure is clearly associated with the development hepatic angiosarcoma.[25,32] There are also rare reports of extrahepatic angiosarcoma associated with this agent.[94]

Radiation exposure has been related to the development of sarcomas; but considering the frequency of radiotherapy, radiation-induced soft tissue sarcomas are uncommon, and there is no doubt that the benefit of radiation for treatment of malignant neoplasms outweighs the risk of developing a sarcoma. The incidence of postradiation sarcoma is difficult to estimate, but reports generally range from 0.03% to 0.80%.[3,69] Much of the data regarding the incidence of postradiation sarcomas are derived from large cohorts of breast cancer patients treated with postoperative radiation therapy. For example, Taghian et al.[111] found 11 postradiation sarcomas among 7620 patients with breast carcinoma treated with postoperative irradiation, for a cumulative incidence of 0.2% at 10 years. Similarly, Pierce et al.[89] reported three cases of postradiation sarcoma in 1624 women undergoing lumpectomy and postoperative irradiation at the Joint Center for Radiation Therapy between 1968 and 1985, for a 10-year actuarial risk of 0.8%. Similar data have been reported from the Swedish Cancer Registry.[48,49]

To qualify as a postradiation sarcoma, the criteria proposed by Cahan et al.[14] and later modified by Arlen et al.[4] must be met. They include documentation that the sarcoma developed in the irradiated field, histologic confirmation of the diagnosis, a period of latency of at least 3 years between irradiation and the appearance of tumor, and documentation that the region bearing the tumor was normal prior to administration of the radiation. Nearly all postradiation sarcomas occur in adults, and women develop them more frequently, an observation that reflects the common use of radiation for treatment of breast and

gynecologic malignancies. In our experience, the most common disease for which patients receive radiation are lymphomas and breast, ovarian, and endometrial carcinomas.

Although it was anticipated that the use of megavoltage radiation would reduce the incidence of postradiation sarcomas, this has not proved to be true. Both orthovoltage and megavoltage radiation may be associated with the subsequent development of sarcomas, and there do not appear to be differences in the type of sarcoma or survival rates between the two groups, although the average dosages associated with orthovoltage radiation are lower and the latency periods longer.[69,119,127]

Postradiation sarcomas do not display the wide range of appearances associated with sporadic nonradiation-induced tumors. The most common postradiation soft tissue sarcoma is malignant fibrous histiocytoma, which accounts for nearly 70% of cases, followed by osteosarcoma, fibrosarcoma, malignant peripheral nerve sheath tumor, chondrosarcoma, and angiosarcoma. Unfortunately, most postradiation sarcomas are high grade lesions and are detected at a relatively higher stage than their sporadic counterparts. Thus the survival rate associated with these lesions has been poor, as most studies report overall 5-year survival rates of 10–30%.[42,58,78,95]

The prognosis is most closely related to the site of the postradiation sarcoma, which in turn probably reflects resectability.[87] Patients with radiation-induced sarcomas of the extremities have the best survival (approximately 30% at 5 years), whereas those with lesions arising in the vertebral column, pelvis, and shoulder girdle generally have survival rates of less than 5% at 5 years.[69,87,123]

The total dose of radiation seems to influence the incidence of postradiation sarcoma, as most of these tumors are reported to occur at doses of 5000 cGy or more.[69,87] Mutations of the *p53* gene have been implicated in the pathogenesis of these tumors.[83] Extravasated Thorotrast (thorium dioxide), although no longer used for diagnostic or therapeutic purposes, has induced soft tissue sarcomas, particularly angiosarcomas, at the site of injection.[91,92]

Oncogenic Viruses

The role of oncogenic viruses in the evolution of soft tissue sarcomas is still poorly understood, although there is strong evidence that the human herpesvirus 8 (HHV8) is the causative agent of Kaposi's sarcoma[15,16,23,46,65] (see Chapter 25). In addition, there is a large body of literature supporting the role of the Epstein-Barr virus in the pathogenesis of smooth muscle tumors in patients with immunodeficiency syndromes or following therapeutic immunosuppression in the transplant setting.[53,60,61,71,105,112,120] Aside from these settings, there is no conclusive evidence that human-transmissible viral agents constitute a major risk factor in the development of soft tissue sarcomas, although electron microscopy has revealed virus particles repeatedly in a variety of soft tissue tumors.

