CHAPTER 13 A Knowledge of Bone at the Cellular (Histological) Level is Essential to Paleopathology

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Introduction

An anthropologist deduces a species from a bone, a face from a skull, and life habits from a skeleton; the paleopathologist deduces disease from dry bone abnormalities by reference to medical museum specimens, pathology texts, and roentgenologic literature. But these "knowns" are classic, extreme and rare. In most instances determining the etiology of a bone lesion is extremely difficult. Bone, like all tissues, has few ways of reacting, so different causes may produce similar results. However, recognizing successive gradual pathologic stages from normal states may reveal the mechanisms of disease. Cells are the effectors of change, and an understanding of them is a necessary foundation for diagnosis. So, knowledge of skeletal dynamics in growth and adaptation is fundamental (Johnson 1966).

This chapter will review the influences that drive the cellular activities that modify mineralized tissue. A dry bone from antiquity is like a fossilized footprint left in mud. Just as the foot is obviously of more interest than the print, so, too, in paleopathology the disease is more interesting than the resulting lesion. One's frame of mind must be to mentally "put the soft tissue that abutted solid substance back on the specimen," to find clues to the host response that modified bone, and then to deduce the

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mechanisms that produced the change. Through this process one might then determine the category of disease provoking the skeletal change, and only then, take a stab at a specific diagnosis.

Basic Principles

Disease is the alteration of living tissue that jeopardizes "ease" and survival. The causes of skeletal disease are aberrations of normal growth, development, and maintenance, rather than the interjection of something totally new, which limits the number of ways in which bone can react. Consequently, "morphologic residua" of different diseases significantly overlap. Even the Basic Categories of disease (discussed below, and see Table 13.2) overlap to some extent, since inflammation includes repair, trauma is associated with circulatory changes, and metabolic diseases may call forth mechanical compensation.

The sequence from normal, through adaptation, to sickness and death is a continuum. However, most of the skeletal alterations that paleopathologists encounter are the result of long-standing disease, which may or may not have led to the death of the individual. Hence, using modern diseases, which are intercepted by medical professionals comparatively early, as reference standards for diagnosing diseases of the past, is problematic as they bear little resemblance to the untreated end stage of the process (Ragsdale 1997). While autopsy specimens are more likely to represent advanced expressions of disease, the morphologic expression is generally modified by therapeutic intervention. Ortner and Putschar's (1981) work is of greater relevance for paleopathological diagnosis, since many of its illustrations are cases collected in the 19th century or come from Dr. Putschar's experiences in underdeveloped countries (Ragsdale 1996). Unfortunately, further complicating the diagnostic process is the fact that well-defined structural change may appear in many diseases, and a particular disease may produce more than one morphologic expression. Only in the presence of a few extreme abnormalities can relatively specific diagnoses be made. Obviously, this casts doubt on the diagnostic specificity of a small slice of dry bone studied histologically.

Further complicating our ability to diagnose the presence of specific disease from dry bone specimens is the fact that pathologic morphology is linked to only three aberrations: circulation, metabolic factors, and mechanical stress. These three influences act on the bone fabric of collagen bundles impregnated with mineral crystals through three cell types. Only osteoblasts produce significant osteoid matrix (bone fabric). Only osteoclasts can significantly resorb (remove) bone (and do so much faster than osteoblasts create bone, so osteopenia is the usual initial expression of a bone reaction). Osteocytes can both resorb and form bone, but only to a limited degree along the walls of their lacunae where they maintain bone, serve as mechanical sensors, and control calcium flux. These three cells are normally active in the daily remodeling and rejuvenation of the living skeleton. No other cell types directly modify bone structure. Pathologic anatomy results when local (pathological) conditions stimulate abnormal activity of these cells. An understanding of these conditions is a necessary background to diagnose skeletal disease, and is facilitated by keeping a few basic principles in mind (Table 13.1).

