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Differential Diagnosis of Soft Tissue and Bone Tumors

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LEA & FEBIGER · 1986 · PHILADELPHIA

THIS BOOK is the outgrowth of more than twenty-five years of my diagnostic experience with the histology and cytology of soft tissue and bone tumors. In my presentation of tumors I have followed a sequence consistent with that followed by pathologists in their examinations. All soft tissue and bone neoplasms, as well as non-neoplastic lesions, are defined and classified, regardless of their histogenesis or organ of origin, according to *histologic pattern* (arranged, spreading, lacy, epithelioid, alveolar, and disarranged) and *cell morphology* (slender spindle cells, plump spindle cells, granular epithelioid cells, clear epithelioid cells, isomorphic giant cells, and pleomorphic giant cells), with consideration of the *appearance of stroma* and the *products of cells*. Some tumors may fit into more than one of these histologic categories and may be listed more than once.

After a brief consideration of the histogenesis of soft tissue and bone tumors (Table 5), in the introductory chapter readers will find the definitions and the synonyms of the most common non-neoplastic lesions (Table 10), benign neoplasms (Table 11), and malignant neoplasms (Table 12) listed along with the most pertinent references.

The clinical presentation, size, site, and gross and radiologic appearance of reactive and neoplastic lesions are presented with reference to age and sex of the patient to augment diagnostic accuracy. To obtain optimal results, the dissection and handling of soft tissue and bone specimens are described.

The tumors presented in depth are those that are most common and those that present the greatest diagnostic difficulties to pathologists. The main portion of the book is devoted to illustrations of the growth pattern, cell morphology, appearance of stroma, and products of cells. All photomicrographs have been taken from hematoxylin and eosin stained sections unless specified. A limited number of photomicrographs illustrate diagnostic features of tissue sections stained with special, histochemical, or immunochemical stains; in addition, ultrastructural features are included to call attention to instances when such studies may contribute to the diagnosis. All photographs have been cropped to show only pertinent features. The pages were laid out with the resemblances of various entities in mind, and I have made a point of selecting illustrations that show features important to the differential diagnosis.

The thousands of cross-references, tables, and illustrations with special markings are designed to save time and facilitate an accurate differential diagnosis. In the last chapters the grading and staging procedure of sarcomas is outlined with consideration of prognosis and differential diagnosis. At the end of the book, in the form of an appendix, the cytologic appearance of soft tissue and bone tumors is illustrated as seen in smears prepared from exfoliative and aspiration specimens and stained by using Papanicolaou's method or hematoxylin and eosin.

In publishing this book my main purpose was to integrate the histologic appearance of soft tissue and bone tumors, and to improve the skills of pathologists in diagnosing intra- and extraskeletal connective tissue tumors by pattern recognition. To render the various terms and classifications suitable for inclusion I had to exercise considerable freedom in selecting the most appropriate ones. I realize that some of the concepts presented in this book may not be accepted by everyone, but I feel as William Cooke did in 1822, when he wrote the following: "The daily observation of disease which baffles the utmost skill, will present to the feeling mind an adequate inducement to cultivate a spirit of diligent research; and where this benevolent principle is the actuating motive, the individual need not be anxious about an apology for the publication of his ideas."

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(215) 922-1330

Library of Congress Cataloging in Publication Data

Hajdu, Steven I.
Differential diagnosis of soft tissue and bone tumors.

Bibliography: p.
Includes index.
1. Sarcoma—Diagnosis. 2. Diagnosis, Cytologic.
3. Diagnosis, Differential. I. Hajdu, Eva M. II. Title.
[DNLM: 1. Sarcoma—Diagnosis. 2. Diagnosis, Differential.
QZ 345 H154d]
RC270.H333 1984 616.99'4075 83-19990
ISBN 0-8121-0895-7

Printed in the United States of America

Print Number: 5 4 3 2 1

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ISBN 0-8121-0895-7

Printed in the United States of America

Print Number: 5 4 3 2 1

"Sarcomatous tumors are of very various kinds, and consequently every attempt to devise appropriate names to distinguish them is at least laudable"

SAMUEL COOPER (1780–1848)

1. Histogenesis and Classification

SOFT tissue and bone tumors arise from derivatives of the embryonic mesoderm. Cytologically, the cells of the embryonic disc have no distinctive features, but once they are organized into specific tissues and organs the microscopic similarity disappears. Most, if not all, organs are derived from at least two of the three germ layers, ectoderm, mesoderm, and endoderm, one of which is very commonly the mesoderm (Fig. 1). The embryonic mesoderm is segmented into a series of somites and split into somatic and splanchnic layers that are the source of the mesenchymal or connective tissues (Fig. 2). Both skeletal and soft tissues are composed of living, constantly changing cells fulfilling specific structural and functional roles. The difference between skeletal and soft tissues depends not so much on the dissimilarity of cellular elements, but on their degree of differentiation, maturation, genetically determined assembly, products, and preordered functional role.

In the course of differentiation, mesenchymal cells become specialized and may assume the cytologic characteristics of fibroblasts, myoblasts, lipoblasts, chondroblasts, osteoblasts, or an endless number of other primitive forms (Fig. 3). The fact that mesenchymal cells are ubiquitous and highly versatile is further complicated by the observation that any well-defined mesenchymal cell may either undergo maturation arrest, so-called "dedifferentiation," or at the conclusion of the mitotic cycle reach a higher level of differentiation by acquiring complex cytoplasmic organelles, depositing biochemically and immunologically active products, and assuming a phenotype different from that of the parent cell. For example, a noncollagenous fibrous histiocytic cell may emerge as a collagenous fibroblast, a fibroblast as a bone-producing osteoblast, or an undifferentiated pericyte as a leiomyoblast.