Immunologic Factors

As mentioned above, immunodeficiency and therapeutic immunosuppression are also associated with the development of soft tissue sarcomas, particularly leiomyosarcomas. In addition, acquired regional immunodeficiency, or loss of regional immune surveillance, may also be the underlying mechanism in the development of the relatively rare angiosarcomas that arise in the setting of chronic lymphedema, secondary to radical mastectomy (Stewart-Treves syndrome),[74,81,107] or congenital or infectious conditions.[24,75,77]

Genetic Factors

A number of genetic diseases are associated with the development of soft tissue tumors, and the list will undoubtedly lengthen as we begin to understand the molecular underpinnings of mesenchymal neoplasia. Neurofibromatosis 1 and neurofibromatosis 2, previously referred to as the peripheral and central forms of the disease, respectively, are classic examples of genetic disease associated with soft tissue tumors.

Neurofibromatosis 1, which commences early in life with the onset of café au lait spots, is later characterized by numerous neurofibromas. Inherited as an autosomal dominant trait, the disease is primarily a neuroectodermal dysplasia, although nonneural tumors may occur as well. In 1–5% of cases, malignant peripheral nerve sheath tumors develop as a result of malignant degeneration of neurofibromas (see Chapter 31). The gene for neurofibromatosis 1 was localized to the pericentromeric region of chromosome 17 and was subsequently cloned. Its gene product is ubiquitously distributed in normal tissues and appears to have tumor suppressor activity.[68]

Neurofibromatosis 2, though lumped with neurofibromatosis 1 in early clinical descriptions, is a clinically and genetically distinct disease. Characterized by bilateral acoustic neuromas, its gene has been localized to chromosome 22[115] (see Chapter 4).

Familial adenomatous polyposis and Gardner syndrome are associated with mutations in the adenomatosis polyposis coli (*APC*) gene on chromosome 5q.[33,82] These syndromes, which are inherited as an autosomal dominant trait, may be associated with mesenteric fibromatosis, and mutations of the *APC* gene have also been detected in these tumors.[76] Studies suggest that mutations of this gene result in a

TABLE 1–2 SOFT TISSUE TUMORS OCCURRING ON AN INHERITED BASIS OR FOLLOWING A FAMILIAL DISTRIBUTION

Tumor Type	Comments
Fibrous tumors	
Palmar, plantar, and penile fibromatosis	Occasionally in several generations of one family and in twins
Deep fibromatosis (desmoid tumor)	Rare familial cases
Mesenteric fibromatosis	Frequently associated with familial polyposis coli and Gardner syndrome
Fibromatosis colli	Occasionally in twins
Myofibromatosis	Rarely in siblings or increased familial incidence
Hyaline fibromatosis	Frequently in siblings
Fatty tumors	
Lipoma	About 5% familial
Multiple lipomas	Increased familial incidence
Angiolipoma	About 5% familial
Angiomyolipoma	Manifestations of tuberous sclerosis complex in about one-third of patients
Fibrohistiocytic tumors	
Xanthoma tuberosum	Occurs in familial hyperlipidemia
Tendinous xanthoma	Occurs in familial hyperlipidemia and in cerebrotendinous xanthomatosis; autosomal recessive mode of inheritance
Muscular tumors	
Cutaneous leiomyoma	Occasional familial cases with pattern suggesting autosomal dominant mode of inheritance
Familial gastrointestinal stromal tumor	Germlike mutation of c-*kit*
Vascular tumors	
Glomus	Occasional familial cases following an autosomal dominant mode of inheritance
Osler-Weber-Rendu disease (hereditary hemorrhagic telangiectasia)	Autosomal dominant mode of inheritance
Blue rubber bleb nevus syndrome (cavernous hemangiomas of the skin and gastrointestinal tract)	Autosomal dominant mode of inheritance in some cases
Neural tumors	
Neurofibromatosis 1	Autosomal dominant mode of inheritance; *NF1* gene localized to chromosome 17
Neurofibromatosis 2	Autosomal dominant mode of inheritance; *NF2* gene localized to chromosome 22
Bilateral (inherited) retinoblastoma	Germline deletion of *Rb1* locus on chromosome 13; associated with secondary sarcomas
Neuroblastoma	Rare familial cases
Paraganglioma	Occasional familial cases suggesting autosomal dominant mode of inheritance
Osseous tumors	
Fibrodysplasia ossificans progressiva	Occasionally increased familial incidence, including in homozygotic twins; autosomal dominant mode of inheritance
Miscellaneous tumors	
Tumoral calcinosis	Increased familial incidence; about 40% in siblings
Li-Fraumeni syndrome	Germline deletion of *p53* locus resulting in familial rhabdomyosarcoma, early onset of breast carcinoma, and other neoplasms