Table 13.1 The twelve basic principles of orthopedic pathology

1. There are seven Basic Categories of disease.
2. There are only three influences which govern cell activities: circulatory dynamics, metabolic factors, and mechanical forces.
3. Only osteoblasts make bone, are favored by elevated pH, passive hyperemia (venous congestion and edema), negative bioelectric charge, and growth hormone. Only osteoclasts delete bone, favored by low pH, active hyperemia (increased arterial input), positive bioelectric charge, and parathormone and work 100 times faster than osteoblasts.
4. Bone formation proceeds on surfaces; what is lost is gone forever, but persisting surfaces can be added to.
5. The "endosteum," if the term must be retained in adults, consists of the mature fat cells that abut internal bone surfaces and are capable of modulating into osteoblasts.
6. The interface between periosteum and cortex along growing bones can be a plane of bone formation (as in additions to diaphyseal diameter) or resorption (as in metaphyseal cutback); these same activities can be reawakened in disease as periosteal new bone or cortical lysis.
7. Turnover and remodeling proceed, even in the presence of disease. In face of disease, the mechanically most important (i.e., the stressed) bone components are preserved the longest and may indeed be strengthened.
8. Fully differentiated mesenchymal cells, e.g., "fibroblasts" and adipocytes of soft tissue and of the marrow, are not irrevocably differentiated cells, but retain a capacity to modulate into other functional cell types as conditions dictate. Fat, fascia, and muscle contribute to "periosteal reactions."
9. All cartilage formed, except for articular, ear/nasal/airway and sarcomatous cartilage, is doomed to resorption (e.g., epiphyseal and fracture callus cartilage).
10. Bone is an enclosed space bound by cortex and internally baffled by cancellous modules. This shields vessels from the mechanical compressive forces operative in soft tissue but makes bone's blood supply vulnerable, especially to compressive obliteration when anything is added to the marrow space.
11. Age epochs modify likely sites of disease, reactive potential and therefore morphologic expression.
12. Benign tumors may stabilize in size, but even so, by strategic position, can incapacitate or kill; malignant tumors inexorably grow and by definition, can metastasize.

Categories of Disease

Factors that influence the speed with which bone lesions evolve leave clues that distinguish chronic from acute skeletal disease. The tempo of the process is a potentially important factor in diagnosis and can be discerned by "morphologic analysis," i.e., attention to the character of margins, periosteal reactions, and presence or absence of regional remodeling effects (Ragsdale 1993a). The location of solitary lesions is also helpful in diagnosis, and the character and distribution of multifocal lesions are similarly important in narrowing a differential diagnosis.

In 1996, Ragsdale and co-workers proposed using seven basic disease categories as part of the diagnosis of paleopathological conditions. These can be easily remembered by use of the acronym VITAMIN (Table 13.2) (Ragsdale and Miller 1996). Approaching differential diagnosis by looking for clues as to which of the Seven Basic

Table 13.2 The seven basic categories of disease

I	V	Vascular
II	I	Innervation/Mechanical
III	T	Trauma/Repair
IV	A	Anomaly
V	M	Metabolic
VI	I	Inflammatory/Immune
VII	N	Neoplastic

Categories of Disease is represented helps minimize the overwhelming bewilderment that can result from attempting to choose from several hundred individual entities that can afflict bone. Thus, paleopathologists should redirect their enthusiasm for diagnosing specific diseases in human skeletal remains, to deducing the less ambitious (but more often correct) classification by disease category. This will enhance the comparability of data within paleopathology.

Vascular disturbances

There are two basic vascular mechanisms which can impact bone. The first is active hyperemia (increased arterial blood flow), which increases tissue oxygen tension, fueling mitochondria-rich osteoclasts that engage in bone resorption. The second is passive hyperemia (slow flow in patulous veins) which creates back pressure and increases permeability, leaking the edematous protein substrate that osteoblasts use to produce matrix. Due to the physics of streaming potentials, these contrasting vascular flows are characterized by opposite local electrical field effects (MacGinitie et al. 1993). Charged solutes in blood moving past fixed charges in vessel walls create energy fields similar to an electromagnet. Active hyperemia engenders a positive electrical environment, favoring osteoclasts, which work best in a slightly acidic pH. Passive hyperemia evokes a net negative field and a basic environment favoring osteoblasts.