The recent reappearance of the term "dedifferentiation" is an unfortunate one, and its use should be discouraged. Cells, mesenchymal cells in particular, do not dedifferentiate, but may undergo maturation arrest or fail to differentiate. Often, it seems that there was a barrier to differentiation. There is ample clinical and experimental evidence that maturation arrest, for example, in embryonal rhabdomyo-

FIG. 1. Histologic section of an 18-day-old human embryo embedded in the endometrium. The endometrium almost completely surrounds the embryo. The cytotrophoblasts *(arrows)* form an irregular solid inner lining. Beyond this are irregular lacunae containing syncytiotrophoblasts *(ST)*. The embryonic side of the cytotrophoblastic lining is covered by extraembryonic mesoderm *(EEM)* that is condensed on its inner aspect to form Heuser's membrane *(H)* around the yolk sac *(Y)*. The amniotic cavity *(A)* is separated from the yolk sac by the embryonic disc *(arrow with tails)*. The embryonic disc is composed of three distinct linings (see insert): ectoderm *(EC)*, embryonic mesoderm, *(EM)*, and endoderm *(EN)*. (From Hajdu, S.I., and Hajdu, E.O.: *Cytopathology of Sarcomas and Other Nonepithelial Malignant Tumors.* Philadelphia, W.B. Saunders, 1976.)

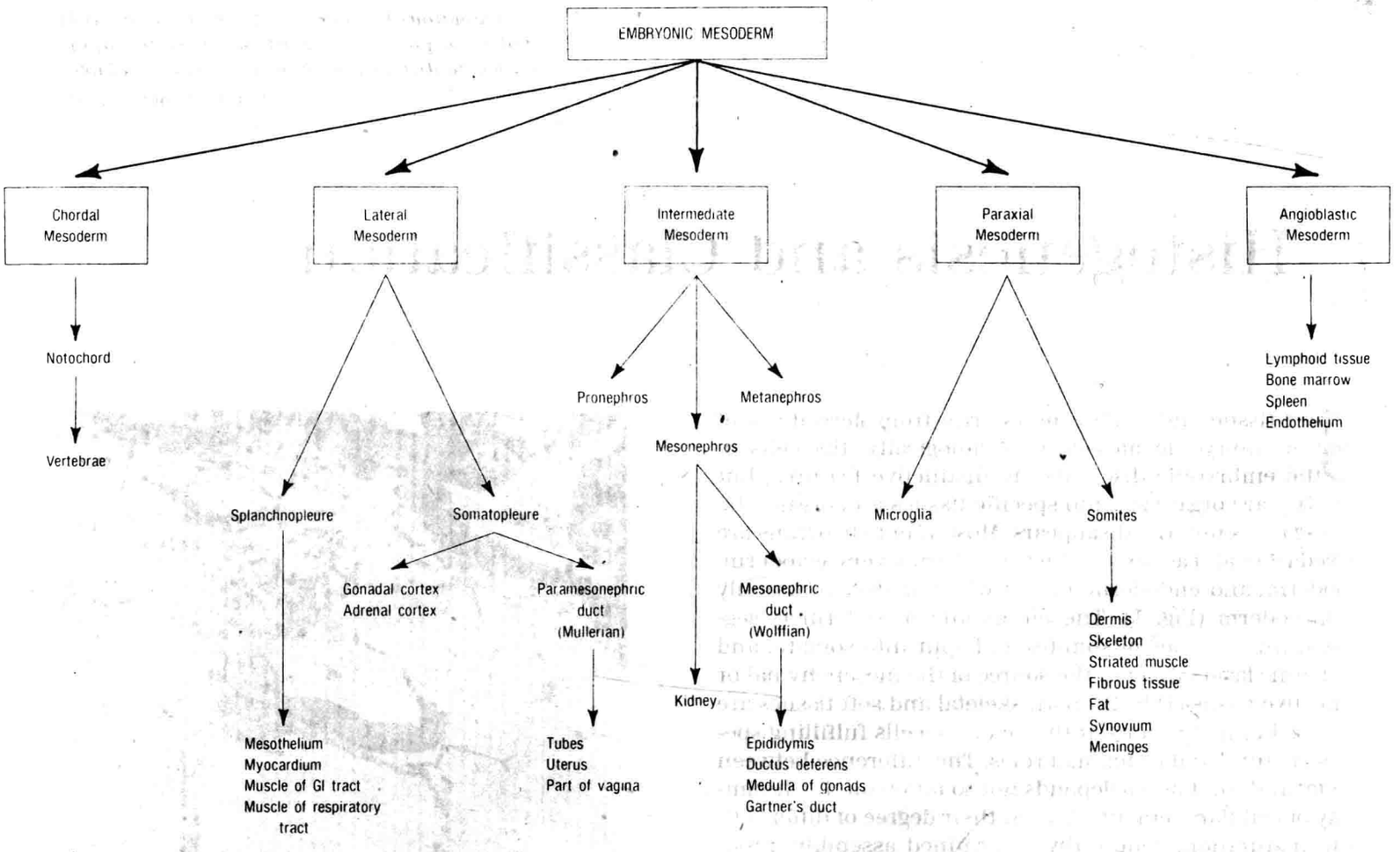

FIG. 2. Schematic illustration of the origin of various organs and organ systems from the embryonic mesoderm through a series of intermediate structures. Note the role of the *lateral mesoderm* in the development of the mesothelial lining, the smooth muscle, and female genitalia. Practically all soft tissues and the skeleton develop from the *paraxial mesoderm*; the entire lymphoreticular system originates from the *angioblastic mesoderm*. (From Hajdu, S.I., and Hajdu, E.O.: *Cytopathology of Sarcomas and Other Nonepithelial Malignant Tumors*. Philadelphia, W.B. Saunders, 1976.)

sarcoma, primitive neuroectodermal tumor, and Ewing's sarcoma, is analogous to that in acute leukemia and some lymphocytic neoplasms (Fig. 4). Similarly, there is no such thing as "malignant degeneration."

Soft tissues and bones are composed of clones of mesenchymal cells such as adipocytes, fibroblasts, osteoblasts, chondroblasts, and hematopoietic elements. The diversity and dissimilarity of these cells are expressed in the tissue pattern of the organs they build. Both differentiated and undifferentiated tumors may be composed of a combination of cellular elements at various stages of differentiation and may grow in a variety of tissue patterns. Once it is recognized that cell morphology and tissue patterns are subject to modulation and changes, and are influenced by local tissue conditions and a host of other factors, it is not difficult to understand that mesenchymal tissues and tumors (primary, recurrent, and metastatic) may assume, permanently or temporarily, dangerously misleading, overlapping, tissue patterns and cell morphology (Fig. 5). Therefore, different pathologists may label primary, recurrent, and metastatic soft tissue and bone neoplasms differently, and occasionally the same pathologist may call the same tumor by different names.

