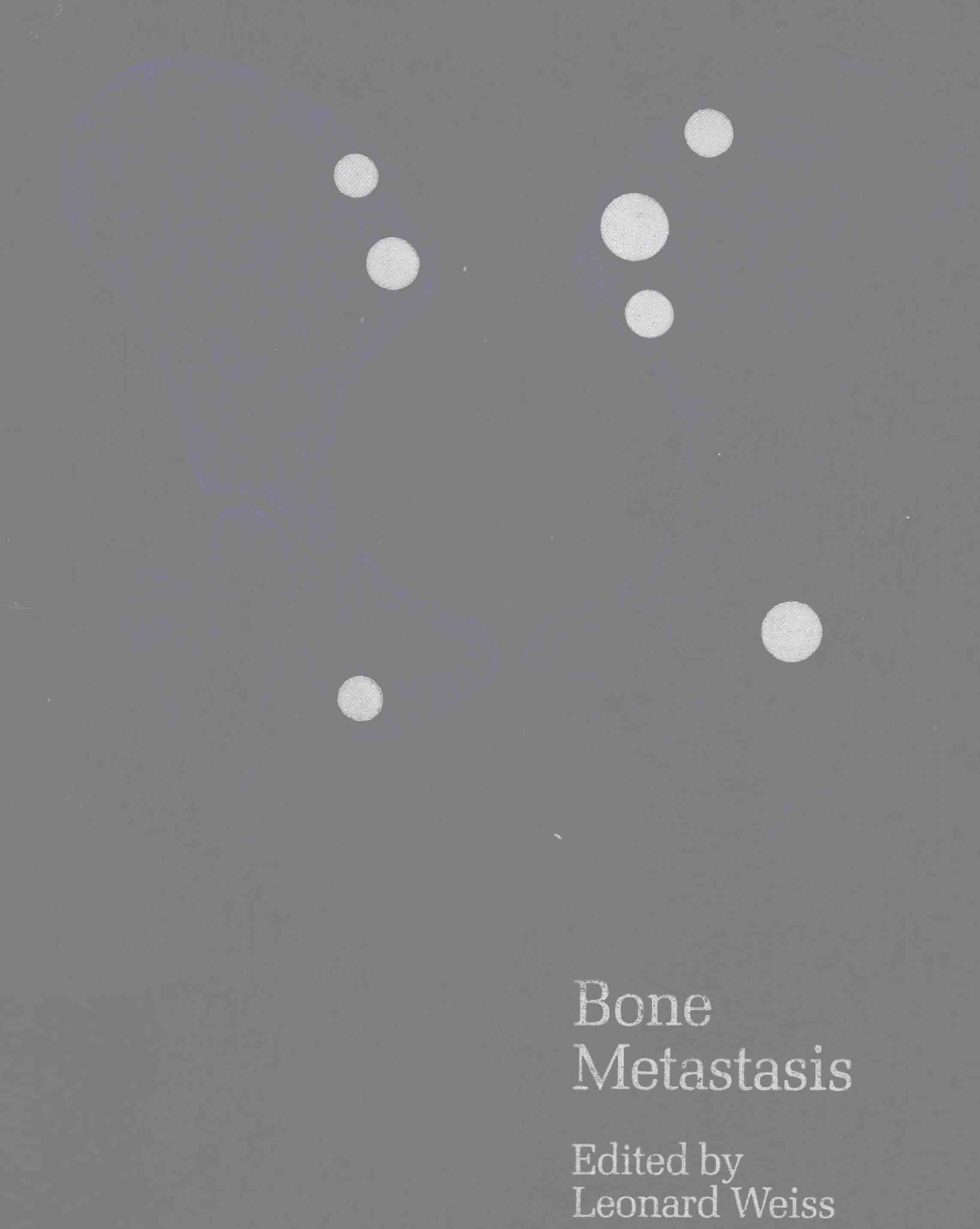

Bone Metastasis

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Dedication

This book is dedicated to the memory of Oscar V. Batson, M.D., Sc.D., who contributed so much to our understanding of skeletal metastases. In recognition of his studies on the vertebral venous system, he is the only anatomist among 225 pioneers listed in *Classical Descriptions in Diagnostic Roentgenology.* Professor Batson showed great interest in this project, and although at age 85 he was not able to attend the workshop, he graciously permitted us to reprint his Caldwell lecture. He died on November 10th, 1979, while the manuscripts were being edited.