protein product that loses the ability to degrade β-catenin, resulting in an elevated β-catenin protein level, which promotes fibroblastic proliferation.[2,63] Soft tissue sarcomas may also be a component of a variety of neoplastic disorders that may affect multiple relatives in a single family (so-called cancer family syndromes). Mutations of the *p53* tumor suppressor gene are critical to sarcoma genesis in patients with Li-Fraumeni syndrome.[64,67,106,113] The inherited, or bilateral, form of retinoblastoma is associated with the development of sarcomas, usually osteosarcomas. In this disease a germline mutation of the *Rb1* locus occurs. When a "second hit" develops in the other allelic site in somatic cells (i.e., retinoblasts), tumors develop. A number of other soft tissue tumors are known to occur in families, but the rarity of these reports indicates that collectively they do not account for a significant proportion of cases. These lesions, which are enumerated in Table 1–2, include various fibromatoses, lipomas, xanthomas, leiomyomas, neurofibromas, neuroblastomas, gastrointestinal stromal tumors, and paragangliomas. An excellent review of familial cancer syndromes was reported by Tsao.[117]

CLASSIFICATION OF SOFT TISSUE TUMORS

Development of a useful, comprehensive histologic classification of soft tissue tumors has been a relatively slow process. Earlier classifications have been

largely descriptive and have been based more on the nuclear configuration than the type of tumor cells. Terms such as "round cell sarcoma," "spindle cell sarcoma," and "pleomorphic sarcoma" may be diagnostically convenient but should be discouraged because they are meaningless and convey little information as to the nature and potential behavior of a given tumor. Moreover, purely descriptive classifications do not clearly distinguish between tumors and tumor-like reactive processes. More recent classifications have been based principally on the line of differentiation of the tumor, that is, the type of tissue formed by the tumor rather than the type of tissue from which the tumor arose.

Over the past two to three decades there have been several attempts to devise a useful, comprehensive classification of soft tissue tumors. They include the Armed Forces Institute of Pathology (AFIP) classifications published in the *Atlas of Tumor Pathology* in 1957,[108] 1967, and 1983[59] and the World Health Organization (WHO) classification published first in 1969[29] and revised in 1994.[126] The classification used herein is similar but not identical to the 1994 WHO classification, a collective effort by pathologists in nine countries.

Each of the histologic categories is divided into a benign group and a malignant group. The various tumors are named according to the tissue they most closely resemble. Rhabdomyosarcomas, for example, show rhabdomyoblastic differentiation rather than that of tumors that arise from voluntary or striated muscle tissue. Most tumors retain the same pattern of differentiation in the primary and recurrent lesions, but occasionally they change their pattern of differentiation or may even differentiate along several cellular lines.

Malignant fibrous histiocytoma and liposarcoma are the most common soft tissue sarcomas of adults; together they account for 35–45% of all sarcomas. The incidence of the different types, however, varies in different series. For example, among 1116 soft tissue sarcomas reviewed by Hashimoto et al.,[41] malignant fibrous histiocytoma (25.1%) and liposarcoma (11.6%) were the most common, followed by rhabdomyosarcoma (9.7%), leiomyosarcoma (9.1%), synovial sarcoma (6.5%), malignant peripheral nerve sheath tumor (5.9%), and fibrosarcoma (5.2%). In the series by Markhede et al.[70] the three most common sarcomas were malignant fibrous histiocytoma (28%), fibrosarcoma (14%), and liposarcoma (9%). Rhabdomyosarcoma, neuroblastoma, and the extraskeletal Ewing's sarcoma/primitive neuroectodermal tumor (PNET) family are the most frequent soft tissue sarcomas of childhood. A histologic classification of soft tissue tumors is presented in Table 1–3.