In many tumors, for example, in epithelial or glial tumors, the differences in growth patterns exhibited by the tumor cells are a reliable guide to the tissue of origin. In soft tissue and bone tumors, however, the relationship between differentiation and cell of origin is often blurred by the nonspecific assembly of undifferentiated cellular elements that may show no apparent structural differences between reactive and neoplastic growths. In 1919, James Ewing wrote that "the capacity of connective tissue to indulge in exuberant reactive or reparative growth is remarkable." No one would deny that actively growing reactive lesions, for example, granuloma, fasciitis, myositis ossificans, or callus, may contain all, or nearly all, the cellular elements that embryonic mesenchyme can produce and may mimic neoplastic growth.

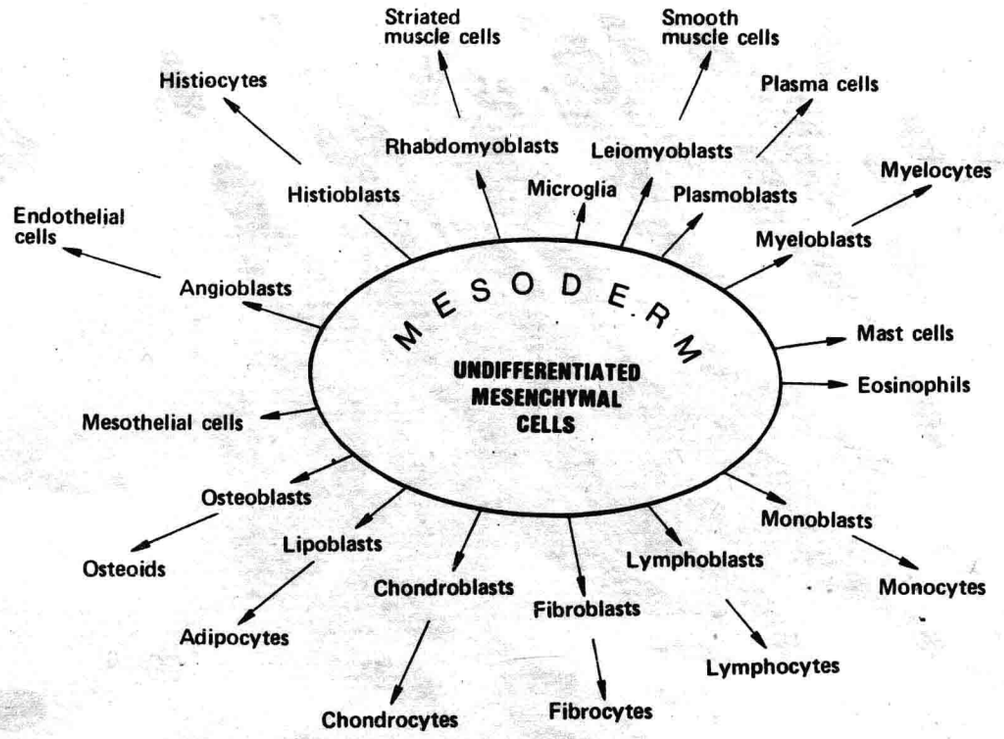

FIG. 3. Primitive mesenchymal cells may produce any of these forms. Undifferentiated, blastic or poorly differentiated, cells may mature and become well differentiated forms (Modified from Hajdu, S.I.: *Pathology of Soft Tissue Tumors.* Philadelphia, Lea & Febiger, 1979.)

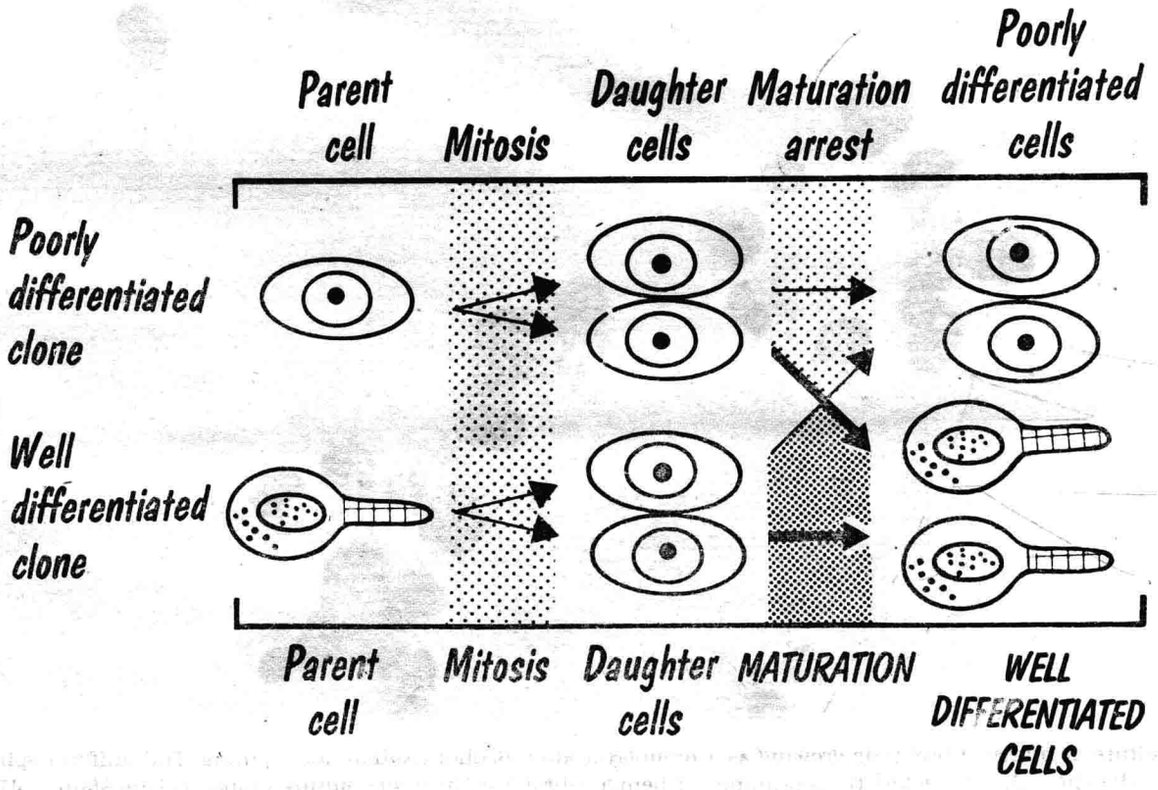

FIG. 4. Poorly differentiated as well as well-differentiated cells may enter mitosis. At the completion of mitosis, the daughter cells may remain undifferentiated, arrested (see right upper half), or may mature and become well-differentiated forms (see right lower half).

