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Research article

Neoplasm or not? General principles of morphologic analysis of dry bone specimens

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ABSTRACT

Unlike modern diagnosticians, a paleopathologist will likely have only skeletonized human remains without medical records, radiologic studies over time, microbiologic culture results, etc. Macroscopic and radiologic analyses are usually the most accessible diagnostic methods for the study of ancient skeletal remains. This paper recommends an organized approach to the study of dry bone specimens with reference to specimen radiographs. For circumscribed lesions, the distribution (solitary vs. multifocal), character of margins, details of periosteal reactions, and remnants of mineralized matrix should point to the mechanism(s) producing the bony changes. In turn, this allows selecting a likely category of disease (e.g. neoplastic) within which a differential diagnosis can be elaborated and from which a favored specific diagnosis can be chosen.

1. Introduction

A dry bone from antiquity is like a fossilized footprint left in solidified mud. From the print the foot can be modeled and is of more interest than the print. Similarly, in paleopathology, the goal is the identification of the disease as deduced from the residual bone imprint. During osteological examination, one's frame of mind must be to mentally "put the soft tissue that abutted solid substance back on the specimen" and thus find clues to the host response (mechanism) that produced the changes. Radiologic images can provide valuable information to supplement and increase the accuracy of macroscopic osteological analysis.

Pathologic bone morphology is the result of disease-related changes in circulation, metabolic factors, and/or mechanical stress, which stimulate the activity of the only three cell types that can modify bone structure: osteoclasts, osteoblasts and, to a much lesser extent, osteocytes. Due to the limitations of bony reaction, at times it can be difficult to distinguish between diseases that trigger similar cellular responses. Furthermore, in the analysis of paleopathology in dry bones, taphonomic processes, anthropogenic body modification, and even trauma can resemble neoplastic lesions and act as a pseudopathology. As a result, no differential diagnosis for skeletal remains is complete without consideration of all disease categories (Table 1) and pseudopathology.

Neoplasms, more commonly known as tumors, can be particularly tricky to diagnose from bone morphology as there are many types to consider. They may be malignant or benign, primary or secondary (metastases), slow or fast growing, manifesting in skeletal remains as lytic, blastic or mixed lesions, originating in, on, or beside bone from a variety of tissue precursors, and they may differentiate into more than one tumor pattern with products that may or may not preserve. Consequently, the ability to distinguish the mechanism(s) responsible for bony reactions through macroscopic and radiographic analysis can be a key factor in identifying the type of neoplastic disease that is represented.

This article provides a guide to the differential diagnosis of neoplastic disease in dry bones through macroscopic and radiologic

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Table 1
The categories (discussed below) overlap to some extent, since the inflammation includes repair, trauma is associated with circulatory changes, and metabolic disease may call forth mechanical compensation. The acronym "VITAMIN" assists in recalling the categories so that each of the Basic Categories of Disease is entertained as a differential possibility.

THE SEVEN BASIC CATEGORIES OF DISEASE		
I.	V	Vascular
II.	I	Innervation/Mechanical
II.	T	Trauma/Repair
IV.	A	Anomaly
V.	M	Metabolic
VI.	I	Inflammatory/Immune
VII.	N	Neoplastic

analysis of bone morphology, mainly by summarizing the relevant points of the publications by Madewell et al. (1981), Ragsdale et al. (1981), Sweet et al. (1981), and Ragsdale (1993). We will briefly address the disconnect between clinical and paleopathological terminology and standards for differential diagnosis, and the importance of radiographic analysis in the diagnosis of pathological dry bone. Following this, guides to the recognition of disease categories and specific diagnosis of neoplastic disease are presented, with a focus on lesion margins, periosteal reactions, and bone matrix patterns. The article concludes with discussions of the difficulties associated with the identification of spinal and cranio-facial neoplasms in skeletal remains and the specific challenges associated with the analysis of bioarchaeological remains. It is hoped that this complete classification of neoplastic evidence in dry bones will be useful in future assessments of bone pathology, and that pseudopathology and the six non-neoplastic disease categories (Table 1) will also be considered in future differential lists for suspected neoplasms.

2. Where are the standards?

Bone morphology exists on a spectrum from healthy normal bone to the manifestations of adaptive or pathological reactions. Clinicians regularly see patients in the early stages of bony change or even prior to the development of bony reactions, while most of the skeletal alterations that paleopathologists encounter are the result of chronic disease, trauma or infection, which may or may not have led to the death of the individual. Modern textbooks of orthopedic pathology and radiology include illustrations based on surgical specimens intercepted at some point short of their full natural history. Autopsy specimens may be more likely to represent more advanced expressions of disease than surgical examples, as the deceased is likely to have lived with the disease longer than a surgical patient, but the morphologic expression is generally modified by therapeutic manipulations, including surgery and pharmacology. The reference work by Ortner and Putschar (1981) is of great relevance; many of its illustrations are cases collected in the 19th century or come from Dr. Putschar's Third World experience.

The modern practice of pathology occasionally presents rare instances where, for one reason or another, treatment is delayed or not given. In such cases, radiographs taken over time present visual documentation of the evolution of a process with skeletal manifestations, carrying it to degrees approaching what might be analogous to the process in antiquity, in the absence of (most) effective treatment. Such cases are better, but not perfect, standards for the natural progression of the disease represented (Ragsdale, 1997). Of equal importance, these cases teach much about the mechanisms, tempo, and personal disability of specific disease states, although individual experience of pain and disability can vary widely.

An additional concern is the lack of standardization in terminology used by researchers referring to neoplastic diseases. Many popular terms and expressions are best avoided since they obscure or misrepresent disease mechanisms. This article will follow the terminology laid out in a series of articles: Madewell et al. (1981), Ragsdale et al. (1981), Sweet et al. (1981), and Ragsdale (1993). Though directed at today's pathologists, radiologists, and orthopedic surgeons, the terminology therein defined can be advocated without alteration for use in paleopathological descriptions.

3. Radiologic examination is an indispensable part of morphologic analysis

In modern diagnostics it has become axiomatic that the histologic diagnosis of bone tumors can be safely attempted when all of the clinical history and roentgenograms are available. This method of triangulation or triple diagnosis technique is essential in arriving at a reliable diagnosis. It gives equal weight to clinical, radiographic, and histopathologic data. Competent pathologists know it is hazardous to make final diagnoses without film review, even more so when attempting diagnosis of a dry bone from antiquity. Radiographs may also reveal lesions not visible macroscopically, meaning that systematic radiographic analysis of human remains is absolutely necessary for the comprehensive study of neoplastic disease in the past. Furthermore, radiologic studies can suggest the optimal plane for sampling or sawing through a gross specimen for destructive analysis. Excavated bones will not likely be exhumed with histories and microbiologic culture results that are of great help in diagnosing a non-neoplastic process simulating a bone neoplasm such as infection (especially Brodie's abscess and granulomatous osteomyelitis), trauma and repair (e.g., osteoporotic and stress fractures), and metabolic disorders (e.g., brown tumor of hyperparathyroidism). Assuming sufficient retention of matrix and mineral, specimen radiographs will be all that most paleo-oncologists can rely upon to test opinions based on surface examination and matrix histopathology; without them no opinion should be taken seriously.

As submitted in consultation to the Orthopedic Branch of the Armed Forces Institute of Pathology in Washington, D.C., Madewell et al. (1981), Ragsdale et al. (1981), Sweet et al. (1981), and Ragsdale (1993) determined that attention to the three parameters of **margins**, **periosteal reactions**, and **matrix patterns**, as disclosed in plain films, permits a diagnostic accuracy in excess of 90% for modern day bone tumors. Special imaging techniques (CT and today's MRI) can settle details of internal structure, however, only rarely do they modify the diagnosis proposed after experienced analysis of plain films. The aforementioned authors went on to point out that generally the most important areas for determining a specific diagnosis are those showing abnormal patterns of mineralization and that the more important areas for assessing biologic activity (benign vs malignant) are radiolucent. The plain film radiograph delineates the lesion's location (one or several bones), the segment of involvement (epiphysis, metaphysis, or diaphysis), growth characteristics, and the presence or absence of mineralized tumor matrix. Combinations of periosteal alterations, margins, and density changes can help refine an "Inflammatory Category" diagnosis into one of the three patterns of skeletal inflammation: suppurative, granulomatous, or angiitic. Post-traumatic and some metabolic (e.g., hyperparathyroid bone disease) changes are also succinctly described with these terms. Madewell et al. (1981), Ragsdale et al. (1981), Sweet et al. (1981), and Ragsdale (1993) emphasized that for accurate description and as a permanent record of a specimen, radiographs are indispensable since choice of descriptive terms in part relies on radiographic appearances.

Some radiographic configurations are distinctive, repetitive, and so typical as to represent radiologic clichés known to radiologists as 'Aunt Minnies'. Examples are: the honeycomb, spoke-wheel, and

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Fig. 1. Angiosarcoma, lower extremity, middle aged adult. A. This aggressive malignancy, spread through the blood stream from its inception, colonizes the skeleton and soft tissue as hemorrhagic spots. B and C. Sharply punched out, long oval lytic lesions (Type IB margins) are aligned with the long axis of the tubular bones, as Wolfe's law dictates to some extent where osteoclasts will erode to accommodate tumor pressure; rapid rate of tumor growth with consequent central infarction has left central sequestra. C. Specimen x-ray brings out many more fusiform lytic lesions than appreciated by surface examination.

corduroy cloth alterations around hemangioma; the bone polyp configuration of osteochondroma; the lobulated sclerotic border around an eccentric metaphyseal fibroxanthoma (a.k.a. nonossifying fibroma); the stippled, flocculent and arc-and-ring matrix patterns of enchondroma; certain reactive/reparative lesions such as fracture/non-union with exuberant callus. Purely radiographic information, such as distribution, may point to the correct specific diagnosis, e.g. a polyostotic distribution (angiomatosis, angiosarcoma [Fig. 1], Ollier's disease, hereditary exostoses, sarcoma [largest lesion] and its metastases [smaller lesions]) or a characteristic distribution in a single limb (melorheostosis).

The roentgen patterns of extremely early tumors are not as identifiable as those that are more advanced because the cortical erosion and periosteal reaction, so important in identification of tumor type and growth characteristics, are not yet fully developed. This diagnostic challenge of a very early tumor is less likely to be found in a paleopathological specimen than the x-ray patterns of extremely overgrown tumors where the characteristic reactions of the cortex and periosteum are obscured or, in time, completely destroyed.