STAGING AND GRADING SOFT TISSUE SARCOMAS

The histologic type of sarcoma does not always provide sufficient information for predicting the clinical course, and grading and staging soft tissue sarcomas are essential for an accurate prognosis for planning and evaluating therapy, and for comparing and exchanging data. *Grading* determines the degree of malignancy and is based on an evaluation of several histologic parameters. *Staging* provides shorthand information regarding the state or extent of the disease at a designated time, preferably at the time of the initial histologic diagnosis. Grading and staging are complicated by numerous, often interrelated variables that are likely to affect clinical behavior. In fact, a grading or staging system that is comprehensive and gives full consideration to all factors that might affect the course of the disease and the results of therapy is too complex for practical purposes. On the other hand, a more limited, more practical system may suffer from the hazards of oversimplification and may result in data that are neither meaningful nor reliable, thereby defeating the purpose for which the system was designed.

The accuracy of grading and staging obviously depends on the input of adequate, precise clinical and pathologic data; staging is best accomplished following biopsy and histologic diagnosis of the primary tumor. Grading and staging of recurrent tumors are of much less significance because they are influenced by the preceding therapy. In fact, grading may not be reliable in some cases following therapy. Moreover, the type of tumor, rather than its grade, provides information as to the likelihood of lymph node metastasis. For instance, lymph node metastasis is common with rhabdomyosarcomas and epithelioid sarcomas but is rare with liposarcomas and malignant peripheral nerve sheath tumors. As with all grading and staging systems, the data are recorded in a standard checklist or protocol.[5]

GRADING

Traditionally, as outlined by Broders et al.[12] in 1939, the grade of a malignancy is determined by a combined assessment of several histologic features: (1) degree of cellularity; (2) cellular pleomorphism or anaplasia; (3) mitotic activity (frequency and abnormality of mitotic figures); (4) degree of necrosis; and (5) expansive or infiltrative and invasive growth. Additional factors include the amount of matrix formation and the presence or absence of hemorrhage, calcification, and inflammatory infiltrate. The amount of matrix formation, such as collagen or mucoid material, is

