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Editorial

Perspectives: Some Roles of Mechanical Usage, Muscle Strength, and the Mechanostat in Skeletal Physiology, Disease, and Research

H. M. Frost,[1] J. L. Ferretti,[2] W. S. S. Jee[3]

[1]Department of Orthopaedic Surgery, Southern Colorado Clinic, 41 Montebello, Pueblo, Colorado 81001, USA
[2]Instituto de Investigaciones Metabolicas, Libertad 836, ler piso, 1012 Buenos Aires, Argentian
[3]Radiobiology Division, Building 586, University of Utah, Salt Lake City, Utah 84112, USA

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Though it is generally known that mechanical factors affect postnatal skeletal physiology, this article concerns the provocative proposal that they dominate most (not all) nonmechanical influences, and the latter could only augment or diminish the mechanical ones. Support for this idea is still short of proof, but enough exists to explain it so others can evaluate it. Since Samuel Johnson had a point (''The only way to teach something new is by example of something known. . .''), an analogy could help to explain the proposal.

An Analogy

A driver (1) uses a car's primary controls (2) to drive it (accelerator pedal, steering wheel, brake pedal, gear shift, ignition switch, etc). They determine what the engine, brakes, steering, and other major assemblies (3) do. Each assembly depends on smaller parts, supplies, and connections (wires, hoses, oil, gasoline, pumps, radiator water, nuts and bolts, bearings, etc) or ancillaries (4) all of which control the car's wheels (5). Only the driver decides when and where the car goes, although without wheels the car goes nowhere. If something malfunctions, the interdependence of all these things can let the driver and/or the car's primary controls compensate for it to keep driving (See Note 1, Appendix). Ignoring feedback, that ''message traffic'' would look like this:

$$1 \rightarrow 2 \rightarrow (3 + 4) \rightarrow 5$$

A skeleton mainly serves mechanical needs [1]. When challenged, it can usually adapt to keep serving those needs. If it fails to adapt, a disease can result. In this analogy, to do that the skeleton's mechanical usage (MU) (1) would use the mechanostat (2) [2] to create and control mediator mechanisms (3) (modeling drifts, remodeling BMUs, and other maintenance activities in bone and their analogs in fibrous tissue and cartilage) that also need ancillaries (4) to work (blood supply, oxygen, hormones, nutrients, cytokines, precursor cells, minerals, genes, etc). The mediator mechanisms would then create and control their own effector cells (5). Here, too, all these things would be interdependent. Still ignoring feedback, control of the directions and goals of skeletal physiology by the message traffic would look like this:

$$1 \rightarrow 2 \rightarrow (3 + 4) \rightarrow 5$$

Or, a driver is to controls are to major assemblies are to wheels in cars, as mechanical usage is to mechanostat is to mediator mechanisms are to effector cells in skeletons. If the analogy's proposal is valid its predictions should be true and others that deny its validity should be false. Some predictions follow. Below, ''the proposal'' refers to the one stated at the beginning of this article.

Some Predictions

The Muscle Strength-Bone Strength Relationship

Except for injuries, the largest forces on skeletons come from muscles which contract against the resistance of body weight multiplied by bad lever arms [1]. The proposal suggests that those forces should dominate most nonmechanical influences on bone strength and mass.

Prediction #1. Increased muscle strength should cause increased bone strength (and mass). That old idea [3] was tested recently in three parts: (1) Better noninvasive bone strength indices (BSIs) were devised and verified. (2) With the aid of these indices muscle strength was compared with the strength of bones loaded by those muscles. (3) Then it became possible to compare results of (1) and (2) with comparisons of nonmechanical influences with other BSIs.