The common diagnostic dilemma of bone vs. soft tissue origin of a tumor can be answered by an x-ray without the preserved contiguous soft tissue component, as only a mummy, preserved in relatively exceptional circumstances, may present soft tissue in ancient remains. The decision is trivial when there are distinct intraosseous mineralization patterns at the intramedullary epicenter (bone tumor) or parallel effects on adjacent bones due to impingement (soft tissue tumor). Encompassing periosteal reactions such as shells connote a bone tumor, but when absent, details of cortical destruction can still distinguish a bone tumor that broke through cortex into soft tissue from extrinsic invasion of bone by a soft tissue process. Pressure and altered regional blood flow are important mechanisms by which soft tissue lesions can affect subjacent bone, for example, vertebral body erosion by an aortic aneurysm. Saucerization of long bone cortex, with or without interrupted periosteal reactions at the extremes, favors the effect of a contiguous soft tissue mass. Soft tissue masses within or adjacent to a joint may secondarily involve bony structures and mimic a bone tumor.

Given a generally lower average age at death in antiquity, skeletal anomalies and benign bone tumors should be more frequently encountered than the malignancies, which emerge with advancing age. Aside from metastatic carcinoma and plasmacytoma, malignant bone tumors tend to be relatively large when first discovered, certainly so in antiquity; one should be cautious in venturing a malignant diagnosis when the lesion is small. The obverse is not valid; large size alone of a mesenchymal tumor (as massive secondary cystic change in benign bone lesions and osteochondromas larger than grapefruit illustrate) does not force a malignant interpretation.

Modern statistical frequency, age of peak incidence, and sexual predilection are of secondary diagnostic importance with solitary bone lesions. Rather than the initial criteria, these should be used to refine (rank in likelihood) a radiographic differential diagnosis based on careful morphologic analysis.

4. Towards a diagnosis: category first

Part of the art of modern pathology is to express opinions in terms that do not exceed the available evidence. A spectrum of terminology is available for this purpose ranging from "diagnostic of" through "suggestive of" and "cannot exclude" to "insufficient for diagnosis". If we need this much latitude in the present in clinical material, so much greater is the challenge in confident diagnosis of endpoints seen in paleopathology for which we have no modern standards. The Paleopathology Association Dry Bone Diagnosis Workshops have shown that an impression as to which of the seven basic categories of disease (Table 1) a specimen belongs to is more likely to be correct than a specific diagnosis (Miller et al., 1996). This and another study by Marques et al. (2011) argue for using the basic disease category as an entry-level impression for purposes of conveying one's impression, prior to taking a stab at the specific diagnosis.

Despite the inclusion of differentials from all disease categories, this article is focused on the neoplastic disease category. Neoplasms, more commonly known as tumors, are overgrowths of cells that commonly arise from antecedent accelerated cell proliferation related to normal growth and development or a sustained reactive state (Johnson, 1953). Benign tumors, generally solitary, may achieve dramatic proportions or stabilize at a lesser size. They can weaken a bone to the point of fracture but remain a local problem. In contrast, malignancy is characterized by inexorable local growth and metastases. Malignant bone neoplasms, arising in bone or coming there from a visceral organ, are rare, all disease considered. Primary bone and joint cancers in particular are quite rare, as the annual number diagnosed in the USA is only estimated to be about 3300 in 2016 (American Cancer Society, 2016).

Metastatic cancer, be it lytic, blastic or mixed, vastly outnumbers primary bone sarcomas and should be kept in mind in the differential diagnosis of solitary bone lesions, no matter how characteristic the radiographic appearance may be for something else. Due to greater blood supply, more cancer cells are delivered to hematopoietic marrow compared to fatty marrow, and so it is no wonder that the spine (80%), femur (40%), ribs and sternum (25%), skull and pelvis (25%), humerus and shoulder girdle (7%) are the common sites for metastasis in autopsy cases (Ortner 2003, p. 534). Tumors arising from the breast, prostate, thyroid, lung, and kidney possess a special propensity to spread to bone (Coleman, 1997), but using modern statistics on the prevalence of various can-

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cers to understand the past must be undertaken cautiously. Large changes in disease incidence are possible over short time intervals and in different cultures, and there is no evidence to indicate that rates of oncogenesis have remained steady throughout the world and human history (Ragsdale, 1995). Furthermore, the age distribution of bone tumors derived from modern surgical pathology series is irrelevant to paleopathology since, benign or malignant, the endpoint in the paleopathological specimen was the death of the individual rather than presentation at a clinic (Ragsdale and Lehmer, 2012).

5. Radiological parameters for assessing neoplasms

5.1. Margins

Patterns of bone destruction manifest as margins that are fundamentally different and not merely stages in a common destructive process. The interface between bone (cancellous or cortical) and disease (the margin) is a zone of cellular activity and its radiographic appearance represents the summation of lysis (osteoclastic activity) and production (osteogenesis), giving information about the composition and tempo of the responsible lesion. They define the segment of the bone involved, and the epicenter position is the initial criterion for narrowing a differential diagnostic tabulation of a solitary lesion. This happens because particular types of primary bone neoplasms occur in that portion of a bone where the normal cells from which they arise are most abundant and active (see Fig. 2). Radiographically well-circumscribed (geographic) lesions tend to be static or only slowly progressive and remain confined within bone, not directly contacting soft tissues; enveloping sclerosis and/or containment by cortical thickening and periosteal shells is likely. Less evidence of circumscription, for example, the moth-eaten and permeative margin patterns, represent more vigorous destruction and an increased growth rate that evokes more exuberant or discontinuous periosteal reactions and a likelihood of escape into soft tissue.

A **Type I** margin is a narrow zone of cancellous bone deletion resulting in a "geographic" lesion with sharp borders. Slow enlargement will allow for peripheral sclerosis (Type IA) whereas a more rapidly enlarging tumor will leave no time for this (the Type IB or "punched out" margin). A Type IC margin is the sign of an infiltrative process where lesional tissue extended through marrow between trabeculae inciting lysis over a wide zone (Fig. 4).

Type IA margins are created by bone cysts, enchondromas, and fibroxanthomas (non-ossifying fibromas, etc.). If sclerosis around the margin fades rather than being a band, think of Brodie's abscess, osteoid osteoma, etc. The prototype tumor associated with a **Type IB** margin is the giant cell tumor (osteoclastoma), but any relatively fast growing neoplasm with a pushing rather than infiltrating contact with its bony bed will create it. The infiltrative **Type IC** margin predicts greater biologic activity as with fibrosarcoma, various high-grade sarcomas and osteomyelitis.

Type II ("moth-eaten") margins result from multiple sites of osteoclasia along the endosteal surface of cortex or in cancellous bone; in vivo they would have been filled with lesion tissue, enlarging and coalescing. Cortex may be perforated by many overlapping rounded defects. Classic for this are metastatic carcinoma, lymphoma, and the granulomatous osteomyelitis of mycobacterial and fungal infections. Rapidly evolving osteopenia as from disuse distal to an extremity fracture or reflex sympathetic osteodystrophy creates this pattern in cancellous bone.

Type III margins connote permeative destruction by aggressive neoplasms and brisk osteomyelitis. Accentuation of haversian canal blood flow to serve tumor or infection turns on osteoclasia, enlarging these longitudinal microscopic tubular spaces so that they show in fine detail radiographs as overlapping oval lucencies along a lengthy cortical segment. Evoking it are marrow infiltrating malignancies with brisk arterial supply such as round cell sarcomas (e.g. Ewing), lymphomas and the most aggressive of fibrosarcomas and matrix-producing sarcomas. These tumors colonize the enlarged intracortical spaces, replacing active hyperemia with tumor pressure as the drive for further cortical lysis. Hyperparathyroidism also evokes this change.

The distinction between Type II and III osteolysis is of little practical importance since the differential diagnosis for either includes the same aggressive lesions and infections. The import of indolent Type I destruction and either Type II or III is of great significance.

5.1.1. Changing margins

Any combination of the above three margin types suggests a change in biology, such as when a benign lesion undergoes malignant transformation or a complication such as fracture or secondary infection (middle panel of Fig. 3) develops. An aggressive secondary malignancy can erase all margins of an antecedent benign primary bone lesion.

5.1.2. Invisible tumor margins

Extremely rapidly growing tumors may pass through cancellous bone and cortex with little or no radiographic alteration since the vascular support and cells necessary for osseous alteration are infarcted along with tumor behind the advancing front that rapidly fills the rigid confines compressing vascular support. Bone encased by necrotic tumor tends to persist with original normal density and architecture since viable cells capable of modifying bone density are no longer operative on the overrun bone surface. Adjacent segments in the same bone and contiguous bones lose density through the combined effects of disuse atrophy and active hyperemia en route to serve viable portions of the tumor. Rapidly growing sarcomas producing unmineralized matrix are most often responsible.

5.2. Periosteal reactions

The interface between periosteum and cortex along the growing long bone is the site of bone formation (increasing diaphyseal diameter) and resorption (metaphyseal cutback, also called funnelization). These same activities reawaken to modify the bone surface in disease. Periosteal reactions can be classified as negative (localized or circumferential cortical erosion) or positive (productive). The latter may be continuous (present over the entire extent of the lesion), interrupted, or complex (Fig. 5).

5.2.1. Negative periosteal reactions (cortical lysis)

Soft tissue processes adjacent to, and especially those abutting periosteum may incite subperiosteal osteoclastic activity by pressure and altering regional vascularity. Neoplasms abutting bone can do this, but so can lesions in the other disease categories, such as vertebral erosion by an aortic aneurysm (Vascular), surface erosion of the tibia under a large cutaneous ulceration of yaws (Inflammatory/Immune), medial resorption of phalanges in hyperparathyroidism (Metabolic), and impact (Trauma Repair). Sustained periosteal active hyperemia stimulates osteoclasts and results in concentric atrophy ("penciling") when circumferential subperiosteal osteoclastic activity is compensated by synchronous endosteal osteoblastic additions as in ainhum, diabetic bone atrophy (due to the sympathectomy effect of diabetic neuropathy), leprosy, severe psoriatic arthritis, and disappearing bone disease.

