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Perspectives

Who's Afraid of the Big Bad Wolff?: "Wolff's Law" and Bone Functional Adaptation

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ABSTRACT "Wolff's law" is a concept that has sometimes been misrepresented, and frequently misunderstood, in the anthropological literature. Although it was originally formulated in a strict mathematical sense that has since been discredited, the more general concept of "bone functional adaptation" to mechanical loading (a designation that should probably replace "Wolff's law") is supported by much experimental and observational data. Objections raised to earlier studies of bone functional adaptation have largely been addressed by more recent and better-controlled studies. While the bone morphological response to mechanical strains is reduced in adults relative to juveniles, claims that adult morphology reflects only juvenile loadings are greatly exaggerated. Similarly, while there are important genetic influences on bone development and on the nature of bone's response to mechanical loading, variations in loadings themselves are equally if not more important in determining variations in morphology, especially in comparisons between closely related individuals or species. The correspondence between bone strain patterns and bone structure is variable, depending on skeletal location and the general mechanical environment (e.g., distal vs. proximal limb elements, cursorial vs. noncursorial animals), so that mechanical/behavioral inferences based on structure alone should be limited to corresponding skeletal regions and animals with similar basic mechanical designs. Within such comparisons, traditional geometric parameters (such as second moments of area and section moduli) still give the best available estimates of in vivo mechanical competence. Thus, when employed with appropriate caution, these features may be used to reconstruct mechanical loadings and behavioral differences within and between past populations. Am J Phys Anthropol 129:484–498, 2006.

The idea that bone form reflects in some way its mechanical loading history during life is fundamental to many paleontological and bioarchaeological studies of skeletal material. While physical context and material culture give clues to past behavior, analysis of the skeletons themselves is the most direct way to reconstruct individual behavior, and to explore intra- and interpopulational differences in behavior (e.g., Larsen, 1997; Drucker and Henry-Gambier, 2005; Scott et al., 2005). Reconstructions of body size and shape from skeletal remains are also dependent to some degree on assumed relationships between mechanical loadings and bone morphology (Ruff, 1995, 2003; Delson et al., 2000; Auerbach and Ruff, 2004). The phenomenon of bone adaptation to imposed mechanical loadings is often loosely referred to as "Wolff's law," although as noted by others (Bertram and Swartz, 1991; Cowin, 2001b; Pearson and Lieberman, 2004; and see below), there are problems with this representation. Regardless of semantic issues, the general concept that bone adapts to its mechanical environment during life, and therefore that differences in morphology can be used to investigate differences in past mechanical environments, is widely accepted among paleoanthropologists and bioarchaeologists.

Several recent studies, however, beginning with the often-cited review by Bertram and Swartz (1991), called into question at least portions of "Wolff's law" as it is generally understood (Forwood and Burr, 1993; Demes et al., 1998, 2001; Lovejoy et al., 2002, 2003; Ohman and Lovejoy, 2003; Lieberman et al., 2004; Pearson and Lieberman, 2004). A number of issues have been raised, including the precise meaning of the "law," the validity of the experimental evidence for bone functional adaptation, correspondence between in vivo strain measurements and bone structure, the genetic vs. environmental determinants of bone form, age dependency of bone functional response to loading, and whether skeletal morphology is mechanically "ideal." Because the general concept of bone functional adaptation is so pervasive in biological anthropology and indeed biology (Roesler, 1987), it is important to carefully evaluate these issues/objections and their implications for current research approaches. We do so here, and attempt to clarify both

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the limits and potential of bone structural analyses. The emphasis here is on cortical bone distribution in long bone diaphyses, in part because most of the above studies also focused on this aspect of skeletal form, and because this has been a very active area of anthropological research over the past several decades (e.g., Endo and Kimura, 1970; Kimura, 1971; Lovejoy et al., 1976; Jungers and Minns, 1979; Lovejoy and Trinkaus, 1980; Ruff and Hayes, 1983; Schaffler et al., 1985; Trinkaus and Ruff, 1989; Demes and Jungers, 1993; Ruff et al., 1993; Runestad, 1997; Trinkaus et al., 1999; Stock and Pfeiffer, 2001; Holt, 2003; Weiss, 2003; Beauval et al., 2005; Carlson, 2005). This list is not exhaustive; in fact, we make no attempt here to provide an encyclopedic review of recent literature on this general topic, which is voluminous (e.g., Martin et al., 1998; Cowin, 2001a; Pearson and Lieberman, 2004). Rather, we confine ourselves to key works that are specifically relevant to addressing the issues posed above and that provide historical context for the ideas of concern.

"WOLFF'S LAW" VS. BONE FUNCTIONAL ADAPTATION

As noted by Cowin (2001b, p. 30–31), current usage of the term "Wolff's law" usually involves only the general concept that "over time, the mechanical load applied to living bone influences the structure of bone tissue." However, he went on to point out that Wolff actually had something much more specific in mind, namely the formulation of strict mathematical rules governing this process, particularly with respect to the development of trabecular orientation in long bones (the "trajectorial theory"), most famously expressed in the proximal femur. Wolff himself nicely summarized this argument in the introduction to his 1892 treatise (Wolff, 1892; translation in Wolff, 1986, p. 1): "Thus the law of bone remodeling is the law according to which alterations of the internal architecture clearly observed and following mathematical rules, as well as secondary alterations of the external form of the bone following the same mathematical rules, occur as a consequence of primary changes in the shape and stressing or in the stressing of the bones."

Many authors criticized Wolff's mathematical treatment of bone modeling/remodeling, which involved both engineering and biological misconceptions (for historical reviews, see Roesler, 1981, 1987; Martin et al., 1998; Cowin, 2001b). The "false premise in Wolff's law" discussed by Cowin (2001b) involves modeling real bones as solid, homogeneous, and isotropic structures subjected to static applied loads, which is strictly incorrect. However, neither Cowin (2001b) nor any of the other recent authors who critiqued Wolff's law denied the importance of mechanical loading in the development of bone form, i.e., the more "general" version. This is an important point, since the two versions have sometimes been confused. For example, the critique by Cowin (2001b) (of the strict version) was cited by Currey (2002, p. 159) (again with reference to the strict version), who in turn was quoted by Ohman and Lovejoy (2003) in their more general critique of Wolff's law. This confounding of the more general with the more specific version of the "law" unnecessarily confuses the issue: like many others, neither Cowin (2001b) nor Currey (2002) intended their critiques to imply a negation of the general version; both authors have, in fact, spent most of their careers refining our knowledge of mechanically adaptive mechanisms in bone.

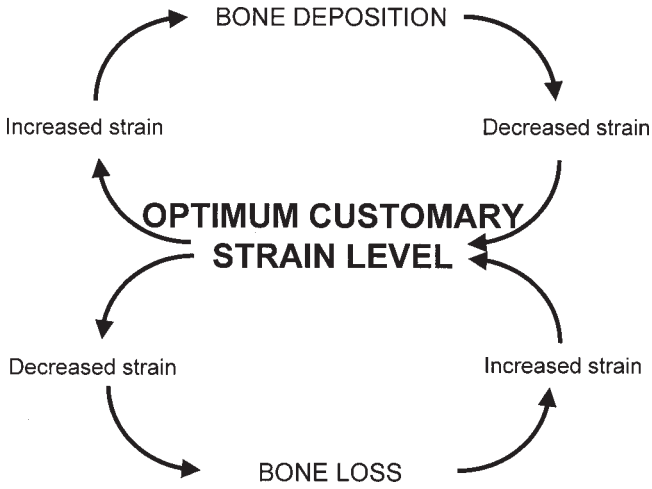

Fig. 1. Simple feedback model of bone function adaptation (from Lanyon, 1982).