Why the need for better BSIs? The fractures of most concern in osteoporoses are of the wrists and hips, due to falls by aging adults with impaired balance. Combined compression, bending, and torque loads cause most such fractures. A bone's shape and size as well as its mass affect its resistance to such loads. Engineering figures of merit, called the rectangular and polar moments of inertia, evaluate the architectural effect on strength in bending and torque, respectively [4]. Since bone mineral density (BMD) and content (BMC) determinations do not account for them very well [5–8], better BSIs could be useful, given that in femurs and tibias of numerous mice and rats, peripheral quantitative computed tomography (pQCT) determined a noninvasive

Correspondence to: H. M. Frost

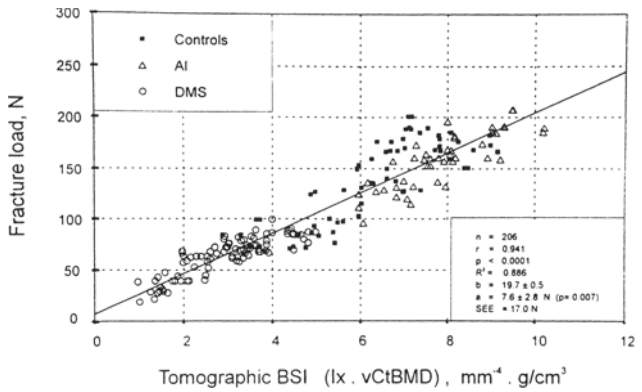

Fig. 1. The graph plots the measured breaking strength of 206 femurs from 103 rats on the vertical axis. The horizontal axis plots the pQCT-derived bone strength index (BSI_f) for the midshaft of the bones (see Note 2). The graph combines data from eight groups of animals. The first four groups include controls and animals given three different doses of oral aluminum for several months. The second four groups include controls and animals given three different doses of dexamethasone for several months. For all groups and animals combined, r = 0.94, ($P < 0.0001$), so this BSI_f provides a good index of a bone's strength (reproduced by permission: Ferretti JL (1995)

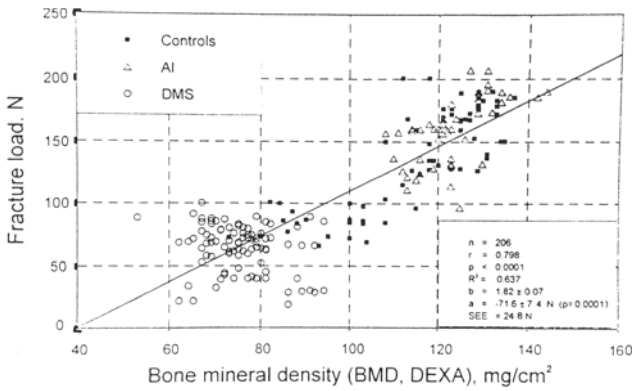

Fig. 2. For the same animals and femurs as in Figure 1, the graph also plots the measured breaking strength on the vertical axis, but against the bone mineral density (BMD) on the horizontal axis. By the BMD criterion, the first four groups of animals separate somewhat from the second four groups. Data for the aluminum-treated animals and their control group, above and to the right, and the dexamethasone-treated animals and their controls group, below and on the left. For all groups, r ≈ 0.7, ($P < 0.0001$). BMD alone did not associate with bone strength as strongly as the BSI_f (reproduced by permission: Ferretti JL (1995)

BSI_f that accounts for a bone's strength in bending and uniaxial loading [9–13] (See Note 2, Appendix). In a mixed group of 206 rat femurs, for example, comparison of that BSI_f with their measured breaking strengths in bending had a correlation coefficient of r ≈ 0.94 ($P < 0.0001$), so the BSI_f associated strongly with that strength (Fig. 1). In the same animals and bones, comparing BMD alone with the breaking strength had a correlation coefficient of r < 0.8 ($P < 0.0001$) (Fig. 2), so that BMD associated less well with bone strength.

In 40 men and women (See Note 3, Appendix) the measured strength of the elbow flexor muscles was compared with a pQCT-derived BSI for the radius and ulna of the same extremity [14]. That BSI_s accounts for bone strength in combined torque and uniaxial loading. The comparison's correlation coefficient, r ≈ 0.93, suggests that increased muscle strength associates strongly with increased bone strength (Fig. 3). In the same people, muscle strength compared with absorptiometrically estimated trabecular bone density (TBD) in the distal radius had a smaller correlation coefficient, i.e., r < 0.7 (Fig. 4). In this study, measured muscle strength did not associate as well with TBD as it did with the BSI_s.