5.2.2. Productive periosteal reactions

It is inconceivable that the periosteum, little thicker than a few sheets of paper, can be the source for all matrix rapidly produced in fracture callus and the sometimes thick periosteal reactions around

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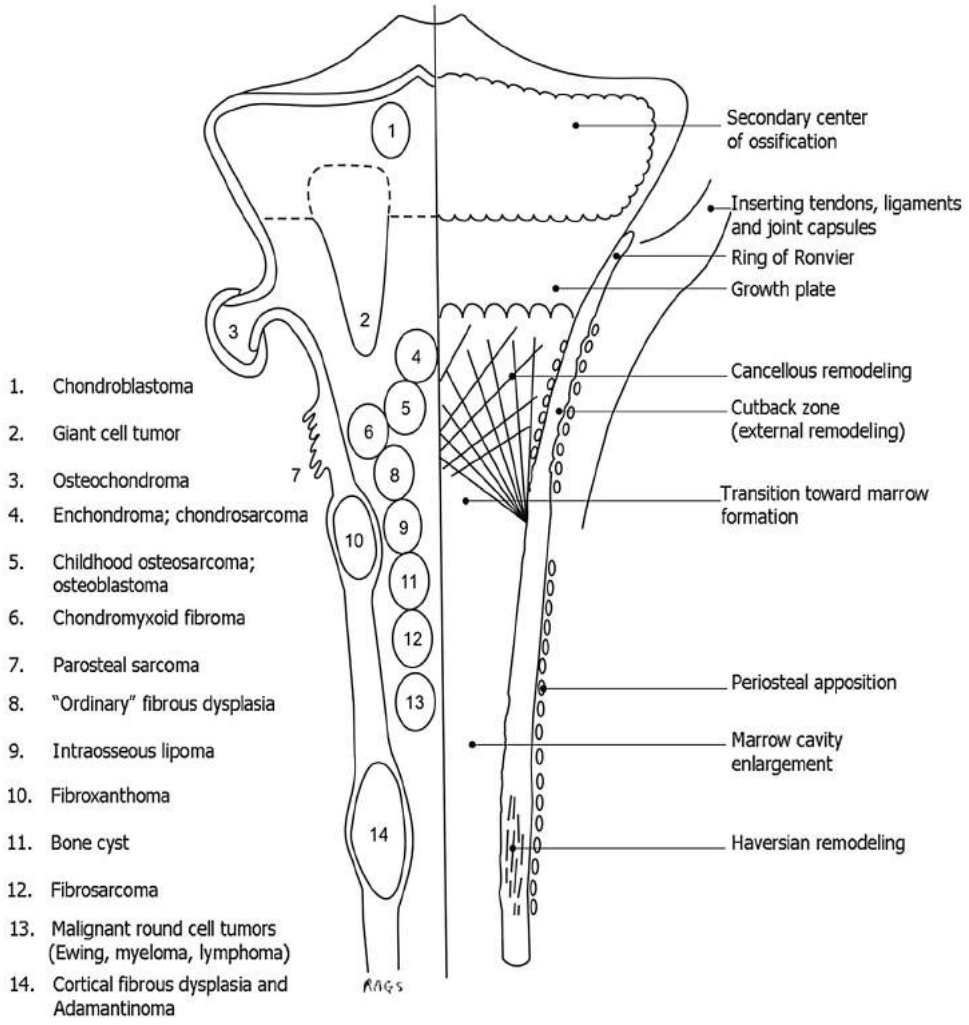

Fig. 2. Typical bone tumors as they relate to events of normal growth and development.
(Reproduced with permission from Blackwell Publishing Ltd. from Ragsdale and Lehmer, 2012, Ch. 13, p. 237, Figure 13.1).

bone tumors. Terms such as "periosteal elevation" and "periostitis" obscure the true mechanisms. Attention to histologic detail, especially in large format histological sections of modern surgical specimens, forces the view that soft tissue contributes in a major way to fracture callus and also to the substance of periosteal reactions around neoplasms (Ragsdale et al., 1981). Similarly, soft tissue is the source of the osteogenic periosteum-like outer coverings of enlarging myositis ossificans lesions in soft tissue. The initial stage is the fibrous involution of differentiated parosteal soft tissues with an increase in cell size as rough endoplasmic reticulum for matrix synthesis expands cytoplasm. One can call the resultant omnipotent cellularity "stem cells", but in their previous life they were merely structural elements in fascia, fat, and skeletal muscle. These condense into a sequential series of osteogenic sheets that have nothing to do with original periosteum that was used up forming the initial increments of a reaction.

"Periostitis" is a poor word for periosteal new bone production because it connotes cellular inflammation that is not usually present. Physical elevation of the periosteum from the cortex, as by tumor or pus, is not a prerequisite for a reaction; other factors are operative, such as compensation for mechanical weakness secondary to underlying osteolysis or the teleologic attempt at tumor containment, altered circulation (passive hyperemia), and bone inductive products emanating from tumors (Brunschwig and Harmon, 1935; Urist et al., 1979).

In general, the amount of periosteal new bone visible in a reaction is proportional to the intensity, aggressiveness, and duration of the inciting process, but this is more prominent on long bones than flat bones and in younger than older individuals. Details of the arrangement of the surface addition bear strongly on the differential diagnosis.

5.2.3. Continuous periosteal reactions with destruction of underlying cortex (shell-type reactions)

Shell-type substitutions for deleted original cortex are as much periosteal reactions as the more exuberant spiculated and lamellated types to be discussed later. This characteristic, as well as the mechanism of formation for these substitutions, is obscured by expressions such as "cortical expansion". Widened bone contour, the preferred descriptor, is always the consequence of periosteal new bone production, since bone is solid and cannot expand like a balloon. As osteoclasts erode the inner surface in response to tumor pressure and active hyperemia, osteoblasts add osteoid to the outer curvature. The most rapid rate of tumor progression is denoted by complete cortical lysis and no periosteal reaction whatsoever.

Eccentric **smooth shells** have gently curving outer contours and tend to be rather thin, signifying less time for periosteal compensation for uniform endosteal erosion. Benign tumors are generally responsible. In contrast, predominantly cystic lesions such as unicameral bone cysts tend to exert hydraulic pressure equally around

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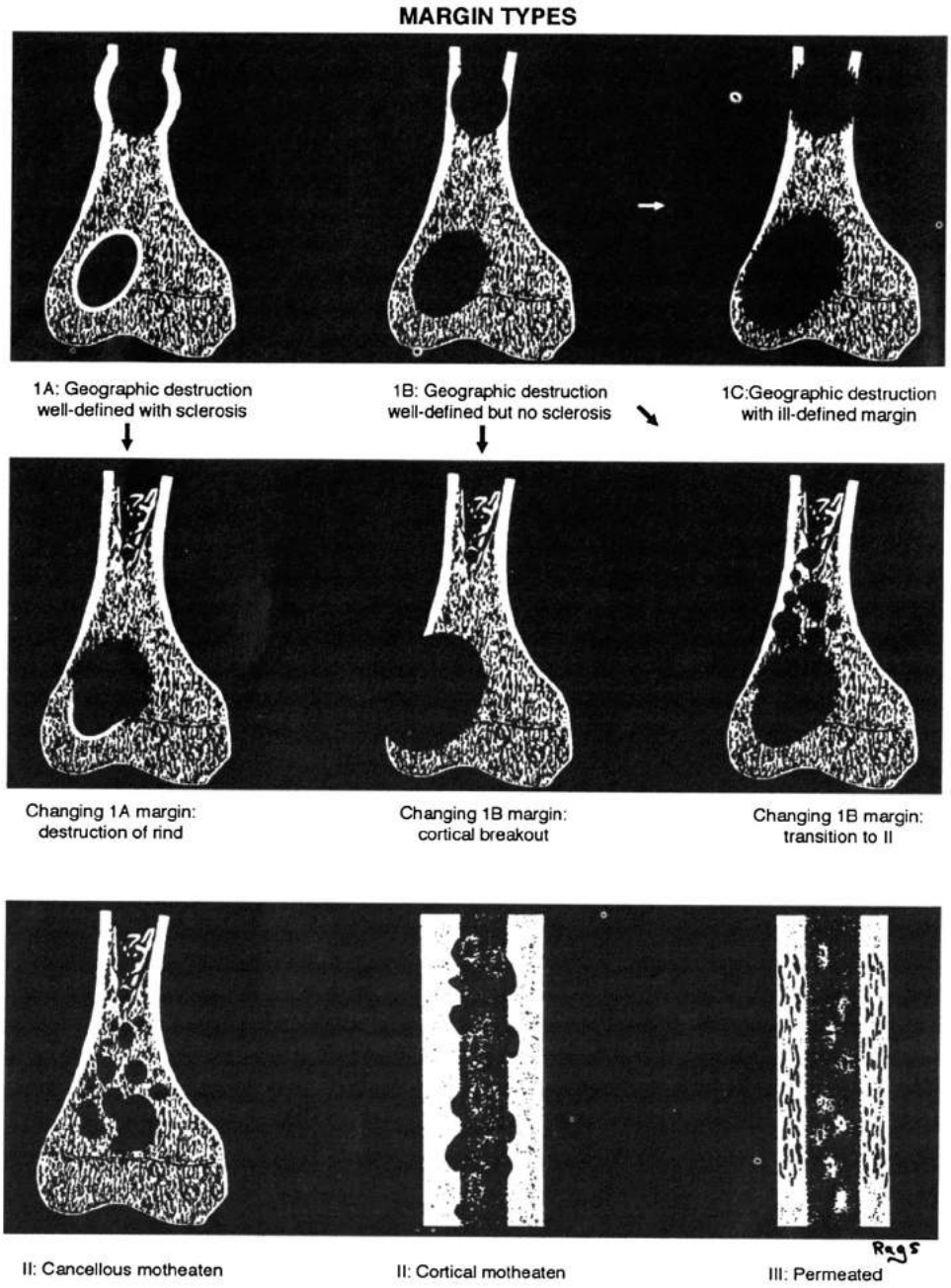

Fig. 3. Schematic margin diagram of patterns of destruction in cancellous and cortical bone. Arrows indicate the most frequent transitions or combinations of the basic margin types. Transitions imply increased activity and greater probability of malignancy.
(Reproduced with permission from Mosby-Year Book, Inc. from Ragsdale, 1993, p. 452, Figure 2).

the endosteal circumference, resulting in circumferential smooth shells. The thickness of a smooth shell reaction over a lesion is inversely proportional to its biologic activity. Slow processes widen the bone outline without notable reduction in cortical thickness as endosteal cortical deletion is balanced by new bone deposits on the exterior. Faster processes leave less time for surface compensation and evoke thin shells that are unlikely to preserve well. A shell type reaction soon contains none of the original cortex.

A **ridged shell**, also known as the trabeculated, septate, or soap bubble reaction, signifies a relatively slow process. It commonly is evoked by masses with a coarse lobular pattern or cavernous peripheral vascularity. The ridged shell-type reaction has a lengthy differential diagnosis that includes fibroxanthomas (nonossifying fibromas), giant cell tumors, enchondromas, chondromyxoid fibroma, chondroblastoma, unicameral bone cyst, hemangioma, and some slowly growing malignancies (chondrosarcoma [Fig. 6], fibrosarcoma, plasmacytoma, and metastatic carcinoma, especially of renal and thyroid origin). Ridged shell reactions also surround large echinococcal bone cysts.

The **lobulated shell** reaction tends to be a more uniform and thinner new bone deposit than the ridged shell-type and is unlikely to survive the ravages of time. Parosteal myositis ossificans commonly has a lobulated shell reaction overlying a saucerized cortex when the periosteum is the epicenter of impact; this was the lesion originally described as an aneurysmal bone cyst (Jaffe and Lichtenstein, 1942), a term which subsequent authors have applied in so many other pathological settings that it has no current specificity.