Given this potential confusion, it may be better to simply discard the term "Wolff's law" in its more general sense, as recommended recently by several authors (Martin et al., 1998; Cowin, 2001b; Pearson and Lieberman, 2004). Following the original lead of Roux (1881), taken up by more recent investigators (Churches and Howlett, 1982; Cowin et al., 1985; Lanyon and Rubin, 1985), the term "bone functional adaptation" seems appropriate for this more general meaning. As summarized by Roesler (1981), the writings of Roux (1881) incorporated two important principles: 1) organisms possess the ability to adapt their structure to new living conditions, and 2) bone cells are capable of responding to local mechanical stresses. Although not without their own problems (Roesler, 1981), the ideas of Roux (1881) encapsulate much of the more general concept of bone functional adaptation as understood today. (In fact, as noted by Cowin (2001b), some researchers suggest renaming the more general version of Wolff's law "Roux's law.")

Figure 1 is a schematic diagram, taken from Lanyon (1982), of perhaps the simplest representation of bone functional adaptation in a more modern sense (see also Lanyon and Skerry, 2001). The bone modeling/remodeling stimulus is based on strain (not stress)—the actual physical deformation of the bone tissue—and acts through feedback loops. Increased strain (e.g., through an increase in activity level) leads to deposition of more bone tissue, which then reduces strain to its original "optimum customary level." Decreased strain (e.g., through inactivity) leads to resorption of bone tissue, which again restores the original strain levels. Many other authors have embraced the general idea of a "customary" or "equilibrium" strain level window above which bone deposition is stimulated and below which resorption is stimulated (e.g., Carter, 1984; Frost, 1987; Turner, 1998), although there are many qualifications to and variations on this general model. One of the most important qualifications is that the "customary strain level" to which bone tissue is adapted is apparently not constant, but varies by skeletal location (Carter, 1984; Hsieh et al., 2001; Lanyon and Skerry, 2001; Lieberman et al., 2001; Currey, 2002) as well as by systemic factors such as age, disease state, hormonal status, and genetic background (Frost, 1987; Lee et al., 2003; Pearson and Lieberman, 2004; Suuriniemi et al., 2004). Also, the type

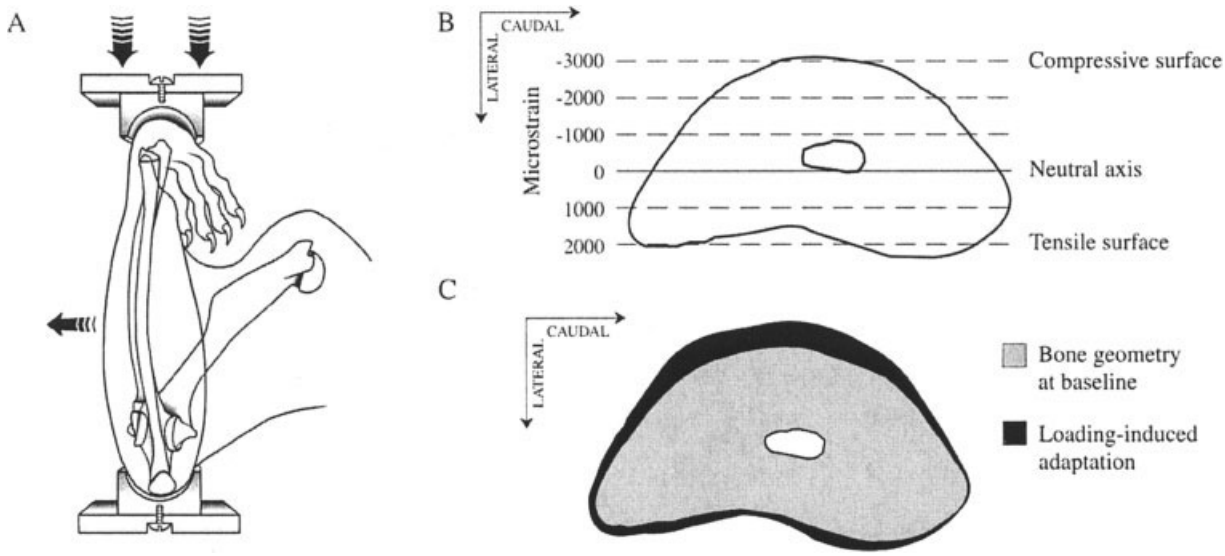

Fig. 2. Results of experimental in vivo overloading of rat ulna by Robling et al. (2002). **A:** Experimental setup: compressive loading creates compression and lateral bending of ulna. **B:** Strain distribution across ulna near midshaft. Maximum strains occur on medial surface (compression), followed by lateral surface (tension). **C:** New bone formation after 16 weeks of intermittent loading. Bone is preferentially added in regions of highest strain (reprinted by permission of authors and *Europa Mediocophysica*, from Warden et al., 2004).

of strain (its frequency and other characteristics), as well as the loading history of the bone cells, are important variables influencing the magnitude of bone response (Turner, 1998; Burr et al., 2002).

These complexities suggest that the general model shown in Figure 1 must be interpreted carefully and within specific contexts (e.g., comparisons between similar skeletal regions in genetically similar animals), and that disentangling the effects of different loading components, such as load magnitude vs. frequency, may be very difficult from morphology alone. But increased complexity does not invalidate application of the general model, which is supported by much experimental evidence, reviewed below, with suitable caution (Lanyon and Skerry, 2001). In any event, arguments regarding the validity of the "strict" version of Wolff's law must be distinguished from those concerning the nature of bone functional adaptation in general.

EXPERIMENTAL EVIDENCE FOR BONE FUNCTIONAL ADAPTATION

A series of now-classic papers from the 1960s through the 1980s appeared to provide clear evidence for bone functional adaptation to mechanical loading and unloading, using various experimental animal models (e.g., Saville and Smith, 1966; Hert et al., 1969; Liskova and Hert, 1971; Chamay and Tschantz, 1972; Uhthoff and Jaworski, 1978; Goodship et al., 1979; Jaworski et al., 1980a; Woo et al., 1981; Churches and Howlett, 1982; Lanyon et al., 1982; Lanyon and Rubin, 1984), as well as observations of human athletes (e.g., Nilsson and Westlin, 1971; Jones et al., 1977) (for a comprehensive review, see Meade, 1989). However, in their critique, Bertram and Swartz (1991, p. 23) argued that much of this evidence was inherently flawed because of problems in experimental design: "While accepting that mechanical load has substantial influence on the development of form in bone, we argue that to date there is no direct evidence of its influence on the healthy mature appendicular skeleton that is not seriously compromised by complications arising from indirect effects of the investigative procedures on other aspects of the organism's physiology." The "complications" that Bertram and Swartz (1991) referred to involve inflammatory responses due to surgical treatment, and repair phenomena (regeneration of injured tissue, or repair of stress fractures), none of which they considered to properly fall under "Wolff's law." With regard to the first of these factors, it should first be noted that the studies above that included surgical intervention generally included surgical controls, i.e., bones in which all surgical procedures except the change in mechanical loading had been carried out, although as Bertram and Swartz (1991) and others pointed out, it is still difficult to completely control for all related effects. There is also some question as to whether woven bone, a typical response (at least at first) to sudden mechanical overload, is "normal" or "pathological" (see also Frost, 1988). However, with regard to this latter issue, Burr et al. (1989, p. 232), in a carefully controlled experiment that intentionally incorporated some features of earlier experimental work, demonstrated that "woven bone can be a normal adaptive response to an intense mechanical challenge, even in the absence of trauma or fatigue-induced damage."