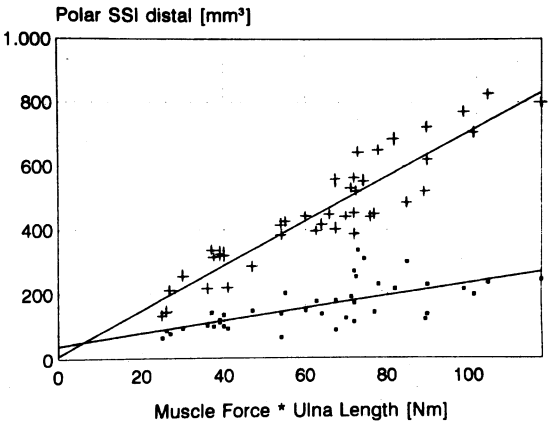

Fig. 3. For 40 men and women, on the vertical axis this graph plots Schiessl's BSI_s as measured in the distal radius (upper line) and ulna (lower line) by pQCT (see Note 3). The horizontal axis plots the measured strength of the elbow flexor muscles of the same extremity, expressed in Newton-meters (the lifting force exerted at the wrist in Newtons, multiplied by the distance from the wrist to the center of rotation of the elbow in meters). Since r = 0.93, muscle strength associated well with bone strength (reproduced by permission: Schiessl H, Ferretti JL, Tysarczyk-Niemeyer G, Willnecker J (1996) In: Schönav (ed) Paediatric osteology. New developments in diagnostics and therapy. Elsevier, Amsterdam, pp 141–146).

Prediction #2. The proposal suggests that muscle strength influences bone strength more than most nonmechanical factors influence it. Many studies compared nonmechanical factors with bone mass and mineral content, often determined by dual X-ray absorptiometry (Dexa), the mass serving as an indicator of bone strength. The factors included, in part, age, body height and weight, sex, dietary calcium, vitamin D and its metabolites, caloric intake, menopausal status, and race. The correlation coefficients, r ≈ 0.3–0.7, often combined with good statistical confidence, $P \ll 0.05$, show that these factors do associate with bone strength positively, but more weakly than muscle strength, mentioned above (See Note 4, Appendix). For example, Figure 5 shows a poor association between age and bone strength in 134 European men and women [14]. These lower correlations than those given above suggest that most nonmechanical factors associate more weakly with bone strength than with muscle strength [15]. If nonmechanical factors dominate the control of bone strength (and mass), one would predict the opposite.

Age-Related Bone Loss and Bone Mass in Women

A direct effect of aging on bone cells has been suggested as

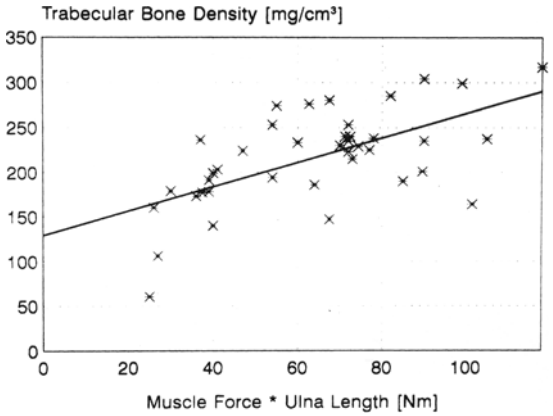

Fig. 4. For the same 40 men and women as in Figure 3, this graph again plots measured muscle strength on the horizontal axis. The vertical axis now plots the corresponding trabecular bone densities (TBD) of the distal radius, as measured absorptiometrically. Since $r < 0.7$, muscle strength did not associate as strongly with TBD as it did with the BSI_s (redrawn from: Schiessl H, Ferretti JL, Tysarczyk-Niemeyer G, Willnecker J (1996) Noninvasive bone strength index as analyzed by peripheral quantitative computed tomography (pQCT). In Schönau E (ed) Paediatric osteology. New developments in diagnostics and therapy. Elsevier, Amsterdam, pp 141–146).