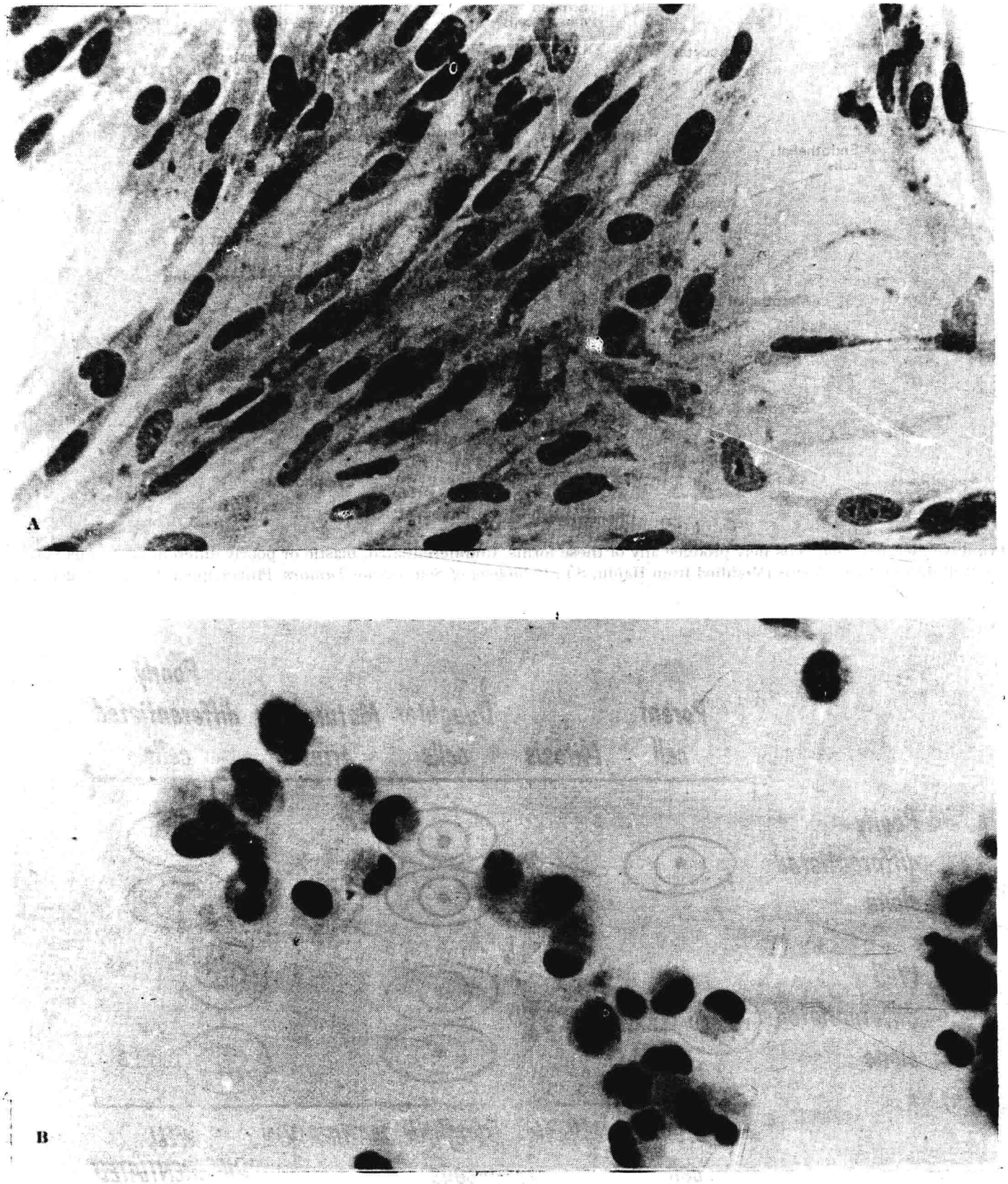

FIG. 5A. Tissue culture of human fibroblasts growing as a monolayer after alcohol fixation and staining. The uniform spindly fibroblasts with regular oval nuclei show the characteristic appearance of benign fibroblasts in tissue culture (Papanicolaou stain, ×470). B. Human fibroblasts identical in origin with that in Figure 5A in a smear prepared from suspension of a trypsinized monolayer tissue culture. Note the striking difference in microscopic appearance of fibroblasts from that of Figure 5A as the result of trypsinization.

Ascertaining the cell of origin for many soft tissue and bone tumors is still problematic, but it seems that there is a general agreement among investigators that soft tissue and bone tumors originate from primitive pluripotential mesenchymal cells. Traditionally, soft tissue and bone tumors have been discussed in different texts, and bone pathology, especially bone tumor pathology, has enjoyed an exclusive status for more than a century and has been promoted in more than three dozen books and monographs. Not until 1979 was the first comprehensive text on the pathology of soft tissue tumors published (Tables 1 and 2). The artificial separation of mesenchymal tumors according to anatomic boundaries (that is, intraskeletal, bone, and extraskeletal, soft tissue) served its purpose, but also produced setbacks and disappointment. Who has not felt frustrated from time to time with the ambiguous, constantly changing, and confusing terminology? And how many pathologists have misused or misunderstood the various names and definitions of soft tissue and bone tumors while evaluating their pathologic and clinical behavior?