Partly in response to such criticisms, a series of investigators beginning in the early 1990s developed new animal models that did not involve invasive surgical procedures (Turner et al., 1991; Torrance et al., 1994; Forwood et al., 1998). These models have since been used extensively to study various aspects of bone modeling/remodeling under altered mechanical loadings (e.g., Hsieh et al., 2001; Burr et al., 2002; Robling et al., 2002).[1] Figure 2

[1]Such studies have amply met the challenge posed by Lovejoy et al. (2002, p. 99) to provide "flexible protocols that carefully monitor bone parameters and *varying* levels of noninvasive specific bone load" (italics original), in order to distinguish direct mechanical from other effects.

shows the results of one such experiment (Robling et al., 2002). In this experiment, the forearms of 6-month-old rats were dynamically loaded in compression, which creates bending stresses in the midproximal region of the bone due to its natural curvature. At this age, the rats can be considered "adults," since no further growth in bone length occurred over the 16-week experimental period. The extra loading produced an increase of 70–100% in bending rigidity (second moment of area) in the plane of bending compared to control limbs, through increased periosteal bone apposition in regions under the highest bone strain (Fig. 2). Bone strength determined through direct mechanical testing after sacrifice increased 64–165%, depending on the loading schedule and strength parameter. Interestingly, these gains were not well-represented by changes in bone mineral content (BMC) or bone mineral density (BMD), the two most commonly measured outcomes of human exercise studies. Conversely, changes in the relevant second moment of area (a geometric property) explained 92% of the variance in strength (ultimate force). Similar results were obtained by Warden et al. (2005), who also demonstrated greatly increased fatigue resistance after experimentally increased loading in the same animal model. These studies noninvasively reproduced and extended similar results of earlier studies (e.g., Lanyon et al., 1982) demonstrating the specificity of bone adaptation to changes in strain distributions, and also the primacy of geometric changes in such adaptations (Woo et al., 1981).

Bertram and Swartz (1991) also argued that much of the change in bone dimensions observed in human athletes, and commonly attributed to increased mechanical loading, was actually a repair process in response to "chronic fatigue damage," and as such did not qualify as support for "Wolff's law." It could be debated whether repair of fatigue-induced microcracks is actually outside the realm of "normal" bone mechanical adaptation, since such repair has been hypothesized to be an important component of bone remodeling throughout life (Martin et al., 1998). Other more recent studies of human athletes and volunteers in exercise intervention studies also showed clear evidence of adaptive bone modeling/remodeling without evidence of fatigue (or stress) fractures, as reviewed below. The varying response of bone to applied loading is probably best viewed as a continuum, involving in some cases rapid deposition of woven bone (which can subsequently be remodeled into lamellar bone), in some cases repair of microcracks, and in other cases direct deposition of lamellar bone, depending on the severity and suddenness with which the loading schedule is implemented (Rubin et al., 1995). Also, not all bone features may react similarly to applied loading: in Robling et al. (2002), the distal ulnar articulations of experimentally loaded groups developed osteophytic reactions, which is perhaps not surprising given the very "abnormal" way in which the carpus was loaded (Fig. 2), and possible constraints on articular remodeling (Ruff et al., 1991; Lieberman et al., 2001) (what this might indicate regarding mechanisms underlying osteoarthritis was not addressed by the authors). However, the response in the diaphysis was "normal" in terms of bone tissue appearance (Fig. 4 in Turner and Robling, 2004). In summary, while experimental and observational studies have their limitations, such studies have clearly demonstrated that functionally adaptive changes in bone structure can be brought about by manipulation of mechanical loadings, supporting the general model shown in Figure 1.

IN VIVO STRAINS AND FUNCTIONAL ADAPTATION

Given that bone adaptation to mechanical loadings very likely involves a response to strains (deformations) engendered by such loadings, direct measurement of bone strains in vivo using strain gauges can provide important information in evaluating adaptive mechanisms (e.g., Fig. 2B, although in this case, strains were calculated in a simulated in vivo loading) (Robling et al., 2002). Three recent studies documented in vivo strains in the long bones of macaques (Demes et al., 1998, 2001) and sheep (Lieberman et al., 2004), and concluded that strain patterns were not well-correlated with cross-sectional geometry of the bones, thereby casting doubt on whether cross-sectional geometry could be used to reconstruct mechanical loading history. Specifically, the bending axes generally did not match well with the neutral axes of sections, or conversely, sections were not reinforced in regions of maximum strain (Lieberman et al., 2004) made a number of other points, which are addressed below). It should be noted that none of these studies examined the effects of exercise per se on bone modeling/remodeling, but rather the normal patterns of strain during locomotion in laboratory animals.

The fact that long bone diaphyses may be customarily bent in planes that are not equivalent to their directions of greatest bending rigidity or strength was noted previously (Lanyon and Rubin, 1985). Together with the observation that long bone curvature often seems to increase rather than decrease strains in vivo, this formed the basis for theories that bone structure may be designed in some cases to confine strains to more predictable patterns, rather than strictly to minimize strains (Lanyon and Rubin, 1985; Bertram and Biewener, 1988). This is not inconsistent with the model shown in Figure 1: some degree of bending could actually be beneficial to bone tissue by maintaining strains within the "optimum customary" window (Lanyon and Rubin, 1985). At the same time, potentially catastrophic strains in "unusual" orientations could be avoided. Because of their more readily available surfaces for attaching strain gauges, the distal limb elements of cursorial animals (horses, sheep, and dogs) were most often used in these experiments (see also Lieberman et al., 2004). These skeletal locations are relatively "unprotected" medially and laterally by muscle tendons (one reason that they are more accessible for strain gauges) (e.g., see Piotrowski et al., 1983; Thomason, 1985). Thus, any unusual bending in the mediolateral plane (e.g., due to turning or walking over uneven ground) is probably less able to be modified by muscles, making this a more "dangerous" loading orientation for the bones. In these situations, it is not unreasonable to postulate a genetically selected difference in strain sensitivity thresholds that would favor the development of an elliptical cross section oriented to increase mediolateral (M-L) bending strength (Lanyon et al., 1982; Piotrowski et al., 1983; Nunamaker et al., 1989; Lieberman et al., 2004).

Of course, postulating genetic mechanisms that alter the "optimum customary" strain sensitivity of bone tissue argues against making comparisons between species that are not closely related, and for whom genetic selection histories may have been significantly different: one would not want to use differences in cross-sectional shape between a human and horse long bone to reconstruct behavioral differences between them! In this respect, we fully concur with the caution by Demes et al.

(2001, p. 264) "against broad behavioral conclusions derived from long bone cross-sectional shape." However, comparisons within species or between closely related species who share the same basic body design and evolutionary history are much less likely to be confounded by such factors (see also Lieberman et al., 2004). In this regard, it is interesting that even in highly cursorial animals, activity patterns appear to affect long bone cross-sectional geometry in predictable ways. Thoroughbred and standard-bred horses differ in cross-sectional geometry of the third metacarpal (cannon bone), such that thoroughbreds, who are subjected to more rigorous training of a type that specifically engenders high strains in the anteroposterior (A-P) plane, have more A-P strengthened bones (Nunamaker et al., 1990). McCarthy and Jeffcoat (1992, p. 35), in an experimental study of young (yearling) thoroughbreds, also documented a site-specific effect of exercise in these animals: "In the unexercised group periosteal bone apposition occurred uniformly around the third metacarpal without selective enlargement of any cortex. The increased thickness of the dorsal cortex in the exercised horses means that the bone is better able to withstand loading of this cortex where very high compressive strains can occur during locomotion."[2] These results are consistent with the view that there is a basic structural model, in part genetically determined, of the horse third metacarpal that can then be modified by specific environmental (mechanical) stimuli (for a very similar argument, see Turner, 1998). This is very much analogous to comparisons of the same skeletal element within or between human populations with different behavioral characteristics (e.g., Ruff, 1987; Stock and Pfeiffer, 2001): because the basic underlying model is similar, variations in morphology are more likely to reflect variations in applied loading throughout life.