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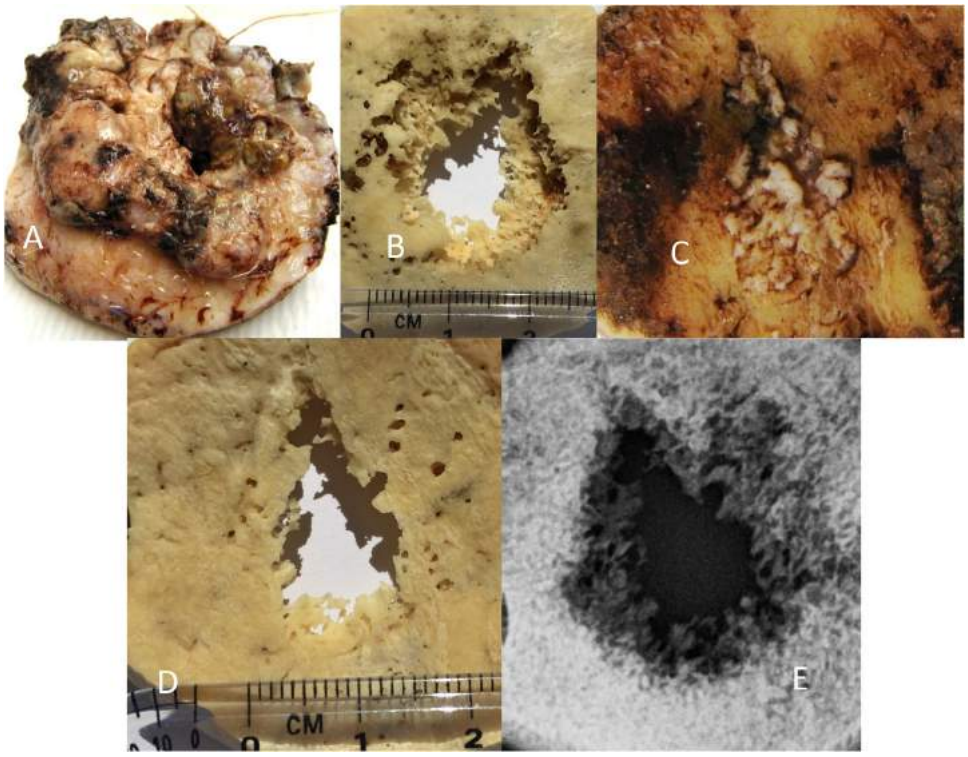

Fig. 4. Cutaneous malignancy, undifferentiated pleomorphic sarcoma (UPS) of dermal origin, perforating calvarium, 89 year old male. A. A 5 cm diameter soft tissue mass is attached to the outer table in this gross photo of surgically resected tumor. B. Tumor invades to and through the inner table in the fresh gross specimen. C and D. Overlapping small rounded lytic foci create the margin in the macerated specimen. E. The radiographic result of such piecemeal lysis is geographic destruction with ill-defined (Type 1C) margins. Advanced cutaneous carcinomas, basal and squamous cell types are similarly reluctant to metastasize and would leave indistinguishable gross lytic defects in dry bone. The natural history of untreated cutaneous cancer of the scalp is invasion through bone to brain with death by pressure effects or meningitis. Often such solitary lesions are dismissed as "metastatic carcinoma" yet constitute a fatal primary cutaneous tumor.

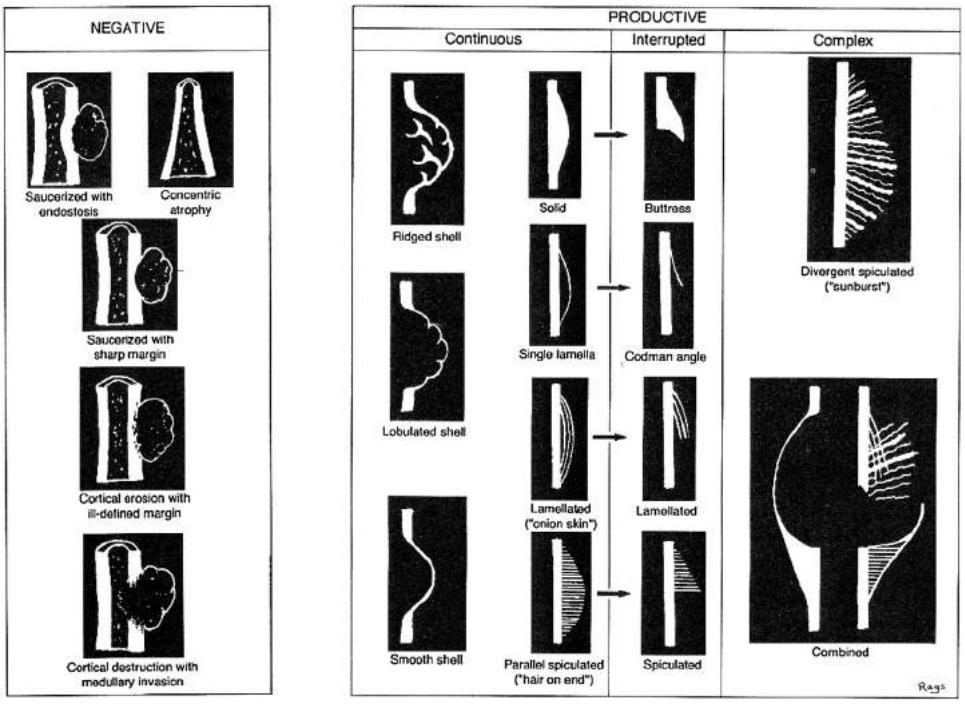

Fig. 5. Schematic diagram of periosteal reactions. Surface reactions may delete (negative) or add (productive) material to bone surface. Productive reactions may be substituted for deleted cortex (shell-type reactions) or be deposited on intact cortex (continuous reactions), possibly to be partly deleted or denied space as lesions exceed cortex (interrupted reactions). Complex reactions may be comprised of divergent rays (sunburst reaction) or combinations of two or more basic reaction types. In general, the likelihood of malignancy increases with reaction types in the lower half of all columns.
(Reproduced with permission from Mosby-Year Book, Inc. from Ragsdale, 1993, p. 462-63, Figure 8).

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Fig. 6. Chondrosarcoma, proximal femur, middle aged male. Tumor growth in gray translucent rounded lobules (e.g. upper-most tumor area above biopsy-related hemorrhage in A) evoke erosion on the inner surface of the ridged shell periosteal reaction (macerate B) and in places do so faster than periosteum can maintain a bony barrier, as brought out in specimen x-ray C.

5.2.4. Continuous periosteal reactions with cortical persistence

These are additions on, rather than substitutes for, original cortex. Transcortical vascular passageways may provide lines of least resistance for tumor tissue extension or inflammatory exudate into periosteal reactions, but "periosteal elevation" by tumor or pus is not a prerequisite for their formation.

Solid continuous periosteal reactions result from slow apposition of new bone to cortex around a chronic lesion within the marrow space, in cortex or in adjacent soft tissue. Also known as the dense elliptical reaction, cortical thickening or merely hyperostosis, it connotes a low rate of progression. It may be formed by the slow apposition of layer after layer of compact lamellar bone without endosteal deletions and with eventual haversianization of the product. Osteoid osteomas and meningiomas are the prototype associations. Button osteomas are just such a product in their entirety. Late-stage myositis ossificans lesions can resemble this reaction when amalgamated to subjacent cortex. If the outer limit of a solid periosteal reaction has an undulating outline, neoplasm is unlikely; consideration should be given to low- grade osteomyelitis, chronic osteitis, true inflammatory periostitis, chronic passive congestion (as due to varicosities or in pulmonary osteoarthropathy), and chronic lymphedema.

A **single lamella** is one sheet of new bone a millimeter or two away from the cortical surface. It may or may not join cortex at its extremes. In three dimensions, it is a curved disk or cylinder, depending on whether partly or completely circumferential. The single lamella reaction has been called the hallmark of a benign process, especially when coarse or thick. It is common with acute osteomyelitis, eosinophilic granuloma, storage disease (e.g., Gaucher's), and very early stages of neoplasms. It confines subperiosteal hematomas, as in scurvy, and it can appear after trauma without bone fracture. Additional lamellae may be added. If the process slows, the space between the shaft and the reactive layer will fill in, producing a solid reaction; unless this occurs, the reaction is unlikely to remain attached to a dry bone.

Concentric cylindrical or discoid layers of ossification create the **lamellated (onionskin) continuous periosteal reaction**. The original periosteum is consumed in producing the first lamella; sequential osseous modulation within subjacent parosteal fascial planes and condensations from other involuted soft tissues are the source. If the responsible tumor is indolent, the layers become thicker and radiographically more distinct with the passage of time as lamellar bone replaces woven bone, increasing the chances of preservation. A benign provocation such as stress fracture or spontaneously resolving infection will be followed by complete filling-in of the interstitial soft tissue spaces by inlays of lamellar bone, a solid transformation analogous to the solidification of early fetal cortex.

The usual explanation of the laminated continuous periosteal reaction as due to repeated phases of rapid periosteal elevation is contradicted by its frequent occurrence in non-neoplastic conditions such as stress fracture, hypertrophic pulmonary osteoarthropathy and venous stasis (Volberg et al., 1977). The more important inciting factor is probably cyclical variation in regional vascular adjustments. The onionskin periosteal reaction is a hallmark of Ewing sarcoma (Ewing, 1922), but can be seen with any cellular bone sarcoma, especially osteosarcomas reluctant to form matrix, eosinophilic granuloma in very young patients, and syphilitic skeletal disease.

A more rapidly unfolding process tends to incite the **parallel spiculated continuous ('hair-on-end') reaction**. Its configuration is actually an interconnected compartmental system resembling a honeycomb. Compartment walls lying parallel to the radiographic beam register as spicules, whereas walls crossed perpendicularly by the beam are inapparent. Regularly spaced, centripetally penetrating periosteal vessels dictate the honeycomb morphology, since bone tends to emerge equidistant from vascular channels. The inciting intramedullary tissue, be it Ewing sarcoma, meningioma, or hyperplastic marrow in thalassemia, may exude through fenestrated cortex and colonize individual compartments (Huggins et al., 1981). This pattern favors a malignant tumor but may be stimulated by certain inflammatory states (syphilis, myositis, and Caffey's disease).

5.2.5. Interrupted periosteal reactions

Interrupted reactions are created by complete cortical destruction with extension of the inciting process into soft tissue. An originally continuous reaction is centrally resorbed, or the mere presence of the abnormal tissue extension beyond the original bone contour may deny space for elaboration of reactive bone. Either way, an interrupted periosteal reaction results.