Due to a sectarian or exclusive club approach, the present generation of pathologists inherited a dozen or more different names of lesions that look microscopically similar or identical in soft tissues and bone (Table 3). Virchow recognized in the mid-1800s that "osteosarcoma is an ossified fibrosarcoma," and Stout stated in 1953 that "extraskeletal

TABLE 1. *Books and Monographs on Soft Tissue Tumors*

Pack, G.T., and Ariel, I.M.: Tumors of Soft Somatic Tissues. New York, Paul Hoebner Inc., 1958.

Saavedra, J.A.: Sarcomas y Lesiones Seudosarcomatosas de Partes Blandas. Mexico, La Prenna Medica Mexicana, 1967.

Stout, A.P., and Lattes, R.: Tumors of the Soft Tissues. Atlas of Tumor Pathology. 2nd Ed. Washington, D.C., Armed Forces Institute of Pathology, 1967.

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TABLE 2. *Books and Monographs on Bone Tumors*

Coley, B.L.: Neoplasms of Bone. Hagerstown, Hoebner Medical Division, 1948.

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Bogumill, G.P., and Schwamm, H.A.: Orthopaedic Pathology. Philadelphia, W.B. Saunders, 1984.

Bullough, P.G., and Vigorita, V.J.: Atlas of Orthopaedic Pathology with Clinical and Radiologic Correlations. Baltimore, University Park Press, 1984.

TABLE 3. *Microscopically Identical Lesions Known by Different Names in Soft Tissue and Bone Pathology*

SOFT TISSUES		BONE
Tendosynovitis	=	Aneurysmal bone cyst
Benign fibrous histiocytoma	=	Nonossifying fibroma
Xanthogranuloma	=	Nonossifying fibroma
Fibromatosis	=	Fibrous dysplasia
Fibroma	=	Desmoplastic fibroma
Desmoid tumor	=	Desmoplastic fibroma
Histiocytic fibrous histiocytoma	=	Giant cell tumor
Osseous metaplasia	=	Desmoplastic bone formation
Hemangiosarcoma	=	Hemangioendothelioma
Scar	=	Callus
Fat necrosis	=	Bone infarct
Abscess	=	Osteomyelitis
Synovial chondromatosis	=	Chondroblastoma
Granulocytic sarcoma	=	Granulocytic leukemia

chondrosarcomas show the histologic characteristics that are generally accepted as characterizing chondrosarcoma of bone." The concept that giant cell tumor of bone is microscopically different from giant cell tumor of soft tissues has no foundation.

A peculiar difference between soft tissue and bone tumors is that a host of reactive lesions and benign tumors are not known to occur in bone, possibly because they are asymptomatic and remain undetected. Consequently, the introduction of new names and terms that do not indicate the tumor's pathophysiologic or histogenetic roots is useless and confusing. Not to realize that osteoid is a specialized form of collagen, or that there is no such thing as synovioma, or that the so-called "osteoclasts" in bone are multinucleated histiocytic forms in soft tissues will lead to the continuation of misuse of terms, propagation of misunderstanding, and mismanagement of patients.

There is no statistically reliable, all-inclusive figure for soft tissue and bone tumors. However, it is estimated that over 6,000 new cases of soft tissue sarcomas and fewer than 2,000 bone sarcomas are diagnosed annually in the United States. While soft tissue sarcomas represent about 1% of all malignant neoplasms in adults and 7% in children, skeletal sarcomas are responsible for less than 0.2% of malignant tumors in adults and 5% in children. Because of their rarity, soft tissue and bone sarcomas represent a rather minor part of the diagnostic experience of pathologists; about a dozen centers are large enough to see a sufficient number of soft tissue and bone tumors to be familiar with the microscopic appearance of all variants. In addition, soft tissue and bone tumors are heterologous lesions, and their wide morphologic range reflects the complexity of mesenchymal tissues from which they stem; there are over 200 more or less well-defined microscopic forms of soft tissue and bone tumors, of which 72 are malignant neoplasms, 69 benign neoplasms, and 85 reactive, non-neoplastic lesions that may resemble neoplasms (Fig. 6).

We must also be cognizant that benign non-neoplastic and benign neoplastic lesions outnumber malignant neoplasms by a margin of about 100 to 1. Due to overlapping morphology of many benign and malignant lesions and the inability of pathologists to recognize "borderline connective tissue lesions" and "sarcoma in situ," connective tissue neoplasms traditionally are called either benign or malignant. This type of classification is fueled by the view held by some workers that most soft tissue and bone sarcomas are malignant de novo, and very few have benign precursors. While it is tempting to take issue with such thinking (Table 4), it is perhaps sufficient to point out that there was a time when lesions, for example, carcinoma in situ of the uterine cervix, the urinary bladder, and the stomach, were not recognized. Some physicians have held on to their views for decades, believing that adenocarcinoma of the colon never develops in a polyp, or that a mammary lesion such as lobular carcinoma in situ does not exist.

Without doubt, a number of problems in regard to the histogenesis and pathology of sarcomas remain to be solved. Whatever the histogenesis, pathologists may enhance the diagnosis of soft tissue and bone neoplasms by knowing the clinical presentation, size, site, radiologic appearance, and age of the patient. It is needless to say that in most cases close cooperation between the surgeon, radiologist, and pathologist is essential in order to arrive at an accurate microscopic diagnosis. It must also be recognized that the role of the pathologist is not ancillary but crucial in the diagnosis of soft tissue and bone tumors, a difficult and complex task with serious therapeutic ramifications. Those who doubt the complexity of diagnosis should remember Osler's advice to his clinical colleagues, "You are as good as your pathologist."

No pathologist should render final diagnosis without having access to clinical history and radiologic findings, for as Lauren Ackerman said, "The pathologist can make enough errors with all available information." The more information the pathologist has the more information the pathologist can give. The proper time to evaluate the clinical information and radiologic findings is after, and not before, the histology has been assessed, but prior to issuing a definitive diagnosis. If a pathologist has been forced to make a diagnostic decision without accurate clinical information, or has been given misinformation and has committed an error in diagnosis, the blame should be placed on those who misled the pathologist. Also, the practice of seeking an unbiased second opinion, that is, asking the pathologist to render a diagnosis without clinical and other information pertinent to the case, should be discouraged. One does well to remember the view held by Boyd: "It is the high function of the pathologist not merely to attach correct labels to lesions, but to reconstruct the course of events from the earliest inception of disease to the final moment of life."