Preface

This book, which is the fourth volume in our series on metastasis by site, is an expanded version of a small workshop on bone metastasis held at the Orthopaedic Hospital, Los Angeles, on September 20th and 21st, 1979. We were fortunate in having as a co-chairman in this specialized field the late David C. G. Monsen, director of oncology at the Orthopaedic Hospital, Los Angeles.

Once again we are indebted to our participants for their contributions to this endeavor, and for enabling us to explore bone metastases in depth. In common with our texts on *Pulmonary Metastasis*, *Brain Metastasis*, and *Lymphatic System Metastasis*, we have brought together in this book, basic aspects of the subject and the clinical problems of diagnosis and treatment. Through our choice of representatives of different treatment centers, we have attempted to present areas of agreement and disagreement in an unbiased manner.

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Leonard Weiss
Harvey A. Gilbert

Introduction

The commonest tumors in bones are metastases. In this volume we present an up-to-date account of some of the basic aspects of bone metastases, their diagnosis and treatment.

In a survey of the history of bone metastasis (Chapter 1) Onuigbo reminds us that all that is old is not wrong, and all that is "new" is not original. We recall Chaucer, in the Parlement of Fowles,

> "For out of olde feldes, as men seith,
> Cometh al this new corn fro yere to yere;
> And out of olde bokes, in good feith,
> Cometh al this newe science that men lere."

An early step in the metastatic cascade is the release of cancer cells from primary cancers. Gullino and Liotta (Chapter 2) describe direct measurements of the release of cancer cells from the MTW9 rat mammary carcinoma, which lead to the estimate that three to four million cancer cells are shed into the blood per gram of tumor per 24 hours. If extrapolations can be made from Gullino and Liotta's animal experiments to people, the magnitude of discrepancy between the numbers of circulating cancer cells and the numbers of metastases developing, emphasize the inefficiency of the metastatic process in terms of cancer cells. Regardless of the mechanisms resulting in metastatic inefficiency, it should be appreciated that in its absence most cancers would be widely disseminated at diagnosis, the prospects of obtaining cures by eradication of primary lesions would be negligible, and all regional cancer therapy would be palliative. The lysis of tumor stroma by pressure and by highly specific enzymes is also described by Gullino and Liotta in terms of microenvironmental alteration and equilibrium, and degradation of basement membrane; both of these processes being central to metastasis. Collagenolysis and enzymatic destruction of tissues are taken up by other authors, as will be discussed.

The delivery of released cancer cells to the site of presumptive metastases is also an essential part of metastasis. Anatomic considerations, particularly in relationship to the extracaval routes to the skeleton by way of the vertebral venous systems, owe much to the pioneering studies of Oscar V. Batson. We are therefore honored to reproduce his Caldwell lecture of 1956 (Chapter 3) in which he described the steps by which he deduced that the vertebral venous system "furnished the only anatomic pattern that coincided with the distribution of prostatic metastases." As described by Galasko (Chapter 4), Batson's major conclu-

sions are generally accepted today, although it is now realized that analysis of distribution patterns is considerably complicated by the metastasis of metastases, as discussed by Viadana and associates (Volume I), and Bross (Volume II) in their concept of metastatic cascades. Another analytic complication is that the inefficiency of the metastatic process is superimposed on anatomic delivery systems.

The mechanisms of osteolysis, which underlie the clinically important pathologic fractures, are discussed by Mundy and Spiro (Chapter 5), Galasko (Chapter 6), and Taylor and Haskell (Chapter 7). Mundy and Spiro consider that bone resorption is caused by the release of enzymes from both cancer cells and osteoclasts that are activated by an osteoclast activating factor (OAF), a lymphokine of tumor products with lymphocytes. The activated lymphocytes apparently will not release OAF in the absence of prostaglandins of the E series that are produced by monocytes, and that stimulate cyclic adenosine monophosphate (cAMP) accumulation in the lymphocytes. It is of interest that in model systems in the presence of drugs inhibiting prostaglandin synthesis (e.g., indomethacin), both cAMP accumulation in, and release of OAF by lymphocytes is inhibited. It is therefore disappointing to note that up to the present, indomethacin has not been proved effective in reducing the incidence of bone metastases in patients with breast cancer.