The **buttress reaction**is a solid-appearing wedge of reactive bone at the edge of indolent lesions that suddenly became more active. The cortex is intact beneath the buttress, but just beyond it the cortex is deleted. There may be an associated shell-type reaction. An originally continuous solid reaction may suffer central deletion signifying malignant change in a long-standing antecedent benign lesion, such as enchondroma or bone cyst. Periosteal lesions and certain soft tissue problems can be associated with this buttress--type reaction, leaving partly eroded or intact cortex beneath the mass.

The name of Codman is linked to the trumpet-shaped cuff of reactive bone at the sides of a lesiondestroying cortex (**Codman angle**). Although a sure indication of subperiosteal extracortical involvement, this interrupted lamella in itself is not diagnostic of sarcoma, since it sometimes occurs at the periphery of inflammation. Most often, however, it connotes an aggressive malignant lesion that has broken out into soft tissue, usually osteosarcoma. If

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not circumferential like a trumpet bell around a mute, the addition may appear only in certain radiographic projections.

The **interrupted lamellated periosteal reaction** can result from the abrupt truncation of an originally continuous onionskin reaction. It generally borders aggressive malignancies, but lamellated reaction can also occur with eosinophilic granuloma in juveniles when complete cortical lysis is followed by invasive deletion of the deeper and thus earlier formed reactive layers.

Central invasion and destruction of a spiculated ("hair on end") reaction creates an **interrupted spiculated reaction** or spiculated wedge. Alternatively, it can form as a localized reactive condensation beside a juxtacortical neoplastic mass. Such a reaction requires rapid development of an extraosseous mass, as occurs with solid and cystic benign and malignant tumors of medullary origin, with or without complete lysis of original cortex, or with exclusively surface lesions such as parosteal sarcoma bordered by an incomplete reaction.

5.2.6. Complex periosteal patterns

The **divergent spiculated pattern**, also known as the "sunburst" reaction, consists of streaks of density of variable thickness pointing to an epicenter within the marrow space. It is the hallmark of osteosarcoma wherein the individual rays may be reactive bone, sarcoma bone, or various combinations thereof (Aufderheide et al., 1997). As the extracortical tumor extension becomes more densely consolidated, the sunburst appearance may disappear. Other tumors such as blastic metastases (Bloom et al. 1987) and hemangioma can evoke the sunburst reaction.

Transitions between, and combinations of, the various patterns previously described are referred to as **combined reactions**. Acceleration in the rate of bone formation may superimpose a spiculated pattern on a lamellated base or interrupt a spiculated or laminated reaction and add a shell. The combination of slow and rapid periosteal reaction patterns in a single lesion signifies acceleration in biologic activity; malignant change of an antecedent benign lesion should be proposed. Superimposed infection or pathologic fracture, by addition of callus, may complicate the radiographic appearance of any periosteal reaction. All periosteal reactions are fragile creations and tend to be lost over time with repeated handling. Thus, their absence may be an artifact of postmortem events.

5.3. Matrix patterns

Mineralized matrix patterns, best assessed in plain film radiographs, provide important diagnostic information, often predicting histologic composition or proving a pre-existing benign lesion underwent sarcomatous transformation as bone infarcts, enchondromas, and osteochondromas occasionally do (Ragsdale and Sweet, 1986).

Matrix-producing tumors are named for their products, e.g. osteosarcoma, chondroma, and various fibromas. Nonmatrix-producing tumors are labeled by cell type (osteoclastoma), gross morphology (cyst), or by eponym (Ewing sarcoma). Some lesions may produce matrix only in some regions (ossifying lipoma) or produce more than one matrix (cartilage and bone in osteochondroma and higher grade "periosteal" sarcomas).

Mineralization of tumor matrix involves precipitation of calcium hydroxyapatite in a pre-existing organic background. This applies equally to chondroid, osteoid, myxoid, hypocellular fibrous tissue, necrotic fat, and connective tissue altered by metabolic disorders (e.g., metastatic calcification in hyperparathyroidism). The radiographic configuration of mineral deposition helps predict what organic background has accepted the mineral and is of major diagnostic importance (see Fig. 7). However, the imperfect organic chemistry of a neoplastic osteoid or chondroid matrix may render it unmineralizable and so an osseous or cartilaginous tumor cannot be excluded from the differential diagnosis of a purely radiolucent lytic lesion.

5.3.1. Mineralization patterns of tumor bone

Bone radiographically visible within a tumor may have formed through (a) the activity of neoplastic osteoblasts (osteoblastoma and osteosarcoma), (b) cellular metaplasia (fibrous dysplasia), (c) cellular injury (e.g., ischemic bone formation around bone infarcts and within ossifying lipomas), (d) replacement of cartilage (enchondral ossification in and around enchondromas), or (e) reaction (e.g., the sclerosing pattern accompanying chronic inflammation).

Slowly progressive neoplastic lesions, such as some primary lymphomas of bone, and prostate and breast cancers, trigger bony additions to adjacent intact trabeculae. Therefore, they can result in a solid ivory-like density or mottled radiographic pattern where focal lucencies are conspicuous in a background of increased radiodensity. Mineralized osteoid will show in radiographs as a region of increased density ranging from solid ivory-like through cloudlike to a diffuse, hazy, or ground glass appearance.

Osteomas and bone islands cast the solid matrix density pattern because they are compact bone and have sharply circumscribed margins. Osteomas are mainly found in paranasal sinuses or budding from the external table of calvarium (button osteoma). Long bone locations pose a differential diagnosis with parosteal sarcoma, separated definitively from the much rarer post-cranial parosteal osteoma only in 1995 (Bertoni et al., 1995). A bone island is a related, probably hamartomatous compact bone lesion situated in a cancellous area. These are to be distinguished from densely sclerotic variants of hemangioma, fibrous dysplasia, and also blastic metastases.

Cloud-like patches of mineralization with indistinct edges predict more active lesions. Borders are ill-defined since osteoid-producing tumors are most mature (therefore, more unmineralized) centrally. Osteoblastomas are benign osteoid-forming tumors. They may have lucent regions where unmineralized osteoid or dense active cellularity is located. Osteoblastomas have a propensity to occur in eccentric metaphyseal regions of adolescent long bones and posterior elements of the spine, particularly at areas stressed by tendinous insertions. They may be intramedullary, central, and large. Their product may mineralize in cloud-like condensations or the entire lesion may remain radiolucent.

Osteosarcomas may arise within the medullary cavity (central) or on the surface of bone (parosteal); the former tend to be high grade and the latter low grade. Radiographs of osteosarcomas often reveal combinations of lytic destruction and variously sized areas of increased density in the medullary cavity ranging from ill-defined and hazy through cloudlike and sometimes solid ivory-like fields. Edges are poorly defined. Such areas correlate with mineralized tumor bone produced by the sarcoma as it infiltrates the marrow space, frequently encasing intact original trabeculae. Sclerosing osteosarcomas result from an almost complete replacement of intertrabecular marrow space by tumor bone. Trabecular thickening through lamellar apposition is stimulated in less virulent forms of osteomyelitis and this can result in homogeneous areas of increased cloudlike density difficult to distinguish from osteosarcoma.

Occasional osteosarcomas that are entirely lytic radiologically may have contained abundant unmineralizing tumor osteoid. The telangiectatic pattern may constitute all or part of an osteosarcoma; such cyst-like lucent areas would have contained a web-like tumor array with unmineralized osteoid in what was mostly a blood-filled space.

The indistinct outer spiculated border of parosteal sarcoma contrasts with the smooth convex margin of an osteochondroma continuous with the cortex. High-grade surface ("periosteal")

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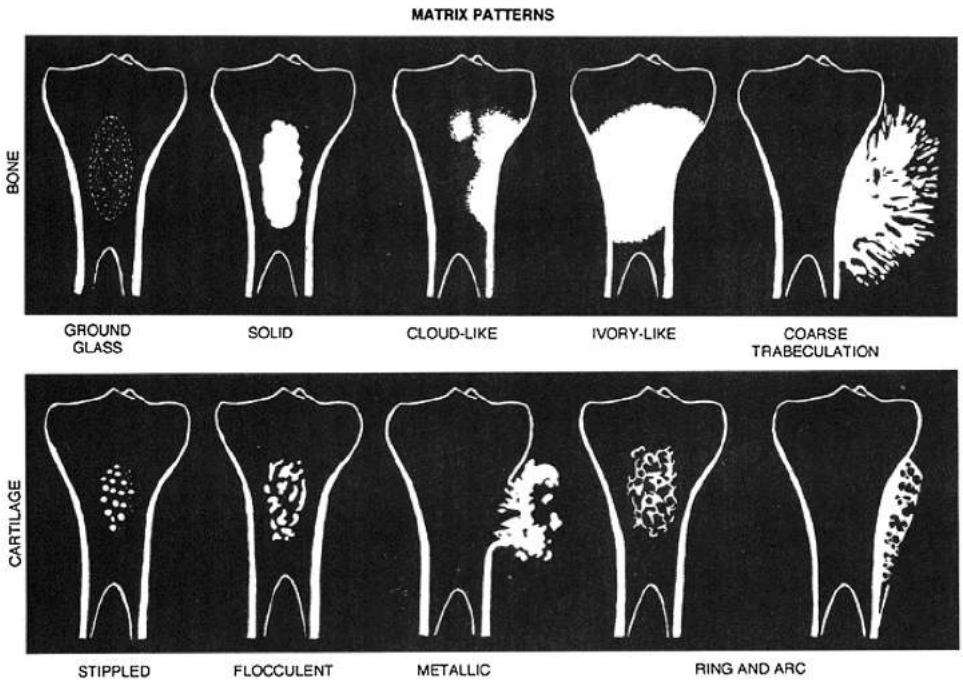

Fig. 7. Schematic diagram of mineralized matrix patterns. The top row configurations predict tumor bone. Tumor bone appears as incised density with a ground glass, solid (sharp-edged) or cloud-like through ivory-like (ill-defined edge), to coarse trabecular patterns. The bottom row configurations predict cartilage. Mineralized cartilage shows up as stippled, flocculent, or metallic densities. Dystrophic mineralization and ischemic osteoid can mimic the stippled, flocculent, or metallic density patterns. The ring-and-arc pattern represents bone rims around and between cartilage lobules.
(Reprinted with permission from Mosby-Year Book, Inc. from Ragsdale, 1993, pg. 471, Figure 10).

osteosarcomas that had a malignant cartilage component should show a rougher dry bone exterior than low grade (parosteal) osteosarcomas that were exclusively fibro-osseous.