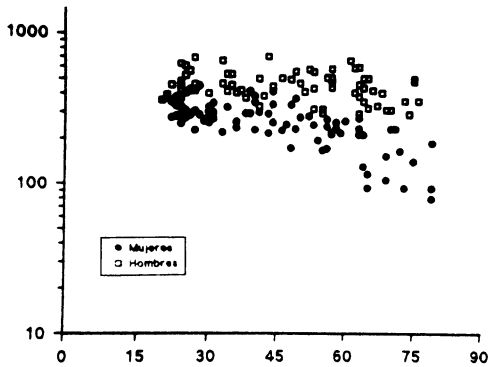

Fig. 5. For 134 European men and women this graph plots on the vertical axis Schiessl's BSI_s for the radius, against the person's age in years on the horizontal axis. Males (□), females (●). Female bone strength lies below that of the males, and begins an obvious decline around age 55–60 years. Here age and bone strength associated poorly (reproduced by permission: Ferretti JL, Capozza RF, Tysarczyk-Niemeyer G, Schiessl H, Steffens M (1995)

a cause of the gradual bone loss in aging humans and other mammals [16, 17].

Prediction #3. Since most aging adults lose considerable muscle strength [18, 19], the proposal would also require that an age-related bone loss occurs. The relative importance of the aging and muscle effects is presently unknown.

Prediction #4. The proposal suggests that women with weaker muscles than men should have less bone and weaker bones, whether or not separate effects of gender on bone cells and mass also exist. The study in Figure 5 illustrates the situation without showing the relative importance of gender and muscle effects on bone strength, which is also unknown.

Roles of the Ancillaries

Many of the things a car needs to function cannot include driving it too. As examples, more electricity in the battery, bigger engines or wheels, more gas in the tank, or more water in the radiator cannot drive it.

Prediction #5. The proposal suggests increasing the supplies of most nonmechanical agents needed for skeletal physiology to function normally should not override the effects of MU and the mechanostat. In support of this idea, no known nonmechanical factors or combinations of them ever normalized the architecture, mass, and strength of bones, joints, tendons, or ligaments in a paralyzed or otherwise amyotonic growing limb, and therefore in the absence of normal muscle forces. Yet those features develop normally in the contralateral normal limb with normal muscle function (See Note 5, Appendix). If nonmechanical factors dominate skeletal physiology, one would predict otherwise. Table 1 lists some nonmechanical factors.

The Effector Cells

Wheels do not drive a car, yet without them it cannot move.

Prediction #6. The proposal suggests cell-level disorders of effector cells, whether intrinsic or extrinsic in origin, would seldom override the mechanostat's control of tissue- and organ-level features. In support of this, so far no cell-level effect of any nonmechanical agent on osteoblasts or osteoclasts ever alone normalized an osteopenic bone mass or strength in intact ambulatory subjects, bedridden patients, or paralyzed limbs. If nonmechanical factors dominate skeletal physiology, one would predict otherwise. The bone-anabolic effects of parathyroid hormone and prostaglandin E_2 come from creating new formation drifts in bone (a #3-4 effect), not from invigorating existing osteoblasts [20–27]. Fluoride effects depend mostly on creating increased numbers of osteoblasts that can even be less vigorous individually than normal numbers (another #3-4 effect) [28, 29].

Prediction #7. The proposal suggests that effector cell responses to an agent in cell-, tissue-, or organ-culture systems should not show all the effects on intact subjects, both good and bad because the dominant mediator mechanisms and mechanostat do not exist in those culture systems [30, 31]; therefore the agent does not affect the mechanisms in those systems as it can in intact subjects. In support of that, no cell-level effect shown in such culture systems correctly predicted an agent's effects on the intact skeleton. If nonmechanical factors dominate skeletal physiology, one would predict otherwise. This argument might disturb animal rights activists who urge discontinuing live-animal research because, in their (mistaken) view, it is no longer needed.

The Mechanostat

(Note 7, Appendix) A broken steering wheel or a jammed brake or accelerator pedal can make an otherwise normal car collide with something or go off the road.