The above reasoning also argues for caution in extrapolating results of strain gauge experiments between skeletal locations or species with very different body plans and evolutionary histories. There is evidence that strain distributions in bones/species that are less specialized for cursorial locomotion more closely match traditional expectations of greater bone strength in directions of higher strain, especially during vigorous movement. Figure 3 shows some of the results of Demes et al. (2001) on strains in the macaque tibial mid-diaphysis during walking and galloping, and of Szivek et al. (1992) on strains in the greyhound femoral mid-diaphysis at various speeds (although the greyhound is certainly well-adapted for cursorial locomotion, its femur is surrounded by muscles in much the same way as a noncursorial animal). In both cases, anterior and posterior strains increased with increasing speed. In the macaque tibia, the bending axis (the axis around which the bone is bent) during galloping moved to within 19° of the M-L axis, and to within about 13° of the neutral axis of the section (the axis about which bending rigidity is greatest) (Fig. 3A). That is, the greatest strains during galloping were experienced in almost the same direction as that of maximum bending rigidity. In the greyhound femur, the bending axis similarly rotated to a more M-L orientation (22° from the M-L axis) as speed increased from 0.61 to 2.44 m/sec, the former a slow walk and the latter a trot (Rubin and Lanyon, 1982) (Fig. 3B). While the neutral axes of sections were not calculated in this study, Szivek et al. (1992, p. 105–106) noted that during running, "the peak strain regions shifted to the anterior and posterior aspects of the bone... The shape of the cross section of the greyhound femur at the mid-diaphysis (i.e., oblong) may be a result of this strain distribution while the dog performs." Carter et al. (1981; see their Fig. 6) obtained very similar results for a mixed-breed dog moving at a speed between the two higher speeds shown in Figure 3B.

It should also be noted that in both of the studies depicted in Figure 3, the magnitude of maximum strain increased substantially in moving from a walk to a trot or gallop, as would be expected (Rubin and Lanyon, 1982). Because the stimulus for bone functional adaptation is dependent on strain rate, which in turn is dependent on strain magnitude and frequency (Turner, 1998), it is likely that more dynamic activities are far more osteogenic than slow walking (although small strains may also be osteogenic; see Fritton et al., 2000). As observed by Rubin and Lanyon (1982, p. 206) in their now-classic review of in vivo strain gauge results, "The association which naturally exists between high peak strains and high strain rates will therefore result in bone architecture being preferentially influenced by the strains encountered during periods of vigorous, rather than more sedentary, activity" (see also Mikic and Carter, 1995). This is closely related to the "cellular accommodation" theory of Turner (1999), whereby bone cells are only stimulated by more "unusual" loadings. It can be presumed that galloping or trotting in the macaques and dogs included in Demes et al. (2001) and Szivek et al. (1992) was a relatively unusual, although certainly not unknown, activity compared to walking. The fact that the cross-sectional shape of both bones better corresponded with strains engendered during running may be a product of the higher strains produced by this more unusual, but still "characteristic" loading. This suggests that bone structure is correlated with activity, and primarily vigorous activity.

In the other study by Demes et al. (1998; see also Demes et al., 2001), maximum strains in the macaque ulnar midshaft were always located closer to the medial and lateral cortices, regardless of speed of locomotion (although the location of peak strain moved slightly toward the anterior and posterior cortices during galloping), while the bones were slightly stronger in the A-P direction. This would seem contrary to the scenario presented above. However, unlike the tibia, the macaque ulna is part of a more "multifunctional" (Schaffler et al., 1985) forelimb complex that serves in a greater variety of roles, both locomotor and nonlocomotor, than do the hindlimb bones. Even during locomotion, the macaque forelimb experiences significant changes in applied loadings, depending on substrate (Schmitt, 2003). Significant load-sharing with the radius, which is actually stronger than the ulna in cercopithecoids (Ruff, 2002), further complicates interpretations. In many ways, then, the loading environment of the macaque tibia is probably simpler and more predictable than that of the ulna, with more stereotypical positioning of the limb, muscle recruitment, and resultant strain patterns (e.g., peak strains in the macaque ulna actually declined from walk-

[2]Comparisons of absolute cross-sectional size or diameter in the exercised and nonexercised animals in this study were partially confounded by differences in body mass gain between them; however, this should not have affected relative cross-sectional shape. A similar difference in cross-sectional shape of the cannon bone of sheep was described by Hammond and Appleton (1932, p. 241), with "semi-wild" breeds (who would be expected to subject their limbs to more vigorous A-P bending loads) having rounder cross sections than more sedentary domesticated varieties, who had less A-P expanded cross sections.

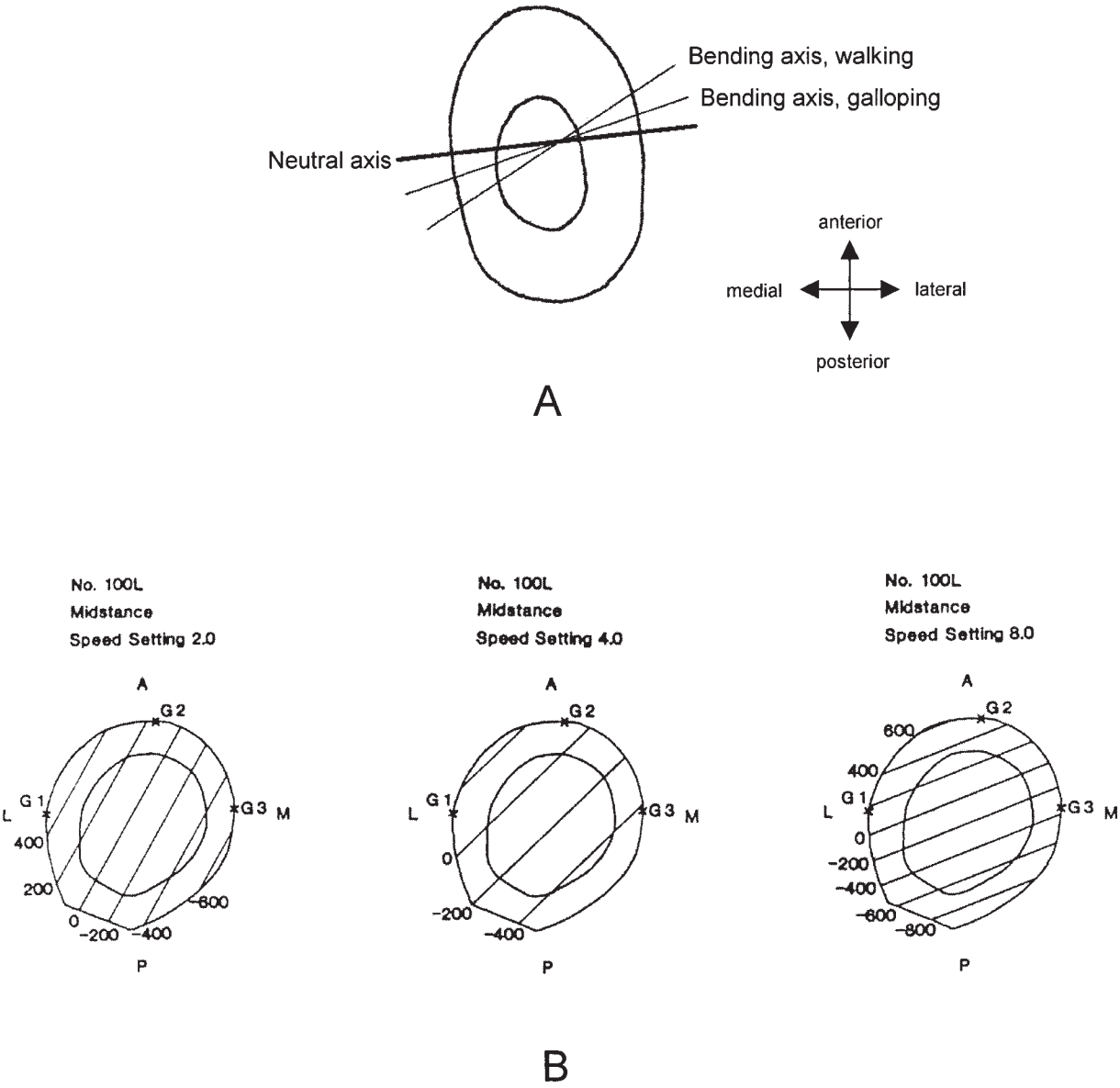

Fig. 3. Effects of increasing speed on strain distributions in macaque tibia (**A**) and greyhound femur (**B**) (not to scale). A is adapted from Figure 3a and Table 2 in Demes et al. (2001). B is reprinted from Figure 4 in Szivek et al. (1992). Speed settings 2.0, 4.0, and 8.0 in B are equivalent to 0.61, 1.22, and 2.44 m/sec, respectively. Isostrain lines shown in B: 0 = axis of bending, negative = compression, positive = tension. 100L: subject matter; A, P, M, L: anterior, posterior, medial, lateral; G1, G2, G3: locations of strain gauges (Fig. 3B © 1992 from Szivek et al. (1992), reproduced by permission of authors and Taylor and Francis Group, L.L.C.).