5.3.2. Metaplastic, reactive and dystrophic ossification

Fibroblastic cells convert (modulate) into functional osteoblasts in fibrous dysplasia and fibroxanthoma (nonossifying fibroma), producing a random woven collagen pattern that is less inclined to mineralize than tumor bone formed directly by neoplastic osteoblasts. The resultant poorly mineralized woven bone is unlikely to preserve (see Monge et al., 2013 for a possible case of fibrous dysplasia in a Neanderthal). Coalescent, patchy, cloudlike densities are more typical with the related lesion, ossifying fibroma of the craniofacial skeleton. With classic eccentrical positioning in metaphyses with type IA margins, fibroxanthomas (nonossifying fibromas) persisting into adulthood commonly ossify, sometimes densely. The uncommon events of sarcomatous change superimposed on fibrous dysplasia or fibroxanthoma and adamantinoma arising in osteofibrous dysplasia (also known as ossifying fibroma of long bone or cortical fibrous dysplasia) may erase part of their otherwise sharp circumscription or superimpose lucent areas on their matrix product.

Marrow transition in the appendicular skeleton from the hematopoiesis of childhood to mostly fat in the adult creates the opportunity for overgrowth into intraosseous lipomas as distinguished by widened bone contour around a lucent defect. By enlarging in rigid cortical confines, lipomas are at risk for compressing surrounding vascularity and therefore suffering infarction. Necrotic central areas may heavily mineralize resulting in the cockade configuration (Bruni, 1986), most often found in the calcaneus.

5.3.3. Mineralized matrix patterns that predict cartilage

Metaphyseal osteochondromas are deemed laterally divergent portions of epiphyseal growth plate that grow perpendicular to the bone shaft and thus are distinguished by a lack of underlying cortex. They may be sessile or pedunculated and develop a thin peripheral bony plate beneath the cartilage cap on cessation of growth; this is analogous to the end plate beneath articular cartilage and serves to distinguish them from parosteal sarcoma. Their risk of malignant change is quite low. Dysplasia epiphysealis hemimelica can be regarded as an epiphyseal osteochondroma.

Cartilage tumors may appear totally devoid of mineralization or accept mineralization in their more mature and hypocellular areas in a fine stippled pattern, coarser flocculent pattern, or some dense mineralization resembling an irregular metallic foreign body (Ragsdale et al., 1989). These three patterns can be seen in the marrow space or outside it and are encountered much more often in benign cartilage lesions (chondromas) than malignancies since calcification requires substantial time and, therefore, connotes chronicity. Chondromas are subclassified based on location as: enchondroma (intra-medullary), cortical chondroma (intracortical), ecchondroma (subperiosteal), and osteochondroma (surface projecting). These proliferative anomalies of growth plate cartilage left behind during longitudinal growth commonly induce enchondral bone formation after provisional calcification of their more mature cartilage areas. This non-neoplastic bone tends to be distributed in arcs-and-rings due to the inherent lobular growth and rims of enchondral ossification in chondromas.

In a conspicuously destructive lesion, such radiographic signs of cartilage matrix are evidence of an antecedent indolent phase and most likely an antecedent enchondroma (Fig. 8), a transition commonly referred to under the biologically imprecise term 'dedifferentiated chondrosarcoma' which refers to a chondrosarcoma in which a group of cells within the tumor has failed to differentiate in the usual progression (Meis, 1991). Chondrosarcomas in today's adults generally can be shown due to sarcomatous change of an antecedent when enough pathologic material or serial radiographs are correlated. Chondrosarcomas, the most common primary bone sarcoma in modern times, are subclassified according to their point of origin as central (medullary), peripheral (e.g., superimposed on

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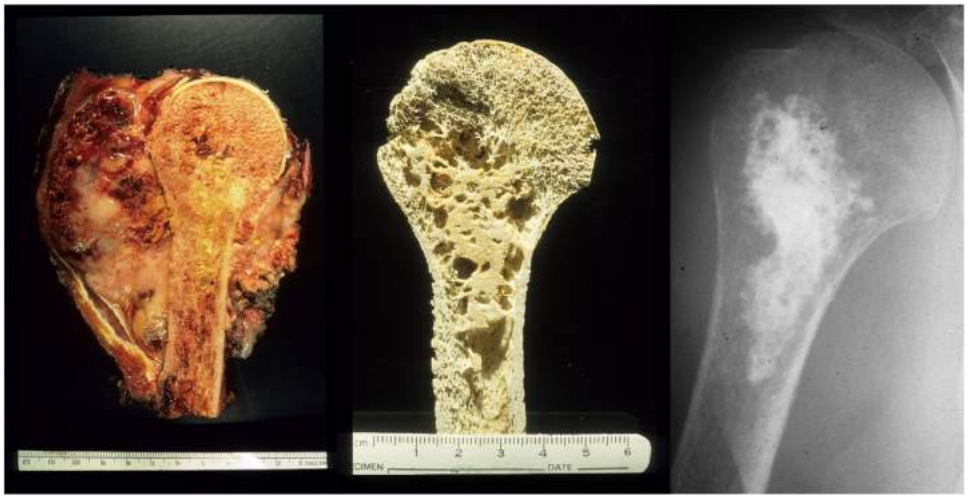

Fig. 8. High grade sarcoma arising around a densely mineralized enchondroma, elderly female. The massive soft tissue extension of the gross tumor (A) is not obvious from the dry bone specimen (B) that has the minute lytic spots of permeative (Type III) margin changes in lateral cortex through which tumor exited the bone; heavily mineralized chunky enchondroma dating back to childhood growth years occupies metaphysis in B. The antecedent enchondroma casts its characteristic flocculent and arc and ring density patterns in the radiograph.

an osteochondroma), or juxtacortical (parosteal). Chondrosarcomas can combine a wide range of margin, periosteal reaction, and mineralization patterns, and they should often be included in the differential diagnoses of solitary bone lesions. A chondrosarcoma that completely fills the marrow space, fails to stimulate destruction of the original cancellous trabecula, does not mineralize, and provokes only a minimal periosteal response will have its extent underestimated from the radiograph.

Occasionally, the collagenous chondroid of an epiphyseal chondroblastoma may accept sufficient mineral to show on a plain film radiograph. Only rarely will an amount of amorphous mineralization sufficiently accumulate in the myxoid background of the eccentric metaphyseal lesion known as chondromyxoid fibroma to register in a plain film, and it surely would be rattling around like dirt in an eccentric lytic defect in an example of it from antiquity. Non-neoplastic dystrophic mineralization, ischemic bone, and mineralized fibro-myxoid areas in ossifying lipomas can mimic the stippled and flocculent mineral patterns of cartilage.

5.3.4. Tumors that produce no mineralizing matrix

Nonmineralized lesions pose the widest differential diagnosis. In addition to entities such as giant cell tumor and bone cyst, consideration also must be given to osteolytic osteosarcoma, unmineralized osteoblastoma, unmineralized cartilaginous and fibrous lesions, etc. Responsible malignancies are those infiltrating the marrow space diffusely and those served by a brisk arterial blood supply, e.g. primary round cell sarcomas and lymphomas, and also the most aggressive fibrosarcomas and matrix-producing sarcomas. These neoplasms tend to colonize the enlarged intracortical vascular channels and replace active hyperemia by tumor pressure as the impetus for further brisk cortical lysis. Regional hyperemia induced by a soft tissue tumor can cause permeative osteolysis of nearby cortical bone through contact, as in the Chilean Pre-Hispanic case published by Pestle and Colvard (2013), or without direct contact. Such a permeative pattern is a sign of an aggressive neoplasm, but can be seen with metabolic conditions (hyperparathyroidism), any cause of sustained active hyperemia such as infection or reflex sympathetic osteodystrophy, and mechanical problems (e.g. stress reaction/fracture).

Distinguishing between the varieties of leukemia (e.g., myelogenous and lymphocytic) based only on skeletal remains is not feasible (Rothschild et al., 1997). The common, slowly progressive leukemia of older adults, chronic lymphocytic leukemia, is reported to increase trabecular bone diffusely. Conversely, childhood acute lymphoblastic leukemia results in the development of generalized osteopenia, transverse metaphyseal lucent bands or less often metaphyseal sclerosis, periosteal reactions, permeative destruction, and in some cases, multiple well-defined, non-corticated radiolucent lesions throughout the skeletal frame (Gallagher et al., 1996). See Klaus (2016) for a probable bioarchaeological case of childhood leukemia.

6. Special considerations for spinal neoplasms

The developmental sequence for the spine is more complex than the relatively simple plan of long bones; an appreciation of this developmental sequence is necessary to understand the spine's differing susceptibility to specific tumors. The vertebral body is a composite of the superior and inferior annular epiphyses and the mass of bone between them. At this stage, the vertebral body becomes essentially a stubby long bone with a lesser (size-proportionate) risk of aberrant development generating a tumor compared to a tibia. All secondary centers unite with the rest of the vertebral body around year 25. Primary tumors of the spine are particularly rare, accounting for 4–13% of published primary bone tumors. Review of the Leeds Bone Tumour Registry found a total of 2750 bone tumors and tumor-like cases (Kelley et al., 2007). Primary bone tumors of the osseous spine constituted only 126 of these, while the most common diagnosis overall was multiple myeloma and plasmacytoma.

The multiple sites of enchondral ossification in vertebral body formation have the potential for chondrogenesis to diverge and result in an osteochondroma, most likely budding from the posterior processes with a predilection for the cervical or upper thoracic regions (Fiumara et al., 1999). Among 150 cases of solitary osteochondroma of the spine found in the clinical literature, there were only four cases (2.7%) of malignant transformation (Gille et al., 2005). As in long bones, unremodeled cartilage remnants from enchondral ossification are the substrate for producing enchondromas and chondrosarcomas, the latter more frequent than the former.

Giant cell tumors (a.k.a. osteoclastomas) are a neoplastic extension of the osteoclastic remodeling activity that, after epiphyseal closure, aligns the epiphyseal cancellous system with the meta-

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physical trabeculae into the mechanically optimal single array of the mature skeleton. In the spine, giant cell tumors quickly become cystic with marked osteolysis; they are often misdiagnosed as "aneurysmal bone cysts" in modern cases. The vertebra does not go through the transition from hematopoietic to fatty marrow as do bones of the extremities. Thus, the relatively common "incomplete maturation anomalies" known as fibrous dysplasia and non-ossifying fibromas, a.k.a. fibroxanthomas, are essentially not encountered in the spine. Osteoid osteomas in posterior elements of the pediatric spine cause scoliosis. Unremodeled vascular beds can persist and enlarge as vertebral body hemangiomas with characteristically thickened longitudinally running trabeculae giving the "corduroy cloth" radiologic appearance.

In utero, the notochord involutes and disappears where the vertebral body surrounds it. Between the vertebrae, the notochord expands to form the nucleus pulposus and subsequently a confining anulus fibrosus condenses around it to complete the intervertebral disc. Excessive longitudinal loading forces the gelatinous nucleus pulpous through fractured end plate cortex to form rounded Schmorl-Putschar nodules (Schmorl, 1927; Putschar, 1927a; Putschar, 1927b) bound by sclerotic type IA margins not to be confused with enchondromas. Remnants of the notochord may persist in the vertebral body centrum and give rise to chordoma, a tumor of adults (50–60 year old) mainly (85%), usually located in the sacro-coccygeal and spheno-occipital regions and also in the cervical spine (Le Charpentier et al., 1988). Today's chordomas are radiologically characterized by osteolysis and slowly enlarge to massive proportions beyond the bone before death.