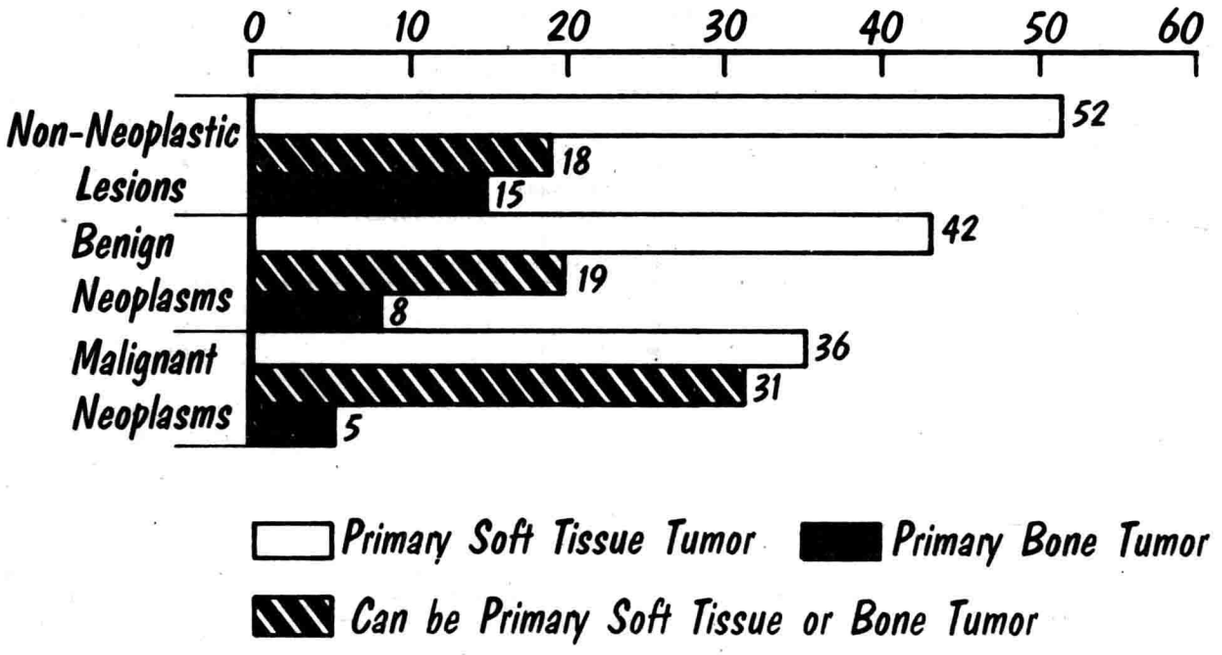

FIG. 6. Comparison of approximate number of soft tissue and bone tumors.

The better understanding of sarcomas was held back for centuries by, among other things, misuse and misunderstanding of various names and definitions that were often due to the unavailability of accurate information or to plain ignorance. Galen defined sarcomas in such a way that many forms of inflammation or infectious swelling, as well as all sorts of benign neoplasms, were called "sarcomas." As late as the mid-1800s, Rokitansky stated that "Sarcomata represent benign new-growths, they are always purely local affections, they are curable by complete extirpation: that is, they do not recur at the same spot, and still less do they multiply in other localities."

Current classification schemes of soft tissue and bone tumors separate tumors whose cell of origin is thought to be known and those whose histogenesis is not known. These schemes are the result of the work of many pathologists, to mention just a few, Johannes Muller, Virchow, James Ewing, Henry Jaffe, and Stout. As new diagnostic techniques develop, it will be possible to establish the histogenesis of soft tissue and bone tumors more and more accurately; and in the great majority of cases, the present classification schemes will need revision. It is hoped though that frequent revision will not take place.

Histogenetic classification, based on characteristic microscopic features, permits subdivision of tumors regardless of the anatomic site of the tumor or age of the patient. A classification that departs from such a scheme would be equivalent to comparing apples with oranges or to classifying dogs as the gypsies did in former times—according to

TABLE 4. *Some Benign Lesions Known to Undergo Malignant Transformation*

Benign fibrous histiocytoma
Scar
Fibromatosis
Fibrous dysplasia
Tendosynovitis
Lipoma
Angiomyolipoma
Angiomyoma
Myositis ossificans
Leiomyoma
Benign glomus tumor
Infarct
Lymphedema
Neurofibroma
Benign schwannoma
Benign paraganglioma
Benign mesothelioma
Chondroblastoma
Enchondroma
Osteochondroma
Osteoblastoma
Paget's disease
Osteomyelitis
Benign thymoma
Benign granular cell tumor
Meningioma
Benign cystosarcoma phyllodes
Benign mesenchymoma