Galasko (Chapter 6) describes his work with the VX2 carcinoma, injected directly into the medullary cavities of rabbits' tibias and ilia, where growth is associated with the two distinguishable ongoing processes of new bone formation and bone destruction. In cancers associated with a suitable fibrous stroma, intramembranous ossification may occur, in addition to the reactive new bone formation similar to callus formation following a fracture. These two types account in part for the radiologic appearance of skeletal metastases (Schreiber, Chapter 10). Galasko considers that in the case of carcinomas metastasizing to bone, the earlier and quantitatively more important phase of osteolysis is caused by osteoclast activity brought about by various stimulating substances secreted by tumor cells. These include prostaglandin, as distinct from OAF, which is the main humoral activator in myeloma and lymphoma. The late phase of osteolysis is due to the direct action of cancer cells.

Taylor and Haskell (Chapter 7) emphasize the equilibrium between osteoblastic and osteoclastic activities in maintaining the architecture of cortical bone, and how metastatic cancer may shift the balance in one direction or the other. They make the case for the necessity of multiple laboratory investigations for the assessment of bone metastases, and consider changes reflecting medullary involvement as distinct from those reflecting involvement of cortical bone. The former may be clinically occult or may be associated with myelophthisic anemia, whereas the latter may be associated with signs of osteoclastic (elevated total urinary hydroxyproline) or osteoblastic activity (elevated serum bone

alkaline phosphatase, total urinary hydroxyproline, and positive radionuclide bone scan). Taylor and Haskell emphasize that ionized serum calcium is the functional form of the element.

Hypocalcemia occurs in some 16% of patients with bone metastasis; this, rather than metastases per se, may be responsible for pain from so-called osteomalacia. The cause of the pain is not known for certain. Hypocalcemic tetany may also be induced by treatment that lyses large numbers of cells, thereby releasing large quantities of phosphate that precipitate calcium into the soft tissues. This provides a good example of regarding treatment as part of the natural history of cancer. Although hypercalcemia occurs in some 10% of patients hospitalized with cancer, it must be remembered that it may not be primarily caused by cancer. It does, however, occur more frequently in these patients. In most of these cases it appears that hypercalcemia is due to uncoupling of bone resorption from new bone formation, but in 30% of patients with hypercalcemia discrete skeletal lesions can be demonstrated. It is of interest that pyrophosphate analogs, the diphosphonates, block osteoclast activity and appear to inhibit tumor-induced osteolysis.

It has been well known for many years that cartilage is one of the most resistant tissues to invasion by metastases in bone; however, the mechanisms for this resistance have only been recently explored in depth. Kuettner and Pauli (Chapter 8) consider resistance in terms of the physical properties of cartilage, the degradability of its matrix, and the presence of inhibitors in the cartilage that prevent invasion by tumor cells and/or the neovasculature on which their growth depends. Kuettner and Pauli review the evidence that invasion of cartilage by either tumor or endothelial cells depends on proteolytic activity, and that an antiinvasive principle (AIF) present in cartilage effectively inhibits the enzymes involved. The fascinating possibility arises of isolating AIF and using it therapeutically to inhibit invasiveness in other tissues, and hence control metastasis. The authors argue that as physiologic invasion is virtually terminated by early adulthood, except for wound healing and sperm migration and capacitation, therapy directed at tumor invasiveness may not be as harmful to the adult organism as is the suppression of cell proliferation. It must be remembered, however, that proteolytic enzymes have important, normal physiologic functions that may also be inhibited by therapy of this type.

Histology remains the acid test of indirect diagnosis, but a controversial point is whether a needle biopsy can (Monsen, Chapter 13) or cannot (Schwinn, Chapter 9) provide an adequate source of material. The limited significance of a negative report on needle biopsies is well appreciated, and Monsen points out the advantages of a so-called controlled biopsy made by the radiologist. The interesting point is made by Schwinn that regardless of biopsy technique, in some 15% of patients with skeletal metastases, the primary sites of their cancers will not be established. Hopefully, the development of better markers will reduce the incidence of unknown primary lesions. At present, however, it is a

moot point whether the determination of sites of primary cancers will be of benefit to the patient.