Metastatic carcinoma with lytic, blastic and mixed lesions, is the most common malignant paleopathological challenge in the spine. The greater blood flow to vertebrae to support hematopoiesis than to the fatty marrow of mature long bones affords more opportunity to receive circulating tumor cells. Thus, in autopsy cases, metastases are most frequent in the spine (80%) (Ortner, 2003, p. 534). The breast and prostate are the most common organs of origin. Metastases to the spine will be evident to the paleopathologist only if in bone. Such metastases, however, can incapacitate by involving the spinal cord, dura around the cord, and the epidural space (Andreula and Murrone, 2005). Metastases from sarcomas favor the lung and so are unlikely to show up in the spine because of their generally brief clinical course.

7. The difficulty of assessing cranio-facial lesions

Nasopharyngeal tumors are over-diagnosed in paleopathological material. Useful and accurate guidelines for the differential diagnosis of oral, nasal, oropharyngeal, paranasal sinus, and salivary gland tumors can be found in an article by Mark (2007).

Different types of tumors may create various types of lesions. A large destructive defect of the cranio-facial skeleton was most likely caused by a skin tumor, if a carcinoma of sinus origin and osteomyelitis have been excluded. Neglected cutaneous basal and squamous cell carcinomas erode bone with a 'moth-eaten' lytic pattern. Basal cell carcinoma of skin, which constitutes 50% of all modern cancer cases, creates Type II (moth-eaten) margins. Second in frequency in skin is squamous cell carcinoma which, untreated, erodes punched out margins without reinforcement (Type IB margins). Either can also arise on sun-exposed skin of the extremities. A final common ultraviolet-related tumor will arise on the bald pate as an "atypical fibroxanthoma" in dermis and achieve massive proportions as an undifferentiated pleomorphic sarcoma infiltrating through calvarium creating ill-defined Type IC margins (Fig. 4). All these skin-derived malignancies are reluctant to metastasize and are more likely to kill by local superinfection.

Multiple destructive lesions on the calvarium are most frequently the result of multiple myeloma or metastatic carcinoma. These conditions can be impossible to distinguish based on lesion morphology alone, particularly in cases with only osteolytic margins (Marks and Hamilton, 2006; Steinbock, 1976). Despite the similarities, metastatic lesions often have more variation in size and shape and are less prevalent in the skeleton than lytic lesions from multiple myeloma (Marks and Hamilton, 2006; Ortner and Putschar, 1981). In the case of metastatic carcinoma, paleopathologists are advised to exercise extreme caution when proposing possible primary tumor sites (Ortner, 2003, p. 539). Distributions of metastatic lesions can vary greatly based on the route of metastasis to the bone, i.e. through the vascular system, the lymphatic system, the cerebrospinal fluid, or through direct spread from tumor to adjacent bone (Waldron, 2009, p. 184). Secondary lesions are usually lytic or sclerotic, and although they may stem from any primary malignancy, there are significant differences in the rates at which each type of cancer tends to spread (Waldron, 2009, p. 184). With this in mind, comparison of lesion distribution patterns in the body, along with vigilant use of modern statistics regarding rates of metastasis, may help narrow the possibilities.

Oral neoplasms in antiquity, whether benign or malignant, are likely to also be represented by a large defect, but distinguished as originating from within the jaws by flaring of outward remodeled peripheral bone from extrinsic invasion of an oral mucosal, salivary gland or skin tumor. Attention to margins of the lesion can narrow the differential diagnosis. See Theodorou et al. (2007a,b) for an overview of tumors and tumor-like lesions affecting the bones of the oral cavity.

Hyperostosis due to slowly growing meningiomas colonizing the calvarium causes a distinctive lesion, while a lytic lesion with impressive damage to the inner table is likely due to its sarcomatous counterpart. Tumors of the brain itself kill by pressure of growth that collapses blood vessels and leaves no mark on bone, apart from pituitary tumors which may cause abnormalities in growth hormone, resulting in gigantism or pituitary dwarfism, e.g. Molto and Kirkpatrick (forthcoming). Occasionally, these tumors may also affect cranial bones and enlarge the sella turcica (e.g. Ortner, 2003, p. 538).

Non-neoplastic conditions may also be confused with cranio-facial neoplasms. These include, but are not limited to: trauma, treponemal disease, porotic hyperostosis, maxillary/mandibular tori, cysts, abscesses, ossified hematomas, myositis ossificans, cherubism, neurofibromatosis, hydrocephaly, encephaloceles, fibrous dysplasia, and erosive or accumulative pseudopathology.

8. Challenges in differential diagnosis

As previously mentioned, a particular disease may produce more than one morphologic expression, and a particular morphology may be created by several specific diseases. Since evidence of neoplastic disease can only present itself as osteoblastic or osteoclastic lesions in bone, there is significant room for misdiagnosis, particularly in fragmentary or incomplete remains. Some examples of conditions that may cause bone lesions that could be mistaken for neoplastic disease include: 1) cysts, 2) developmental abnormalities like fibrous cortical defects, hyperostosis, or Paget's disease of bone, 3) rheumatic diseases including arthritis and enthesopathies, and 4) infectious diseases affecting the skeleton, such as osteomyelitis, treponematosis, leprosy, tuberculosis, and brucellosis, 5) trauma and its subsequent healing may also mimic osteoclastic or osteoblastic neoplastic lesions (e.g. fractures that are walked upon, partially healed cranial puncture wounds and myositis ossificans with impact epicenter on cortex). In addition to alternate pathologies, cultural practices, such as trephination,

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particularly in healing stages, may also occasionally cause defects that could be mistaken for lytic lesions. In intact remains with late stage disease, experienced paleopathologists can often tease apart these conditions through macroscopic observation and radiologic correlation to present a complete differential diagnosis.

Another aspect that may complicate the formation of differential diagnoses is pseudopathology (Wells, 1967), or taphonomic changes that may mimic neoplastic lesions. For example, post-mortem growth of algae or fungi can create tunnel-like canals in bone that may combine to create larger holes, resembling "vestiges of a metastasizing tumor" (Schultz, 2003, p. 79). Conversely, the erosion produced by metastatic carcinoma may be overlooked and attributed to post-mortem taphonomy (Schultz, 2003, p. 106). To confuse the matter further, pathological lesions may be altered by superimposed erosions or incrustations (Capasso, 2005) and can be more vulnerable to post-mortem damage, making the task of differentiating between pathology and pseudopathology even more difficult, and sometimes impossible (Aufderheide and Rodriguez-Martin, 1998, p. 11). This same principle may also contribute to the confusion of post-mortem rodent, insect or carnivore activity with osteoclastic lesions in fragmentary remains (See Haidle, 1995; in which an osteolytic lesion resembles post-mortem bone gnawing). Proteolytic enzymes secreted by insects can dissolve organic bone material, which leaves the remaining water-soluble bone material vulnerable to disintegration, creating holes in the bone that may resemble pathological lesions (Aufderheide and Rodriguez-Martin, 1998, p. 16). Inexperienced paleopathologists may also mistake non-taphonomic and non-pathological conditions attributable to normal skeletal variation, such as penetrating defects caused by bilateral thinning of the parietal bones, to neoplastic disease (Aufderheide and Rodriguez-Martin, 1998, p. 15). All of these risks for misdiagnosis may be minimized through extensive study of comparative osteological specimens, as well as radiological and histological examinations when possible (Aufderheide and Rodriguez-Martin, 1998, p. 11). However, it must be noted that radiology may also present pseudopathologies through the misidentification of sand, crystal deposits, petrological and metallic bodies, or other burial inclusions (Aufderheide and Rodriguez-Martin, 1998, p. 18).

In addition to the possibility of misidentification of skeletal lesions known to modern medicine, paleopathologists must also consider that some disease conditions of antiquity may have been eliminated by evolutionary selection and have no modern counterpart. Diseases and human immune responses also change and evolve over time, and may not have resulted in the same pathological morphology as modern variations of the disease. These uncertainties recommend that paleopathologists be cautious when diagnosing specific diseases in skeletal populations of the past.

9. Conclusion

Paleopathologists often refer to medical museum specimens, pathology texts, and roentgenologic literature when developing a differential diagnosis for dry bone pathologies. But these "knowns" are classic, extreme, and rare. In most instances, determining the etiology of a bone lesion is very difficult. Modern day clinical experience with successive gradual pathologic stages from normal to the extreme clarifies how disease modifies bone structure and has shown that these mechanisms are aberrations of normal growth, development, and maintenance, rather than the interjection of something totally new. Consequently, the limited options for bony reaction to pathology and trauma complicate differential diagnosis based on dry bone. Nevertheless, the elucidation of pathological mechanism(s) should guide one to the category of disease provoking the skeletal change, and only then should one take a stab at a specific diagnosis. Understanding this is a necessary background for diagnosing skeletal disease, and a few basic principles must be kept in mind (Ragsdale and Lehmer, 2012).

Aside from the necessary consideration of all disease categories and mechanisms of disease when assessing a presumed neoplasm, paleopathologists must also consider pseudopathology in the analysis of skeletal remains. All possibilities must be considered in a differential diagnosis, and the full list of differentials should be presented for consideration in published case studies. This will enable readers to review and assess the criteria used in the determination of a preferred diagnosis and allow fellow paleo-oncologists to more easily replicate and/or reassess the differential diagnosis. The use of a table presenting information regarding the differential diagnosis is a succinct and useful tool for the comparison and presentation of differentials. Bone inventory and lesion distribution maps should also be considered and included in case studies, as patterns of lesions can be useful in the identification of disease and this visual aid can provide insight into important missing information in the cases of absent or fragmentary bones.

In addition to the use of classic paleopathological tools and references, paleopathologists should also consult the clinical literature for current understandings of disease processes and definitions. However, one should always be cautious when using clinical literature, as it may lack accurate information about the late stages of disease, since such literature is based on modern examples that have usually been subjected to medical intervention, unlike most paleopathological cases. Modern clinical statistics may also be used in the later stages of paleopathological differential diagnosis, though they should also be used with caution as there is no data to support the assumption that modern clinical statistics are representative of past disease prevalence.