ing to galloping (Demes et al., 1998), which has not been reported in studies of other bones/species). In terms of behavioral reconstructions, interpretations of forelimb bone cross-sectional shape will be similarly complex, although overall forelimb relative to hindlimb strength proportions are still informative regarding general locomotor behavior (Stock and Pfeiffer, 2001; Ruff, 2002).

We should also remember that, in adults at least, strain gauges measure deformations in bones that have *already* adapted to mechanical loading. As noted above, if the most osteogenic strains are those that occur under vigorous loadings such as running, the bone will adapt by altering its geometry accordingly, following the general model in Figure 1. The strains developed during less vigorous (but more common) loadings such as walking would thus be, in effect, "residual" strains that are insufficient to stimulate modeling/remodeling (Turner, 1999). This could lead to misinterpretations of strain gauge data in terms of in vivo loadings. For example, if large A-P bending loads of certain limb bones occur during running that create large strains on the anterior and posterior surfaces, which in turn stimulate bone deposition on those surfaces, then during walking (where A-P bending loads are probably much smaller), anterior and posterior surface strains will be small, and medial and lateral surface strains relatively larger. This does not, however, indicate that bending loads (even in walking) are typically larger in the mediolateral direction. Thus, one must be careful in extrapolating from *strains* to *loads*.

The strain gauge study in sheep by Lieberman et al. (2004) addressed two other issues relevant to interpretations of long bone cross-sectional geometry: does the axis of bending of a long bone pass through the section centroid, and does this axis remain in a similar position throughout locomotion (stance)? Both questions were answered in the negative. The first result is similar to that obtained by other researchers or implied by their results (e.g., Carter et al., 1981; Rubin and Lanyon, 1982; Szivek et al., 1992). Because of the superimposition of axial compressive on bending loads in most long bones, overall compressive strains are higher than tensile strains; the axis of bending (0 strain) correspondingly shifts toward the tensile side, thereby no longer passing through the section centroid (Fig. 3B; see also Fig. 2 in Lieberman et al., 2004). This is significant because geometric section properties that reflect bending rigidity and strength (second moments of area and section moduli) are typically calculated around axes that pass through the section centroid (e.g., Ruff and Hayes, 1983; Sumner et al., 1985). Thus, rigidity or strength estimates based on such properties will be in error, by as much as 30–50% (Lieberman et al., 2004). It should be noted, first, that these results do not affect past interpretations of the *pure bending* rigidity/strength of long bones; second moments of area and section moduli, as traditionally calculated, are still valid representations of such properties. What is strictly invalid is the implied assumption that in vivo loadings are, in fact, pure bending loads. In studies that can be used to directly assess this assumption in vivo, the degree of deviation of bending axes from section centroids can be quite variable, even at the same skeletal location and within the same species: between different phases of the stance cycle, different animals, right and left limbs of the same animal, and even in repeated trials of the same limb of the same animal (e.g., Figs. 2 and 5 in Szivek et al., 1992). The bending axis may shift from one side of the section centroid to the other, depending on these factors (Szivek et al., 1992; Demes et al., 2001). In other words, there is no consistent "correction" factor that can be incorporated into section property analyses to account for these variable deviations.

This is closely related to the second of the results of Lieberman et al. (2004): because of changes in ground reaction forces, limb positioning, and muscle forces during locomotion, bending axes cannot remain in exactly the same position relative to the cross section. This is clearly implied by earlier studies, such as Carter (1978), based on work originally reported by Lanyon et al. (1975), of strains in the human tibia during walking and jogging, in which longitudinal strains on one surface of the cortex shifted between tensile and compressive within one gait cycle. Because in this study, strain data were collected on only one surface (anteromedial), strain distributions cannot be determined; however, these results necessitate a major shift in the bending axis across the tibial cortex during gait. This is perhaps not surprising, given the variable position of the human tibia relative to the body's center of gravity and changing muscle actions during gait (Inman et al., 1981).

Thus, even with in vivo strain gauge data in hand, it is not possible to precisely define the position of the bending axis of a long bone section, because it varies constantly during use of the limb, both between and within individuals. Therefore, it is not possible to factor this into bone structural analyses, except perhaps in a general sense (Griffin and Richmond, 2005). In fact, it might be counterproductive to attempt to do so, at least quantitatively, because the particular choice of bending axis could bias results in unpredictable ways. Thus, it is probably advisable to continue to report section properties (second moments of area and section moduli) relative to centroidal axes, with the understanding that these are only approximations of true bending rigidity and strength in vivo. In this respect, it is reassuring that Lieberman et al. (2004) obtained correlations of about 0.9 or better between section properties measured to centroidal axes and those measured to an average bending axis determined experimentally. Also, since the main interest of many anthropological and paleontological studies is the *relative* importance of different types of mechanical loadings, deviation of *absolute* estimated rigidities or strengths from actual values (even if such values were constant and could be determined) is of less concern, provided that the basic mechanical model is similar between the individuals being compared (see above).

Finally, as recognized by the investigators themselves, strains measured in laboratory animals moving on a treadmill at constant (and usually fairly low) speeds and in a straight line are not representative of the full range of variability present during normal activities (Lieberman et al., 2004), and only occasionally measure strains at the more important (see above) higher gait velocities. As noted by Dickinson et al. (2000, p. 105) in a wide-ranging review of animal locomotion, "In nature, unlike in the laboratory, straight-line, steady-speed locomotion is the exception rather than the rule." Variable directionality of movement may explain, for example, why bones subjected primarily to A-P bending in typical treadmill exercises are still reinforced mediolaterally (Fig. 3, and see above). Mikic and Carter (1995, p. 465) were more explicit:

> "One difficulty that is encountered when using bone strain data in studies of functional adaptation is that reported data are often far from a complete record of strain over an experimental period. On the contrary, the reported results generally consist of a few average cyclic strain parameters that are extracted from a short period of recordings while an animal performs a very restricted task. Most investigators agree, however, that a much more complete record of strain history is required to relate bone biology and morphology to strain. Such records should include the many diverse activities of the animal, including cage activity."

This is admittedly a very difficult task, and may not be totally achievable, even for animals in a controlled laboratory environment (but see Fritton et al., 2000, for example). Thus, researchers have turned to theoretical modeling approaches (extrapolated from available in vivo data) in an attempt to determine the influence of overall loading history on bone morphology (e.g., Carter, 1987; Beaupre et al., 1990; van der Meulen et al., 1993; Mikic and Carter, 1995). However, these observations emphasize some of the problems inherent in using data of this kind.

This is not to say that in vivo strain gauge studies cannot provide very valuable information: strain studies in animals have been critical in investigating general bone adaptive mechanisms (e.g., Fig. 2), and the few in vivo studies of strain in human (Lanyon et al., 1975;

Burr et al., 1996; Aamodt et al., 1997; Carter, 1978) and nonhuman primate (Swartz et al., 1989; Demes et al., 1998, 2001) long bones helped clarify mechanical loadings of these skeletal elements. Any morphological studies should carefully consider such evidence and its implications for reconstructing behavior. However, we also need to carefully consider the limitations of such data when applied to "real life" situations, i.e., the total loading history of a bone.