Examples of hyperemic conditions include:

Active hyperemia: Enlarged cortical penetration ports of vessels near any inflammation; lytic phase of early acute osteomyelitis; juxta-articular osteolysis in rheumatoid arthritis; pencil deformity (concentric atrophy) of ainhum; loss of neuroregulation in dysvascular responses (Sudeck's atrophy, post-traumatic osteolysis) and leprosy; increased blood flow demanded by metastatic carcinoma.

Passive hyperemia: Dense medullary edema around a Brodie's abscess supplies protein substrates for marginal sclerosis; back pressure in varicose veins or distal to an atriovenous fistula evokes an edematous periosteal reaction; calvarial hyperostosis due to invasive meningioma clogs venous outflow (Huggins et al. 1981); and pachydermohyperostosis (Uehlinger disease) is its systemic manifestation.

Biphasic hyperemias: Circulation is initially active and later passive: acute osteomyelitis transitioning into chronic; diabetic osteopathy; Charcot joint; melorheostosis; hypertrophic pulmonary osteoarthropathy; Paget's disease.

Importantly, the mechanical, hematopoietic, and fat reserve functions of bone are dependent on an adequate blood supply, i.e., viability. Injury or disease elicits a vascular response. There are three noteworthy peculiarities of the vascular supply to bone which directly impact pathological processes in bone.

The first is that bone is a completely rigid compartment. The blood vessels in bone are totally protected from the mechanical compressive forces operative in soft tissue and have, therefore, thin walls. This confers a susceptibility to hydrostatic compression by anything that is added to the marrow space such as edema, pus, fat cell swelling, histiocytes filled with abnormal lipid or mucopolysaccharide, tumor, etc. Cessation of flow leads to ischemia and necrosis. At the end of a bone and in cuboidal bones this is "avascular (aseptic) necrosis." Conversely, ischemic necrosis in metaphyses or diaphyses is a "bone infarct." This can be seen with storage diseases (Gaucher's disease), vasculitis, and sickle cell disease. Bone infarcts are uncommon in the modern era and likely less so in antiquity.

Ischemic aseptic necrosis is most commonly found today in the femoral head, a precariously supplied spheroid with narrower inlet (the neck) than equatorial girth. Anything that swells fat cells (e.g., alcoholism, steroid therapy, genetically caused storage diseases like Gaucher's) will compress the only thing that can yield in the closed space defined by the cortex-marrow vessels: blood vessels. Hip dislocation and femoral neck fracture simply transect vessels, vasculitis occludes them with thrombus, and sickle cells clog them. Avascular necrosis of the femoral head in a child (Legg-Calvé-Perthes) follows a growth spurt that is unaccompanied by sufficient vascular remodeling. Whatever the cause, the attempt at repair of a dead femoral head segment begins with removal of dead cancellous bone along a reactive interface which cuts away the necrotic segment, followed by collapse and eventual severe osteoarthritis due to the resultant shape change and head fragmentation.

The second peculiarity of the vascular supply to bone is that only one-third to one-half of the vascular network in bone is open at any given time. Blood is shunted from regions of lesser to greater need by chemo-sensors (the glomoid system) that act over neural pathways to modify arterial caliber (Johnson 1971). The periosteal, osseous and medullary vascular "fields" constantly shift (take turns) from moment to moment. This is regulated by the angioglomic system that is commonly upset in disease. Therefore, circulatory disturbances are regional, affecting bone segments or bones served by the same vascular trunk.

Thirdly, the capacity of the venous system in bone is 6–8 times that of the arterial system. The shared vascular connections between muscle and bone play an important part in blood movement. The loss of bone density that accompanies disuse and muscle paralysis is in part due to the loss of the muscular "pump's" assistance to venous return. This results in progressive distention of intraosseous sinusoids caused by osteoclastic removal of bone. A further effect of disuse is the removal of the mechanical stimulus for bone formation while the lysis of physiologic turnover proceeds.

Innervation and mechanical disease

Mechanical factors operate through bioelectric signals proportional to use or disuse. Bone is a composite, crystalline substance. Hydroxyapatite hexagonal prisms solidify the periodic organic crystal fabric of collagen. Electric charge generated by pressure