TABLE 1-3 HISTOLOGIC CLASSIFICATION OF SOFT TISSUE TUMORS

- Fibrous tumors
  - Benign
    - Nodular fasciitis (including intravascular and cranial types)
    - Proliferative fasciitis and myositis
    - Organ-associated pseudosarcomatous myofibroblastic proliferations
    - Ischemic fasciitis (atypical decubital fibroplasia)
    - Fibroma (dermal, tendon sheath, nuchal types)
    - Elastofibroma
    - Nasopharyngeal angiofibroma
    - Giant cell angiofibroma
    - Keloid
    - Desmoplastic fibroblastoma (collagenous fibroma)
    - Fibrous hamartoma of infancy
    - Infantile digital fibromatosis
    - Myofibroma and myofibromatosis
    - Hyalin fibromatosis
    - Gingival fibromatosis
    - Fibromatosis colli
    - Calcifying aponeurotic fibroma
    - Calcifying fibrous pseudotumor
    - Infantile-type fibromatosis
  - Intermediate
    - Adult-type fibromatosis
      - Superficial (including palmar, plantar, penile fibromatosis, knuckle pads)
      - Deep (including extraabominal, abdominal, intraabdominal, mesenteric, pelvic fibromatosis)
    - Inflammatory myofibroblastic tumor (inflammatory fibrosarcoma)
    - Infantile fibrosarcoma
  - Malignant
    - Adult-type fibrosarcoma
      - Usual type
      - Myxoid type (myxofibrosarcoma, low grade myxoid malignant fibrous histiocytoma)
      - Low grade fibromyxoid type with or without rosettes (low grade fibromyxoid sarcoma)
      - Sclerosing epithelioid type
- Fibrohistiocytic tumors
  - Benign
    - Fibrous histiocytoma (cutaneous and deep)
      - Cellular
      - Epithelioid
    - Juvenile xanthogranuloma
    - Reticulohistiocytoma
    - Xanthoma
    - Extranodal (soft tissue) Rosai-Dorfman disease
  - Intermediate
    - Atypical fibroxanthoma
    - Dermatofibrosarcoma protuberans (including pigmented forms)
    - Giant cell fibroblastoma
    - Angiomatoid fibrous histiocytoma
    - Plexiform fibrohistiocytic tumor
    - Soft tissue giant cell tumor of low malignant potential
  - Malignant
    - Malignant fibrous histiocytoma
      - Storiform-pleomorphic type
      - Myxoid type
      - Giant cell type (malignant giant cell tumor of soft parts)
      - Inflammatory type
- Lipomatous tumors
  - Benign
    - Lipoma [solitary, multiple, cutaneous, deep (including intramuscular and perineural)]
    - Angiolipoma
    - Myolipoma
    - Chondroid lipoma
    - Spindle cell/pleomorphic lipoma
    - Angiomyolipoma
    - Myelolipoma
    - Hibernoma
    - Lipoblastoma or lipoblastomatosis
    - Lipomatosis
      - Diffuse lipomatosis
      - Cervical symmetric lipomatosis (Madelung's disease)
      - Pelvic lipomatosis
  - Intermediate
    - Atypical lipoma (well differentiated liposarcoma of superficial soft tissue, atypical lipomatous tumor)
  - Malignant
    - Well differentiated liposarcoma
      - Lipoma-like
      - Sclerosing
      - Inflammatory
      - Spindle cell
    - Myxoid-round cell liposarcoma
    - Pleomorphic liposarcoma
    - Dedifferentiated liposarcoma
- Smooth muscle tumors and related lesions
  - Benign
    - Leiomyoma
    - Angiomyoma
    - Angiomyofibroblastoma
    - Palisaded myofibroblastoma of lymph node
    - Intravenous leiomyomatosis
    - Leiomyomatosis peritonealis disseminata
  - Malignant
    - Leiomyosarcoma
- Extragastrointestinal (soft tissue) stromal tumors
  - Benign
    - Benign extragastrointestinal stromal tumor
    - Benign extragastrointestinal autonomic tumor
  - Malignant
    - Malignant extragastrointestinal stromal tumor
    - Malignant extragastrointestinal autonomic nerve tumor
- Skeletal muscle tumors
  - Benign
    - Cardiac rhabdomyoma
    - Adult rhabdomyoma
    - Fetal rhabdomyoma
      - Myxoid (classic)
      - Intermediate (cellular, juvenile)
  - Malignant
    - Embryonal rhabdomyosarcoma
      - Usual type
      - Botryoid type
      - Spindle cell type
    - Alveolar rhabdomyosarcoma
    - Pleomorphic rhabdomyosarcoma
    - Rhabdomyosarcoma with ganglion cells (ectomesenchymoma)
- Tumors of blood and lymph vessels
  - Benign
    - Papillary endothelial hyperplasia
    - Hemangioma
      - Capillary hemangioma (including juvenile)
      - Cavernous hemangioma (including sinusoidal)
      - Venous hemangioma
      - Epithelioid hemangioma (angiolymphoid hyperplasia)
      - Pyogenic granuloma
      - Acquired tufted hemangioma
      - Hobnail hemangioma
      - Spindle cell hemangioma
    - Lymphangioma
    - Lymphangiomyoma and lymphangiomyomatosis

Table continued on following page

TABLE 1–3 HISTOLOGIC CLASSIFICATION OF SOFT TISSUE TUMORS *Continued*

- Angiomatosis
- Lymphangiomatosis
- Intermediate
  - Epithelioid hemangioendothelioma
  - Hobnail hemangioendothelioma
    - Retiform type (retiform hemangioendothelioma)
    - Dabska type (endovascular papillary angioendothelioma)
  - Kaposiform hemangioendothelioma
- Malignant
  - Angiosarcoma
  - Kaposi's sarcoma