GENETIC DETERMINATION OF BONE MORPHOLOGY

The pace of discovery of new genetic mechanisms underlying bone growth and development has increased dramatically over the past several decades (for recent reviews in the anthropological literature, see Chiu and Hamrick, 2002; Lovejoy et al., 2003; Pearson and Lieberman, 2004). Building on these discoveries, Lovejoy et al. (2002, 2003) argued forcefully for the importance of genetic mechanisms in the determination of bone morphology, and conversely, the relative insignificance of "mechanoanabolism," or the functional adaptation of bone to perceived mechanical stimuli during life. These arguments tend to dichotomize genetic and environmental effects: "The most relevant issue for anthropologists is the degree to which adult bone structure is indicative of genetic background versus its history of load transduction" (Lovejoy et al., 2003, p. 101), with genetic influences argued to be paramount: "External bone morphology now appears to be largely dictated by an integrated system of sequentially expressed gene arrays" (Lovejoy et al., 2002, p. 99). While we fully agree that a better understanding of bone developmental genetics is important for explaining the evolution of skeletal morphological variation (e.g., Shubin et al., 1997; Hallgrimsson et al., 2002; Hamrick, 2003), we believe that this rather polarized view is counterproductive: because genetic mechanisms are important does not mean that direct environmental stimuli are not; in fact, in certain respects, the two may be inseparable (Martin et al., 1998, p. 270–271; also see below). As shown above, it is obvious that mechanical loading during life can have a strong effect on variation in bone morphology. Minimizing the importance of mechanical effects artificially restricts the scope of inquiry, and hinders attempts to provide a complete explanation for this variation.

Another factor that must be carefully considered in this context is variability between different types of skeletal features in the extent to which they are environmentally modifiable during life. For example, long bone articular size appears to be less affected by changes in mechanical loading than cross-sectional diaphyseal size (Ruff et al., 1991; Lieberman et al., 2001). The great majority of developmental genetic studies of the skeleton examined variation in gross morphological features (e.g., patterns of limb element organization); bone "size" features such as mass, volume, and length; or bone "density" (usually not true tissue density). Heritability estimates for bone mineral content (BMC) and bone mineral density (BMD), the most commonly measured bone parameters, average about 60–70% in humans, but if covariation with body mass is accounted for, this falls to about 50% (for an excellent review, see Prentice, 2001). However, such skeletal traits do not provide estimates of mechanically relevant parameters (Sievanen et al., 1996; van der Meulen et al., 2001). Volkman et al. (2003, 2004) carried out a more relevant study in which they assessed genetic effects on cross-sectional geometric and other mechanical properties of the mouse femur, using quantitative trait loci (QTL) analysis. They found evidence for complex genetic control of these characteristics, but at a low level: genetic markers accounted for only 3–22% of trait variances. They discussed several possible pathways through which genes may influence bone structure: 1) a direct influence on bone size and shape (i.e., directed activity of osteoblasts and osteoclasts); 2) an indirect effect on factors such as body weight, muscle strength, and activity level, which in turn alter mechanical load and thus bone structure; and 3) an effect on responsiveness of bone to applied mechanical loading (i.e., "set points" in a "mechanostat"-like mechanism; see Frost, 1987; Martin et al., 1998, p. 270–271). The interaction between genetic and environmental effects is prominent in the second two of these proposed mechanisms. Other investigators, in fact, demonstrated varying mechanosensitivity in different mouse strains (Kodama et al., 2000; Robling and Turner, 2002).

Many other recent studies found evidence for some heritability of various bone structural traits, sometimes sex-linked (e.g., Peacock et al., 2005, and references therein). It is important to note that these studies do not provide estimates of actual genetic determination of traits, however (Prentice, 2001), and that as noted above, final adult morphology is likely to be a complex product of genetic-environmental interactions. A good example of this is the interaction between the gene(s) encoding for the estrogen receptor α (ER-α) and physical exercise: both the receptor and increased mechanical loading are necessary to increase bone mass (Lee et al., 2003; Suuriniemi et al., 2004). As Lanyon and Skerry (2001, p. 1938) pointed out, "although systemic influences may modify mechanically adaptive processes, they cannot substitute for them," i.e., regardless of genetic background, appropriate mechanical loading is necessary to develop normal adult form. This was demonstrated in experiments early in the last century in which bones isolated from mechanical loading during growth still developed the general features of their normal counterparts, but not the specific morphological details (Murray, 1936). The major evolutionary features of skeletal morphology (e.g., what makes a horse skeleton different from a human skeleton) may be principally genetic, but what makes one horse (or one human) skeleton different from another is likely to be a product of both genetics and environment, with different skeletal features more or less environmentally modifiable. Thus, understanding both genetic and environmental influences is critical to understanding morphological variation.

AGE-DEPENDENCE OF BONE FUNCTIONAL ADAPTATION

Another issue discussed by Bertram and Swartz (1991) was the apparent age-specificity of bone response to changes in mechanical loading, particularly a reduction in mechanical loading (e.g., Jaworski et al., 1980b), which might argue against a universally applicable "Wolff's law." Bertram and Swartz (1991, p. 267) also noted a distinction between modification of growth patterns and functional adaptation in the "mature" skeleton: "It appears to us that many of the adjustments of bone form associated with mechanical loads result from the interaction of load with the developmental/growth

process, which in bone normally persists into young adulthood (mid-20's or later in human studies)." It is important to recognize that the "growth" period, as they defined it here, includes early adulthood, extending beyond adolescence as usually defined. This would correspond to the "positive" period of skeletal growth where bone mass is normally increasing, even though growth in bone length has largely ceased (Riggs and Melton, 1992).

Forwood and Burr (1993) reviewed earlier animal and human exercise studies across different age groups. They concluded that while the main function of mechanical loading in the adult skeleton was to conserve or maintain existing bone, "exercise can, in fact, add small amounts to bone mass of the adult skeleton," on the order of a few percent, although this adaptation "is modest when compared with that in growing bone" (Forwood and Burr, 1993, p. 100). They also noted that very intensive exercise can stunt growth in growing bones. Pearson and Lieberman (2004) reviewed the evidence for a reduction in osteogenic potential on a cellular level with aging. It should be noted, however, that the most drastic reductions occur in aged or senescent adult cells, so this factor may not be as applicable to comparisons between juveniles and young adults.

With respect to anthropological reconstructions of past behavior, the key question raised by these studies is: to what extent is the morphology of adult bones indicative of the mechanical loading of these bones during adulthood? This question can be subdivided into two related questions: first, can mechanical loading significantly change bone morphology after the childhood and adolescent years, and second, regardless of the answer to the first question, is adult bone morphology still informative with regard to adult loadings?

The first question can be answered in the affirmative, although it is also apparent that the bone response to mechanical stimuli is more marked in juveniles than in adults (Forwood and Burr, 1993; Turner et al., 2003). Part of the problem with evaluating bone sensitivity to mechanical loading in adults is that the response is probably slower than in juveniles; thus, long-term longitudinal studies may be necessary to clearly document effects. Many prospective exercise studies of human adults also have problems in study design, including nonrandomization of subjects, poor compliance, small samples, failure to control for other confounding effects, and failure to measure effects at the actual site of skeletal loading (Kerr et al., 1996), all of which may contribute to inconsistency of results across studies (Pearson and Lieberman, 2004). One of the best-controlled studies in older adults was by Kerr et al. (1996), who examined the effects of weight-training on BMD at several skeletal sites in postmenopausal women (mean age, 58 years at start of program) over a period of 1 year. The weight-training, three times per week, was carried out on either the right or left upper and lower limbs, with the opposite limb serving as an internal control, thus inherently accounting for systemic variables such as genetic influences, diet, hormonal status, and body weight. Their results for the distal radius are shown in Figure 4. As with many such studies in adults, the effects were relatively small (an average gain of 2.4% on the exercised side, compared to a loss of 1.4% on the control side), but significant. Statistically significant positive effects of exercise were also seen in the hip region. Interestingly, exercises aimed at increasing strength (higher weights, lower number of repetitions) had a more positive effect than those aimed at increasing endurance (lower weights, more repetitions). This suggested that the magnitude of loading (or rate of change in magnitude of loading) was more important than the number of loading cycles, which agrees with some animal experimental results (see references above).