Mummies aside, only bone will record paleo-oncologic events and the relationship between a neoplasm and its host. Using the information provided in this article, cautiously supplemented with clinical literature and statistical data, a reasonably plausible specific diagnosis for neoplastic disease can often be made if attention is paid to dry bone details and their radiologic expression, assuming the examiner is sufficiently schooled in skeletal growth, development, pathobiology, pseudopathology, and radiologic interpretation. The concurrent rapid evolution of radiologic techniques has created new frontiers for correlating imaging studies with pathologic anatomy. The availability of such techniques, in concert with interdisciplinary research on neoplasms both in clinical and archaeological contexts, promises exciting new possibilities for analysis of neoplastic conditions, both in field and laboratory settings.

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References

American Cancer Society, 2016. What Are the Key Statistics About Bone Cancer? [Internet]. Available from http://www.cancer.org/cancer/bonecancer/detailedguide/bone-cancer-key-statistics.

Andreula, C., Murrone, M., 2005. Metastatic disease of the spine. Eur. Radiol. 15 (3), 627–632.

Aufderheide, A., Rodriguez-Martin, C., 1998. The Cambridge Encyclopedia of Human Paleopathology. Cambridge University Press, Cambridge.

Aufderheide, A., Ragsdale, B., Buikstra, J., Ekberg, F., Vinh, T., 1997. Structure of the radiological sunburst pattern as revealed in an ancient osteosarcoma. J. Paleopathol. 2, 101–106.

Bertoni, F., Unni, K.K., Beabout, J.W., Sim, F.H., 1995. Parosteal osteoma of bones other than of the skull and face. Cancer 75 (10), 2466–2473.

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Bloom, R.A., Libson, E., Husband, J.E., Stoker, D.J., 1987. The periosteal sunburst reaction to bone metastases: a literature review and report of 20 additional cases. Skeletal Radiology 16, 629–634.
Bruni, L., 1986. The cockade image: a diagnostic sign of calcaneum intraosseous lipoma. Rays 11 (1), 51–54.
Brunschwig, A., Harmon, P.H., 1935. Studies in bone sarcoma: III. An experimental and pathological study of role of the periosteum in formation of bone in various primary bone tumors. Surg. Gynecol. Obstet. 60, 30–40.
Capasso, L.L., 2005. Antiquity of cancer. Int. J. Cancer 113, 2–13.
Coleman, R.E., 1997. Skeletal complications of malignancy. Cancer 80 (Suppl. 8), 1588–1594.
Ewing, J., 1922. A review and classification of bone sarcomas. Arch. Surg. 4, 485–533.
Fiumara, E., Scarabino, T., Guglielmi, G., Bisceglia, M., D'Angelo, V., 1999. Osteochondroma of the L-5 vertebra: a rare cause of sciatic pain. Case report. J. Neurosurg. 91 (Suppl. 2), 219–222.
Gallagher, D.J., Phillips, D.J., Heinrich, S.D., 1996. Orthopedia manifestations of acute pediatric leukemia. Orthop. Clin. North Am. 27 (3), 635–644.
Gille, O., Pointillart, V., Vital, J.M., 2005. Course of spinal solitary osteochondromas. Spine 30 (1), E13–19.
Haidle, M.N., 1995. A multiple myeloma of the late middle ages from Unterregenbach, Southwestern Germany. Int. J. Osteoarchaeol. 5, 359–367.
Huggins, T.J., Ragsdale, B.O., Schnapf, D.J., 1981. Radiologic-pathologic correlation from the Armed Forces Institute of Pathology: calvarial invasion by meningioma. Radiology 141, 709–713.
Jaffe, H.L., Lichtenstein, L., 1942. Solitary unicameral bone cysts-with emphasis on the roentgen picture, the pathologic appearance and the pathogenesis. Arch. Surg. 44, 1004–1025.
Johnson, L.C., 1953. A general theory of bone tumors. Bull. N. Y. Acad. Med. 29 (2), 164–171.
Kelley, S.P., Ashford, R.U., Rao, A.S., Dickson, R.A., 2007. Primary bone tumours of the spine: a 42-year survey from the Leeds Regional Bone Tumour Registry. Eur. Spine J. 16 (3), 405–409.
Klaus, H.D., 2016. A probable case of acute childhood leukemia: skeletal involvement, differential diagnosis, and the bioarchaeology of cancer in South America. Int. J. Osteoarchaeol. 26, 348–358.
Le Charpentier, Y., Bellefqih, S., Boisnic, S., Roy-Camille, R., 1988. Chordomas. Ann. Pathol. 8 (1), 25–32.
Madewell, J.E., Ragsdale, B.D., Sweet, D.E., 1981. Radiologic and pathologic analysis of solitary bone lesions: I. Internal margins. Radiol. Clin. North Am. 19, 715–748.
Mark, S., 2007. Nasopharygeal carcinoma: a review of its causes and diagnosis in skeletal material. Int. J. Osteoarchaeol. 17, 547–562.
Marks, M.K., Hamilton, M.D., 2006. Metastatic carcinoma: palaeopathology and differential diagnosis. Int. J. Osteoarchaeol. 17, 217–234.
Marques, C., Santos, A.L., Cunha, E., 2011. Better a broader diagnosis than a misdiagnosis: the study of a neoplastic condition in a male individual who died in early 20th century (Coimbra, Portugal). Int. J. Osteoarchaeol. 26 (3), 664–675.
Meis, J.M., 1991. Dedifferentiation in bones and soft-tissue tumors. A histological indicator of tumor progression. Pathol. Annu. 26 (1), 37–62.
Miller, E., Ragsdale, B.D., Ortner, D.J., 1996. Accuracy in dry bone diagnosis: a comment on paleopathological methods. Int. J. Osteoarchaeol. 6 (3), 221–229.
Molto, J.E., Kirkpatrick, C.L., Forthcoming. How Short is Short? A Possible Case of Proportionate Dwarfism in Egypt's 3rd Intermediate Period in the Dakhleh Oasis, Egypt.
Monge, J., Kricun, M., Radovčić, J., Radovčić, D., Mann, A., Frayer, D.W., 2013. Fibrous dysplasia in a 120,000+ year old Neandertal from Krapina, Croatia. PLoS One 8 (6), e64539, http://dx.doi.org/10.1371/journal.pone.0064539.
Ortner, D.J., Putschar, W.G.J. (Eds.), 1981. Identification of Pathological Conditions in Human Skeletal Remains. Smithsonian Institution Press, Washington D.C, pp. 391–398.
Ortner, D.J. (Ed.), 2003. Identification of Pathological Conditions in Human Skeletal Remains. , 2nd ed. Academic Press, New York, pp. 503–544.
Pestle, W.J., Colvard, M., 2013. A disease without history? Evidence for the antiquity of head and neck cancers. In: Radosevich, J.A. (Ed.), Head & Neck Cancer: Current Perspectives, Advances, and Challenges. Springer, Dordrecht, pp. 5–36.
Putschar, W.G., 1927a. Uber Knorpelinsein in den Wirbelkorpern. Verh. Dtsch. Path. Ges. 22, 262–266.
Putschar, W.G., 1927b. Zur Kentniss der Knorpelinseln in den Wirbelkonpern. Beitr z Path Anat u Allgem Path 79, 150–165.
Ragsdale, B.D., Lehmer, L.M., 2012. A knowledge of bone at the cellular (histological) level is essential to paleopathology. In: Grauer, A. (Ed.), A Companion to Paleopathology. Blackwell Publishing Ltd., Oxford, pp. 227–249.
Ragsdale, B.D., Sweet, D.E., 1986. Benign antecedents of malignancy (in the skeleton). In: Henson, O., Albares-Saavedra, J. (Eds.), Pathology of Incipient Neoplasia. WB Saunders Co., Philadelphia, pp. 381–423.
Ragsdale, B.D., Madewell, J.E., Sweet, D.E., 1981. Radiologic and pathologic analysis of solitary bone lesions: II. Periosteal reactions. Radiol. Clin. North Am. 19, 749–783.
Ragsdale, B.D., Sweet, D.E., Vinh, T.N., 1989. Radiology as gross pathology in evaluating chondroid lesions. Hum. Pathol. 20, 930–951.
Ragsdale, B.D., 1993. Morphologic analysis of skeletal lesions: correlation of imaging studies and pathologic findings. In: Weinstein, R.S. (Ed.), Advances in Pathology and Laboratory Medicine. Mosby, New York, pp. 445–490.
Ragsdale, B.D., 1995. Comment – appearance of cancer in de-fleshed human bones. Paleopathol. Newsl. 90, 7–8.
Ragsdale, B.D., 1997. The irrelevance of contemporary orthopedic pathology to specimens from antiquity. Paleopathol. Newsl. 97, 8–12.
Rothschild, B.M., Hershkovitz, I., Dutour, O., Latimer, B., Rothschild, C., Jellema, L.M., 1997. Recognition of leukemia in skeletal remains: report and comparison of two cases. Am. J. Phys. Anthropol. 102 (4), 481–496.
Schmorl, G., 1927. Uber die an den wirbelbandscheiben vorkommenden ausdehnungs–und zerreisungsvorgangeund die dadurch an ihnen und der wirbelspongiosa hervorgerufenen veranderungen. Verh. Dtsch. Path. Ges. 22, 250.
Schultz, M., 2003. Light microscopic analysis in skeletal paleopathology. In: Ortner, D.J., Putschar, W.G.J. (Eds.), Identification of Pathological Conditions in Human Skeletal Remains. Academic Press, New York, pp. 73–106.
Steinbock, R.T., 1976. Paleopathological Diagnosis and Interpretation: Bone Diseases in Ancient Human Populations. C.C. Thomas, Springfield.
Sweet, D.E., Madewell, J.E., Ragsdale, B.D., 1981. Radiologic and pathologic analysis of solitary bone lesions: III. Matrix patterns. Radiol. Clin. North Am. 19, 785–814.
Theodorou, S.J., Theodorou, D.J., Sartoris, D.J., 2007a. Imaging characteristics of neoplasms and other lesions of the jawbones: part 1. Odontogenic tumors and tumorlike lesions. Clin. Imaging 31 (2), 114–119.
Theodorou, S.J., Theodorou, D.J., Sartoris, D.J., 2007b. Imaging characteristics of neoplasms and other lesions of the jawbones: part 2. Odontogenic tumor-mimickers and tumor-like lesions. Clin. Imaging 31 (2), 120–126.
Urist, M.R., Grant, T.I., Lindholm, T.S., 1979. Induction of new bone formation in the host bed by human bone tumor transplants in athymic nude mice. J. Bone Jt. Surg. 61, 1207–1216.
Volberg Jr., F.M., Whalen, J.P., Krook, L., Winchester, P., 1977. Lamellated periosteal reactions: a radiologic and histologic investigation. AJR 128, 85–87.
Waldron, T., 2009. Palaeopathology. Cambridge University Press, Cambridge.
Wells, C., 1967. Pseudopathology. In: Brothwell, D., Sandison, A.T. (Eds.), Diseases In Antiquity. C.C. Thomas, Springfield, pp. 5–19.

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