Perivascular tumors
- Benign
  - Glomus tumor
    - Usual type
    - Glomangioma
    - Glomangiomyoma
    - Glomangiomatosis
  - Benign hemangiopericytoma/solitary fibrous tumor
  - Myopericytoma
- Malignant
  - Malignant glomus tumor
  - Malignant hemangiopericytoma/malignant solitary fibrous tumor

Synovial tumors
- Benign
  - Tenosynovial giant cell tumor
    - Localized type
    - Diffuse type
- Malignant
  - Malignant tenosynovial giant cell tumor

Mesothelial tumors
- Benign
  - Adenomatoid tumor
- Intermediate
  - Multicystic mesothelioma
  - Well differentiated papillary mesothelioma
- Malignant
  - Diffuse mesothelioma
    - Epithelial type
    - Sarcomatoid type
    - Biphasic type

Peripheral nerve sheath tumors and related lesions
- Benign
  - Traumatic neuroma
  - Glial heterotopia
  - Mucosal neuroma
  - Pacinian neuroma
  - Palisaded encapsulated neuroma
  - Morton's interdigital neuroma
  - Nerve sheath ganglion
  - Neuromuscular hamartoma
  - Neurofibroma and neurofibromatosis
    - Usual type (localized)
    - Diffuse
    - Plexiform
    - Epithelioid
  - Schwannoma and schwannomatosis
    - Usual type
    - Cellular schwannoma
    - Plexiform schwannoma
    - Degenerated (ancient) schwannoma
    - Epithelioid schwannoma
    - Neuroblastoma-like schwannoma
  - Melanotic schwannoma
  - Perineurioma
    - Intraneural perineurioma (localized hypertrophic neuropathy)
    - Extraneural (soft tissue) perineurioma
  - Granular cell tumor
  - Neurothekeoma
  - Ectopic meningioma
- Malignant
  - Malignant peripheral nerve sheath tumor (MPNST)
    - Usual type
    - MPNST with rhabdomyoblastic differentiation (malignant Triton tumor)
    - Glandular malignant schwannoma
    - Epithelioid MPNST
    - MPNST arising in a schwannoma
    - MPNST arising in a ganglioneuroma
  - Malignant granular cell tumor
  - Clear cell sarcoma of the tendon and aponeurosis
  - Malignant melanocytic schwannoma
  - Ectopic ependymoma

Primitive neuroectodermal tumors and related lesions
- Benign
  - Ganglioneuroma
  - Pigmented neuroectodermal tumor of infancy (retinal anlage tumor)
- Malignant
  - Neuroblastoma
  - Ganglioneuroblastoma
  - Ewing's sarcoma/primitive neuroectodermal tumor
  - Malignant pigmented neuroectodermal tumor of infancy (retinal anlage tumor)

Paraganglionic tumors
- Benign
  - Paraganglioma
- Malignant
  - Malignant paraganglioma

Extraskeletal osseous and cartilaginous tumors
- Benign
  - Panniculitis ossificans and myositis ossificans
  - Fibroosseous pseudotumor of the digits
  - Fibrodysplasia ossificans progressiva
  - Extraskeletal chondroma or osteochondroma
  - Extraskeletal osteoma
- Malignant
  - Extraskeletal chondrosarcoma
    - Well differentiated chondrosarcoma
    - Myxoid chondrosarcoma
    - Mesenchymal chondrosarcoma
  - Extraskeletal osteosarcoma

Miscellaneous tumors
- Benign
  - Congenital granular cell tumor
  - Tumoral calcinosis
  - Myxoma
    - Cutaneous
    - Intramuscular
  - Juxtaarticular myxoma
  - Aggressive angiomyxoma
  - Parachordoma
  - Amyloid tumor
  - Pleomorphic hyalinizing angiectatic tumor of soft parts
- Intermediate
  - Ossifying fibromyxoid tumor of soft parts
  - Inflammatory myxohyaline tumor
- Malignant
  - Synovial sarcoma
  - Alveolar soft part sarcoma
  - Epithelioid sarcoma
  - Desmoplastic small round cell tumor
  - Malignant extrarenal rhabdoid tumor