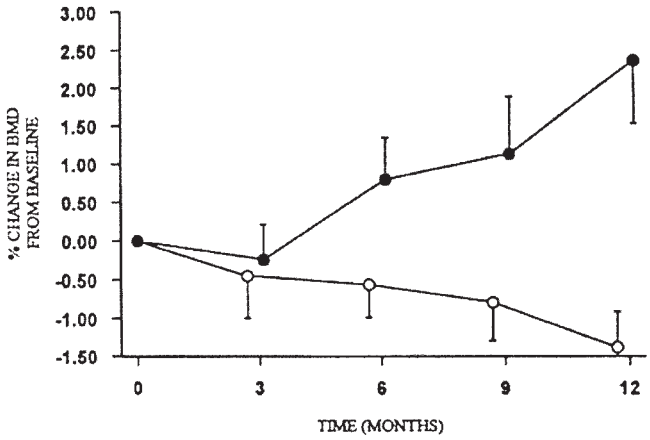

Fig. 4. Percent change in bone mineral density of distal radius over 1 year in bilaterally paired exercised (solid circles) and nonexercised (open circles) limbs in 28 postmenopausal women (mean ± SE) (Kerr et al., 1996; reproduced by permission of authors and American Society for Bone and Mineral Research).

Another observation apparent in Figure 4 is that a shorter-term study of a few months would not have picked up the significant effect of the exercise treatment. This factor should be kept in mind when evaluating results of shorter-term exercise studies in humans, or in other large, relatively long-lived mammals. Because of variable exigencies such as subject compliance and retention (in human studies) and caretaking expenses (in animal studies), these investigations are commonly carried out over short periods relative to total lifespan. This also has more general implications regarding interpretations of mechanical loading effects in adults: response to loading may be slower than in juveniles, but the total adult period available for functional adaptation is longer; thus, *cumulative* effects (positive or negative) may be larger than would be predicted by short-term studies.

This point was emphasized in a recent long-term longitudinal study of young adult female soccer players (Valdimarsson et al., 2005). The subjects averaged 18 years of age at the beginning of the study and were followed for 8 years, a long time period compared to most prospective studies. Bone mineral content and density of the whole body and BMD at various anatomical locations were evaluated using dual X-ray absorptiometry (DXA) at baseline and at follow-up. A control group of nonathletes of similar age was also followed over the same time period. In players who remained active throughout the period, BMC and BMD increased, and differences from controls increased (from 4% greater at baseline to 9–12% greater at the end in the total body, and from 7% at baseline to 14% greater in the leg; our calculations). Players who had retired from play during the follow-up period began with higher values than controls, but then showed no further increase over controls. Valdimarsson et al. (2005, p. 910) noted that while "exercise in adulthood has been described as at best conferring BMD benefits of a few percentage points ... this notion is only

supported by short-term prospective controlled studies spanning, at best, 24 months." The age period evaluated in this study can appropriately be termed "postadolescent" (there was no change in height among the active players), but it does fall within the early adult "developmental/growth" period as defined by Bertram and Swartz (1991) (see above).

The bilateral asymmetry model used by Kerr et al. (1996) was also exploited in a series of studies of the playing and nonplaying upper limbs of athletes in racket sports. In one such study (Kannus et al., 1995), the age-dependence of exercise effects was specifically addressed by comparing bilateral asymmetry in upper limb BMC of adult "national-level" female tennis and squash players who had started playing at ages varying from young childhood to young adulthood. All individuals had played for at least 5 years, and the number of years of training was not a significant covariate. A progressively greater effect on bilateral asymmetry was seen in individuals who had started playing earlier: in the humeral shaft, the earlier starters averaged 20–24% asymmetry, while the older starters averaged 8–10% asymmetry. This result has been repeatedly cited as providing evidence for the age-specificity of mechanical loading on bone (Fig. 6 in Turner and Robling, 2003; Fig. 12 in Pearson and Lieberman, 2004; but note misattribution of data to another study), and it does appear to demonstrate a declining response after early adolescence. However, it is also noteworthy that even the oldest starters in this study, averaging 34 years of age when they began playing, still had about three times greater bilateral asymmetry than the controls included in the study. Thus, even in this age range, increased mechanical loading appears to significantly increase bone mass. Because the study was cross-sectional in design, it is not possible to say for sure how much bone was actually gained during the playing period. However, from an anthropological perspective, the greater asymmetry in the older-starting players would be correctly interpreted as reflecting greater asymmetric use of the upper limbs during adulthood.

As noted earlier, BMC and BMD are not true mechanical characteristics, and their interpretation can be confounded by nonconcordant and nonlinear changes in subperiosteal and endosteal breadths during growth and young adulthood (Frisancho et al., 1970; Ruff et al., 1994; Petit et al., 2004). Significant changes in bone strength can occur with relatively small changes in BMC or BMD (Robling et al., 2002; Warden et al., 2005). A number of studies incorporated more mechanically relevant properties into evaluations of exercise effects in human subjects, using the upper limb bilateral asymmetry model. Ruff et al. (1994) and Trinkaus et al. (1994) reanalyzed radiographic data originally collected by Jones et al. (1977) for male and female professional tennis players (mean age, 25 years; mean starting age, 10 years). Median asymmetry in the polar second moment of area, J (a measure of bending/torsional rigidity), of the mid-distal humeral shaft was 57%, compared to median asymmetries near 10% in recent "normal" populations. We also found an age effect, with players who started playing earlier showing more asymmetry due to greater subperiosteal expansion. However, the individual in the sample who started playing the latest (a male who started playing at age 19 years) still showed asymmetry in J of 31%. Haapasalo et al. (2000), using peripheral quantitative computed tomography (pQCT), found mean bilateral asymmetries of 39–46% in second moments of area of the humeral midshaft in male Finnish "national top-level" tennis players (mean age, 30 years; mean starting age, 10 years). No evidence for any exercise effect on cortical bone density was found, i.e., mechanical adaptation to increased loading appeared to be all geometric (paralleling animal exercise studies, e.g., Woo et al., 1981). Kontulainen et al. (2002), also using pQCT, measured bilateral asymmetry in geometry and bone density of the upper limb bones in a subset of the same sample studied by Kannus et al. (1995). Mean asymmetry in a strength index that combined J and bone density of the humeral midshaft was about 26% in "young starters" (mean starting age, 10 years; measured at 26 years) and 11% in "old starters" (mean starting age, 26 years; measured at 44 years), compared to about 4% in nonathletic controls. Again, younger starters showed more subperiosteal expansion, and there was no evidence for an exercise effect on cortical bone density. Bass et al. (2002) reported similar results for young (8–17-year-old) female "competitive" tennis players, with greater subperiosteal expansion of the playing-side humerus prior to menarche, and greater endosteal contraction after menarche. Interestingly, no significant bilateral asymmetry in bone lengths was found (Bass, personal communication), again highlighting the variable sensitivity of different bone structural features to mechanical loading history (Trinkaus et al., 1994).

All these studies consistently indicate greater effects of increased mechanical loading on long bone cortical geometry in children and early adolescents, due to stimulation of greater subperiosteal expansion, but also a significant effect on older individuals, primarily through endosteal contraction. Thus, long bone cross-sectional geometry in adults reflects mechanical loading in both juveniles and adults, albeit in different ways (Ruff et al., 1994). These results contradict the opinion of Lovejoy et al. (2003, p. 101) that "Comparative cortical thickness data on extinct hominids are thus of very limited value, unless we regard some vague index of the level of subadult play as being important!"