TABLE 5. *Histogenetic Classification of Soft Tissue and Bone Tumors**

	NON-NEOPLASTIC LESIONS	BENIGN NEOPLASMS	MALIGNANT NEOPLASMS
Undifferentiated Connective Tissue Tumors	● Aneurysmal bone cyst ● Giant cell granuloma ● Hyperparathyroidism ○ Xanthogranuloma ◑ Foreign body granuloma	◑ Benign fibroblastic fibrous histiocytoma ◑ Benign histiocytic fibrous histiocytoma ◑ Benign pleomorphic fibrous histiocytoma ● Nonossifying fibroma	◑ Malignant fibroblastic fibrous histiocytoma ◑ Malignant histiocytic fibrous histiocytoma ◑ Malignant pleomorphic fibrous histiocytoma
Fibrous Tissue Tumors	○ Fasciitis ○ Fasciitis ossificans ○ Scar ○ Keloid ○ Fibromatosis ○ Fibromatosis ossificans ● Fibrous dysplasia ○ Elastofibroma ○ Collagenoma	○ Fibroma ● Desmoplastic fibroma ● Ossifying fibroma	◑ Desmoid tumor ◑ Fibroblastic fibrosarcoma ◑ Pleomorphic fibrosarcoma
Tendosynovial Tumors	○ Tendosynovitis ◑ Tendosynovial cyst ○ Tendosynovial chondromatosis ○ Tendosynovitis ossificans ○ Granulomatous tendosynovitis ○ Rheumatoid arthritis ◑ Osteoarthritis ○ Gouty arthritis ○ Pseudogout ○ Carpal tunnel syndrome	○ Fibroma ○ Lipoma ○ Benign histiocytic fibrous histiocytoma	○ Biphasic tendosynovial sarcoma ○ Monophasic tendosynovial sarcoma, spindle cell type ○ Monophasic tendosynovial sarcoma, pseudoglandular type ○ Epithelioid sarcoma ○ Clear cell sarcoma ○ Chordoid sarcoma ○ Malignant histiocytic fibrous histiocytoma
Adipose Tissue Tumors	◑ Fat necrosis ◑ Lipogranuloma ○ Proliferative panniculitis ○ Panniculitis ossificans ○ Lipodystrophia ○ Adiposis dolorosa ○ Steatopygia ○ Piezogenic papule	◑ Well-differentiated lipoma ◑ Myxoid lipoma ◑ Fibroblastic lipoma ○ Lipoblastoma ◑ Pleomorphic lipoma ◑ Angiolipoma ○ Angiomyolipoma ○ Myelolipoma ○ Hibernoma	◑ Well-differentiated liposarcoma ◑ Myxoid liposarcoma ◑ Lipoblastic liposarcoma ◑ Fibroblastic liposarcoma ◑ Pleomorphic liposarcoma
Muscle Tumors	○ Proliferative myositis ○ Myositis ossificans ○ Fibromatosis ○ Atrophy ○ Dystrophy ○ Polymyositis ○ Rhabdomyolysis	◑ Leiomyoma ○ Leiomyomatosis ○ Rhabdomyoma ○ Lipoma ◑ Angiomyoma	◑ Leiomyoblastoma ◑ Leiomyosarcoma ○ Embryonal rhabdomyosarcoma ○ Alveolar rhabdomyosarcoma ○ Myxoid rhabdomyosarcoma ○ Rhabdomyoblastoma ○ Pleomorphic rhabdomyosarcoma
Tumors of Vessels	○ Pyogenic granuloma ○ Angifollicular lymphoid hyperplasia ◑ Arteriovenous malformation ◑ Hereditary hemorrhagic telangiectasia ◑ Vasculitis ◑ Infarct ○ Lymphedema ○ Cystic hygroma	◑ Capillary hemangioma ◑ Cavernous hemangioma ◑ Arteriovenous hemangioma ○ Venous hemangioma ○ Hypertrophic hemangioma ◑ Hemangiomatosis ◑ Papillary endothelial hyperplasia ○ Hemangioblastoma ○ Angiofibroma ○ Angiomyoma ◑ Angiolipoma ○ Angiomyolipoma ◑ Benign glomus tumor ○ Lymphangioma ○ Lymphangiomatosis ○ Lymphangiomyoma ○ Lymphangiomyomatosis	◑ Hemangiopericytoma ◑ Hemangiosarcoma ○ Lymphangiosarcoma ◑ Leiomyosarcoma ◑ Malignant glomus tumor ○ Malignant angiomyolipoma

	NON-NEOPLASTIC LESIONS	BENIGN NEOPLASMS	MALIGNANT NEOPLASMS
Tumors of Peripheral Nerve	○ Traumatic neuroma ○ Hypertrophy ○ Degeneration	◑ Neurofibroma Pacinian neurofibroma Myxoid neurofibroma Plexiform neurofibroma Benign Triton tumor Neurofibromatosis ◑ Benign schwannoma Benign glandular schwannoma Benign nevoid schwannoma Benign pigmented schwannoma ◑ Benign undifferentiated peripheral nerve tumor Benign neuroepithelioma	◑ Neurofibrosarcoma Malignant Triton tumor ◑ Malignant schwannoma Malignant glandular schwannoma Malignant nevoid schwannoma Malignant pigmented schwannoma ◑ Malignant undifferentiated peripheral nerve tumor Primitive neuroectodermal tumor Malignant neuroepithelioma
Tumors of Autonomic Nerve		◑ Neuroma ◑ Ganglioneuroma ○ Benign paraganglioma	○ Neuroblastoma ○ Ganglioneuroblastoma ○ Malignant paraganglioma
Mesothelial Tumors	○ Mesothelial hyperplasia ○ Hydrocele ○ Mesothelial cyst	○ Benign epithelioid mesothelioma ○ Benign fibrous mesothelioma ○ Adenomatoid tumor	○ Malignant epithelioid mesothelioma ○ Malignant fibrous mesothelioma
Cartilage-producing Tumors	◑ Chondroid metaplasia ○ Tendosynovial chondromatosis ● Callus ● Prolapsed intervertebral disc	● Chondroblastoma ● Chondromyxoid fibroma ◑ Chondroma ● Osteochondroma	◑ Well-differentiated chondrosarcoma ◑ Poorly differentiated chondrosarcoma ◑ Myxoid chondrosarcoma ◑ Mesenchymal chondrosarcoma
Osteoid-producing Tumors	● Paget's disease ● Enostosis ◑ Osteoid metaplasia ● Callus ◑ Periostitis ○ Fibromatosis ossificans ○ Fasciitis ossificans ○ Panniculitis ossificans ○ Myositis ossificans ○ Fibrodysplasia ossificans progressiva	● Osteoblastoma ● Osteoid osteoma ○ Osteoma ● Ossifying fibroma	◑ Osteosarcoma Fibrous histiocytic osteosarcoma Fibrosarcomatous osteosarcoma Chondrosarcomatous osteosarcoma Osteoblastic osteosarcoma Telangiectatic osteosarcoma Sclerosing osteosarcoma ◑ Parosteal osteosarcoma ● Paget's sarcoma
Lymphoreticular Tumors	◑ Eosinophilic granuloma ◑ Histiocytosis ◑ Lymphoid hyperplasia ○ Lymphocytoma cutis ● Leukocytosis ○ Mastocytosis ● Osteomyelitis ◑ Plasma cell granuloma ○ Thymic cyst ○ Angiofollicular lymphoid hyperplasia ○ Angiomatous lymphoid hamartoma	○ Benign thymoma	◑ Granulocytic sarcoma ● Leukemia ○ Mycosis fungoides ◑ Malignant lymphoma ○ Hodgkin's disease ◑ Plasmacytoma ● Plasma cell myeloma ○ Malignant thymoma
Miscellaneous Tumors	◑ Amyloidoma ◑ Gaucher's disease ◑ Osteogenesis imperfecta ◑ Mucopolysaccharidoses ● Hypophosphatasemia ● Hyperphosphatasemia ● Osteoporosis ● Osteomalacia	○ Benign granular cell tumor ○ Meningioma ○ Benign cystosarcoma phyllodes ◑ Benign mesenchymoma ● Ecchordosis physaliphora	○ Malignant granular cell tumor ○ Alveolar soft part sarcoma ○ Kaposi's sarcoma ○ Meningeal sarcoma ○ Malignant cystosarcoma phyllodes ◑ Ewing's sarcoma ● Chordoma ● Adamantinoma ◑ Angioendotheliomatosis ◑ Radiation induced sarcoma ◑ Chemotherapy induced sarcoma ◑ Malignant mesenchymoma ◑ Undifferentiated sarcoma