The value of radionuclide scans in detection of metastases in bone is discussed by Low (Chapter 11), who considers that scans are not highly useful in asymptomatic patients, but that in patients with bone pain, scans may well initiate surgical or other therapy. At present, technetium Tc 99m and radiolabeled diphosphonate compounds are currently the reagents of choice; however, there are indeed possible alternatives. Ballou and associates (1979) are the most recent of a number of workers who have attempted to localize tumors in people and experimental animals by external scintigraphy, by the use of radiolabeled specific antibodies. All of these past methods suffered from the nonavailability of purified specific antibodies, and background activity caused by circulating antibody-antigen complexes and/or unbound antibody. The work of Ballou and his colleagues is particularly interesting as they used highly specific monoclonal antibodies labeled with iodine 125 produced in "hybridomas" against murine teratocarcinomas. After many false starts, it appears the hitherto elusive cancer-specific, tumor-associated antigens can be identified in human melanomas, some lung tumors, osteosarcomas, and breast cancers. Thus by use of the hybridoma technique, monoclonal antibody markers one day could hopefully be used in people. In this context, the question of specificity is important. For example, in a recent paper, Kempner and his colleagues (1979) describe human lung tumor-associated antigens that were present in 13 of 13 lung tumors. The antigens were also present in fetal tissue, normal brain, 2 of 8 colon tumors, 2 of 9 prostate tumors, and various cultured cell lines; however, they were not constituents of normal liver, kidney, lung, colon, or prostate tissue.

Schreiber (Chapter 10) discusses the value of standard x-ray procedures, not only as confirmatory in asymptomatic, scan-negative areas, but also as an independent approach. Although the presence of multiple destructive or blastic lesions in the skeleton of a person of middle age or older is strong evidence for metastasis, multiplicity itself is not absolutely diagnostic. Schreiber emphasizes that solitary metastatic foci can mimic almost any other solitary lesion. In Chapter 12, Kori, Krol, and Foley make note of the usefulness of computerized tomographic (CT) scans in the diagnosis of paraspinal masses and other soft tissue masses in the evaluation of specific bone pain syndromes, although CT scans are not used for assessing bone metastases per se.

An indication of the usefulness of the early diagnosis of lytic lesions in the treatment of metastasis in bone is given by Monsen (Chapter 13) and Harrington (Chapter 20). They emphasize the value of aggressive prophylactic reinforcement of regions with a high probability of pathologic fractures.

The therapy of metastases in bone must be evaluated in terms of quality of life. This involves much more than pain or anatomic instability from individual bone metastases, as indicated in a purely physical

sense by Taylor and Haskell's (Chapter 7) discussion of paraneoplastic syndromes. The quality of life, which was also discussed in the companion volume *Brain Metastasis*, is difficult to quantify. We are therefore indebted to McKenna (Chapter 14) for drawing on his considerable experience in the adaptation of patients to their environment, or in rehabilitation.

Drug therapy, of course, involves treating the whole patient, not just bone metastases. The section on chemotherapy begins with a general discussion by Cohen and Chan (Chapter 15) of drug distribution, particularly in bone. They review pharmacokinetic models, including those based upon physiologic values in which the patient is considered as a series of discrete regions interconnected by the circulatory system. This physiologic model should permit prediction of drug levels in tissues, other than blood, that cannot readily be sampled. An example of this approach is provided by their studies on Adriamycin clearance from the blood and tissue concentrations.

The chemotherapy of bone metastases is discussed by Bredt (Chapter 16), and Chlebowski and Block (Chapter 17). Note is made of the difficulty in assessing the response of skeletal metastases to therapy. Metastases from primary cancers of the breast, prostate, and lung (small cell carcinomas) may respond to chemotherapy and result in extended periods of palliated survival.

In patients with hormonally responsive tumors, hormone therapy may be beneficial, particularly if metastatic disease is widespread. Van Scoy-Mosher (Chapter 18) describes healing of bone lesions after hormonal manipulation. These responses may be relatively long-lasting and, compared with many chemotherapeutic agents, hormones are nontoxic.

Our earlier comments on the quality of life point to the effective use of analgesic drugs. Foley (Chapter 19) both analyzes causes of bone-related pain and rationalizes appropriate selections and doses of medications that achieve pain relief with minimal side effects.

Surgical management of pathologic fractures associated with metastases is covered in some detail by Harrington (Chapter 20). Although patients with pathologic fractures of their long bones have widespread malignancy, they should not be regarded as terminal events, as more than 20% of these patients survive for at least one year. If the fractures are treated with bed rest, few will heal, and the patients' immobility will generate other medical complications. An aggressive treatment of fractures, or prophylaxis by fixation with metal devices and acrylic cement in patients with a prognosis exceeding several months, results in restoration of mobility in or out of bed, and often allows healing after subsequent radiation therapy.

During the workshop, Dr. Ronald Rooney (formerly of the Memorial Hospital, N. Y.) emphasized that en bloc excision of bone metastases is only rarely useful. Thus, fewer than 2% of all patients with renal cell cancer metastatic to bone have an indolent, isolated boney