There is also the important consideration of adult retention of bone structural features which themselves may be largely established during subadult growth and development. This addresses our second question posed above: regardless of how much new bone can be added in adults due to increased mechanical loading, is bone structure in adults still informative with respect to adult loadings? Many authors (e.g., Forwood and Burr, 1993) emphasized that the primary effect of exercise in at least older adults may be to conserve or maintain bone laid down earlier in life rather than to add new bone. But if this is the case, then different levels of exercise in adults will still affect bone morphology, by either stimulating the retention of bone laid down earlier or not. The evidence for how long the positive effects of increased mechanical loading in younger individuals are retained in older adults is mixed, but it seems likely that in the longer term at least, reduced physical activity in adults will lead to loss of some of the bone accumulated earlier in life (Valdimarsson et al., 2005) (reviewed in Pearson and Lieberman, 2004). Reduction of mechanical loading due to loss of function (e.g., through paralysis, bedrest, or weightlessness) also leads to bone loss in adults as well as juveniles (Whedon and Heaney, 1993), with the major effects again subperiosteal in juveniles and endosteal in adults (Uhthoff and Jaworski, 1978; Jaworski et al., 1980a,b).

In summary, there are age-specific differences in the way bone responds to mechanical loading, but sensitivity to mechanical loading does not end with the end of the juvenile "growth" period. Relatively slow but cumulatively significant changes in bone mass and structure occur in adults, especially younger adults, under conditions of altered loading. In addition, bone maintenance in adults is dependent on continuation of "normal" mechanical loadings established earlier in development. Therefore, differences in adult bone morphology will reflect, in part, differences in adult behavior.

It is also noteworthy, as pointed out by Pearson and Lieberman (2004), that in most "traditional" societies (and presumably most prehistoric societies), behaviors characteristic of adults are actually initiated in adolescence, if not sooner (see contributions in Hewlett and Lamb, 2005). Therefore, the effects of "adult" patterns of behavior should be recognizable even in bone laid down during the later preadult "growth" period. For example, sexual dimorphism in lower limb bone structure that may be related to sexual division of labor (Ruff, 1987) is apparent as early as late adolescence (Ruff, 2000). In fact, later adolescence and early adulthood, when bone responsiveness to mechanical loading is still high (see above), may represent the most "typical" periods to sample in terms of reconstructing behavioral differences between populations, for example, due to subsistence strategy, mobility, gender roles, and/or technology.

MECHANICAL "IDEALS"

Finally, there is the issue of whether all observed bone modeling/remodeling in response to mechanical loading is mechanically "ideal," or most mechanically efficient, and what this signifies with respect to "Wolff's law" or bone functional adaptation. This point, like so many of the issues discussed here, was first raised by Bertram and Swartz (1991) in relation to the observed endosteal, rather than periosteal, apposition of bone in the well-known pig exercise study carried out by Woo et al. (1981). As Bertram and Swartz (1991, p. 261) pointed out, "Although thicker cortices do indeed increase the structural strength and bending stiffness of the exercised bone [bending rigidity increased 21–27% in the exercised versus control animals in Woo et al., 1981], endosteal thickening is not an efficient means for improving bone strength. A much smaller volume added to the periosteal surface would provide the same mechanical effect." This same theme was taken up by Lovejoy et al. (2003) and Ohman and Lovejoy (2003), who applied it to the tennis-player asymmetry results of Jones et al. (1977), where both periosteal expansion and endosteal contraction of the playing-arm humeri were observed: "This does not conform to the Wolffian prediction of increased strength with economy of bone" (Ohman and Lovejoy, 2003, p. 161). Both of these observations are, in fact, in accord with the age-dependent model of bone mechanical adaptation presented above, whereby the subperiosteal surface is more responsive prior to midadolescence, and the endosteal surface thereafter (Ruff et al., 1994; Bass et al., 2002).[3] (The pigs in the study by Woo et al. (1981) were immature at the start of the study, when they were 1 year of age, but were skeletally mature at the end of the study, when they were 2; thus, they are probably best considered as analogous to human adolescents.) The reasons for this apparent age-dependent change in bone envelope sensitivity are complex and not completely understood, although they probably involve systemic hormonal influences, which in turn may be in part related to other nonmechanical functions of the skeleton, e.g., as a calcium reservoir (Jarvinen et al., 2003; Saxon and Turner, 2005).

This highlights another very important point: *the function of the skeleton is not purely mechanical, and therefore its mass and morphology represent a compromise between different physiological demands, of which mechanical competence is only one*. Other competing physiological influences on bone include diet, hormonal status, reproduction, marrow storage, and bone mineral absorption in the gut (for a good review, see Turner, 2001). Systemic influences probably largely act to change bone modeling/remodeling thresholds, and may alter the effectiveness of bone adaptive responses to mechanical loading (Lanyon and Skerry, 2001). (In a way, this is turning the argument of Lovejoy et al. (2002)—that mechanical loading provides a threshold above which genetic influences determine bone morphology—on its head.) As emphasized throughout this paper, understanding the interactions between these various systems is critical for interpreting bone morphology. The interaction between the gene(s) encoding for the estrogen receptor α (ER-α) (and possibly ER-β; Saxon and Turner, 2005) and exercise was one such example discussed earlier. Another is the possible interaction between dietary calcium intake and exercise on bone mass and geometry (Specker, 1996; Specker and Binkley, 2003).

This also hearkens back to the original distinction made here between the "strict" and more general versions of "Wolff's law:" to interpret the "law" as requiring perfect compliance with only mechanical requirements, or any particular mechanical requirement, is unrealistic. As noted by Murray (1936, p. 179) many years ago, "Every bony structure is a compromise and no compromise is perfect." Even Bertram and Swartz (1991, p. 261) conceded, "There is, of course, no reason to expect that the bone is obliged to solve all mechanical problems in the most efficient manner." After all, as pointed out by many researchers, if bone mechanical adaptation were perfect, there would not be the huge increase in age-related fractures (i.e., osteoporosis) characteristic of so many Western societies. Considering the influence of other competing factors does not diminish the importance of mechanical loading on bone morphology, though. For example, during aging, mechanically mediated subperiosteal apposition of bone appears to minimize reductions in bone strength, despite loss of bone mass due to systemic (hormonal, dietary, and genetic) factors (Ahlborg et al., 2003). Expecting mechanical "perfection" is indeed "Wolffian" in the strict sense, but given our current understanding of bone physiology, this concept is anachronistic.

CONCLUSIONS

Many experimental and observational studies have demonstrated that bone adapts to changes in its mechanical environment. Methodological objections raised to earlier studies of this kind have been addressed by more recent investigations using noninvasive experi-

[3]However, as shown in Robling et al. (2002) and other experimental studies (e.g., Lanyon et al., 1982), subperiosteal apposition of bone under conditions of increased mechanical loading can occur in adults.

mental techniques and better-controlled human studies. Bone response to mechanical loading is reduced, but not eliminated, in adults relative to juveniles. Given the apparent differences in levels and types of response at different ages, age effects should be taken into consideration in comparisons. The in vivo strain environment that drives bone functional adaptation is complex and variable. Given this variability, and the fact that we do not (and probably will not) have direct strain data available for a broad, representative array of activities, species, and skeletal locations, it is advisable to continue to use "idealized" geometric section properties in functional analyses, with the understanding that correspondence of these with actual strain distributions will only be approximate. Because there are likely genetic controls over both basic bone form and bone response to mechanical loading, it is also advisable to limit comparisons of bone shape to similar skeletal locations in closely related species. Interactions between mechanical and other physiological factors, such as diet and hormonal status, should be considered in any interpretations of bone structure.

Finally, to avoid confusion regarding the original, strict version of this concept and more modern formulations, "Wolff's law" should probably be replaced by the more general term *bone functional adaptation*.

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