*○ Primary soft tissue tumor; ● primary bone tumor; ◑ can be primary soft tissue or bone tumor.

the length of the tail, the size of the body, the shape of the ears, and whether the dog belonged to the king. No one would deny that soft tissue and bone tumors are often difficult to classify, especially in limited material, according to their histogenesis. The histogenesis of a tumor is, after all, a conclusion arrived at by inference and deduction based on experience, not by seeing the cell of origin. Although determining the histogenesis of a tumor may remain problematic and controversial in many instances, it should not be ignored and must be included in therapeutic planning.

Contrary to the wishes of some writers to create more and more new labels, it is perhaps time to concentrate on the comparison, organization, and redefinition of existing entities. Lumping histogenetically related but microscopically and prognostically different lesions is not done for the sake of "convenience," but because the lesions are common in origin. Furthermore, it is logical, scientific, and practical: who would deny that uterine stromal sarcoma, leiomyosarcoma, and mesodermal mixed tumor, despite different histologic appearance and behavior, are histogenetically related uterine neoplasms? Consequently, it should not take too much effort to recognize that histogenetically such diverse neoplasms may originate in a common organ or an organ system, although they look unrelated in microscopic appearance: who would deny the microscopic and behavioral dissimilarity of various gliomas, pulmonary neoplasms, bone neoplasms, skin tumors, or peripheral nerve tumors?

Some writers do not attempt to distinguish between benign neoplasms and non-neoplastic, reactive lesions because they believe "it has no practical value." So simplistic an approach cannot be anything but the result of detachment from clinical reality. Is it practical to distinguish inflammatory pseudopolyps of the colon from villous adenoma, parathyroid hyperplasia from parathyroid adenoma, giant cell granuloma from giant cell tumor, or mastitis from duct hyperplasia? If the answer is affirmative, I propose that the subdivision of soft tissue and bone tumors for non-neoplastic lesions, benign neoplasms, and malignant neoplasms is to be retained until there is satisfactory proof that such a classification is obsolete (Table 5).

Soft tissue and bone tumors often pose a diagnostic challenge and, no matter how well experienced the pathologist is, there will be a certain number of tumors that cannot be placed in existing categories because a number of tumors are characterized by microscopic similarities. There is no perfect classification and none should be written in stone. In 1939, Bucy and Gustafson said that "Classification must be regarded as providing merely arbitrary pockets into which we can place tumors in order that they may be more easily considered." It would be wrong to call every pleomorphic neoplasm that contains a fibrous histiocytic, undifferentiated mesenchymal component a fibrous histiocytoma, just as it would be a mistake to label all neoplasms that have pericytic areas hemangiopericytomas.

Like other neoplasms, soft tissue and bone neoplasms must have a beginning, developing from the preneoplastic and incipient (borderline or equivocal) phases to the established (or in-situ) and invasive phases (Fig. 7). It must be remembered that a biopsy from a tumor, at a given phase, is like a single frame from a movie film and the time it takes to progress from one phase to another may vary from tumor to tumor, for as James Ewing said, "Beyond the autonomy of growth, it is difficult to add any element that will apply to all tumors."

Our inability to detect the submicroscopic changes that take place in the DNA during the preneoplastic or induction phase hinder early detection. It may require years before the neoplasm passes through the preneoplastic phase and enters the incipient (proliferative cellular, atypical or borderline) phase. A neoplasm may remain for months or years in the incipient phase and may be characterized by an unclearly defined cytologic and histologic mutation; as a rule, it usually remains small and asymptomatic, and it is seldom diagnostic. Most sarcomas in the established (in-situ) phase are symptomatic, reach variable size, and can be diagnosed, though not without difficulty. Sarcomas may remain in the invasive phase for weeks or months prior to entering the metastatic phase.

Most malignant soft tissue and bone neoplasms are diagnosed in the invasive phase because they are symptomatic. In general, they are about 5 cm in size, exhibit characteristic growth patterns, and show identifiable cytologic abnormalities (Table 6). The earlier the lesion, the greater the margin of uncertainty in histologic diagnosis. The fact that sarcomas can be mistaken for benign lesions is proof of their deceptively harmless microscopic appearance during the initial phases of growth. This complicates matters further, for as Mackenzie said, "Innocent morphology is not always accompanied by innocent behavior." Experience may reduce the margin of uncertainty but does not abolish it. If a clear distinction between a benign and a malignant neoplasm cannot be made, the use of the term "borderline" is advisable to express our uncertainty as to its potential behavior (Table 7). The interpretation of the borderline or histologically equivocal neoplasm is a difficult one, and may vary from pathologist to pathologist because borderline neoplasms show the earliest structural changes. Once the neoplasm has entered the metastatic phase, the local tissue conditions, resistance of the host, aggressiveness of the neoplastic clone, and effectiveness of the therapy are what decide the duration and the outcome of the disease.

The cause of soft tissue and bone tumors is, with a few exceptions, unknown. The list of forms and types non-neoplastic lesions may assume is endless. Most known benign neoplasms have known malignant counterparts. Those few benign neoplasms that do not are listed in Table 8. Likewise, there are only a dozen malignant neoplasms without corresponding benign forms (Table 9).