Prediction #8. The proposal suggests that a disordered mechanostat could make normal mediator mechanisms and

Table 1. Some nonmechanical factors that can influence skeletal physiology

Natural agents		
Estrogen	Androgens	Growth hormone
Calcitonin	Somatomedins	Insulin
Parathormone	Thyroxine	Vitamin D
D meteabolites	Vitamin A	Other vitamins
Dietary calcium	Magnesium	Iron, copper
Growth factors	Morphogens	Mitogens
Membrane pumps	Ligands	Membrane receptors
Apoptosis	Other cytokines	Paracrine effects
Autocrine effects	Cell-cell interactions	ACTH, FSH, TSH
Amino acids	Lipids	Prolactin
SER, RER	DNA, RNA	Genes
Cell-intercellular matrix interactions		Others
Drugs and other artificial agents		
Hormone analogs	Vitamin analogs	Bisphosphonates
External electric fields	External magnetic fields	
All other synthetic agents, or chemically modified natural ones		
Fluoride	Nonsteroidal antiinflammatory agents	
Others		

SER = ; RER = ; ACTH = adrencorticotropic hormone; FSH = follicle-stimulating hormone; TSH = thyrotropin-stimulating hormone

effector cells do abnormal things in skeletons, noting that mechanical, cell- and/or molecular-biologic factors could cause mechanostat disorders (Note 7, D, Appendix). As examples, malfunctioning mechanostats can provide plausible explanations for osteogenesis imperfecta [31], true osteoporoses as opposed to physiologic osteopenias [32], most hernias, many arthroses, myositis ossificans, heterotopic cartilage formation, and Dupuytren's contracture (Note 6, Appendix) [33, 34]. A change in the criteria that the mechanostat uses to monitor and fit bone mass to MU can plausibly explain postmenopausal bone loss, granting that "plausible" need not necessarily mean correct also [31, 35].

The Plateau Phenomenon

Prediction #9. The proposal suggests that if mediator mechanism or effector cell malfunctions begin to change some aspect of skeletal physiology or architecture, the mechanostat should begin to limit further changes and make them tend to plateau. Such plateaus are well known in skeletal physiology, disease, and in response to many pharmaceuticals.

Prediction #10. The proposal suggests that after stopping the treatments that cause the above-mentioned bone-anabolic effects, the mechanostat should cause remodeling to remove the added bone. That does happen by that means [25], aided by some feedback described elsewhere [1,2] and acknowledging that both the agent and the mechanostat might increase remodeling at first. Still, if nonmechanical factors dominate the control of bone mass, one might predict that the added bone would stay.

Growth Hormone

This separately reported test of the proposal is summarized here [36]. It is often assumed that growth hormone enables osteoblastic activity to increase bone formation and bone mass in gigantism and acromegaly [37]. If so, removing the hormone should reduce or stop bone formation throughout a bone. In growing mammalian skeletons, sudden partial disuse decreases bone modeling and the associated osteoblastic activity. Yet, simultaneously in secondary spongiosa, BMU-based remodeling and the associated osteoblastic activity continue or even increase [38–43].

In superb experiments, young hypophysectomized (HYPOX) rats were allowed to grow for 5 weeks with cortisol and thyroxine supplements [44, 45]. Compared with aging controls, dynamic histomorphometry revealed that modeling activity and the associated osteoblastic activity stopped, but remodeling and osteoblastic activity continued in the same bone at the same time (in passing, likewise for osteoclastic activity). Cell-level control of osteoblasts by a hormone or other circulating agent cannot easily explain such effects. Compared with controls, the HYPOX animals also gained little or no weight, longitudinal bone growth and muscle growth stopped, and they became less active than aging controls. Therefore their bones entered partial mechanical disuse.

Prediction #11. The proposal would require that partial disuse to cause the bone effects just summarized. If the hormone dominated MU effects, one would predict otherwise. This argument does not deny that this or other hormones can act on effector cells; many such effects are known. Instead, it suggests that MU effects on the organ would usually (not always) dominate, and if necessary would try to compensate for any direct hormonal effects on effector cells.

Primary, Secondary, Tertiary, and Combined Effects

Determinants #1–#5 represent major targets for agents (or other factors) that can affect skeletal physiology. The agents might directly change the behavior of any determinant (as

growth hormone in prediction #7 affected muscles and MU, determinant #1), which could begin to change the skeleton in some way. Then other determinants could react to that change in ways that tend to compensate for the first effect (Note 1, Appendix). This secondary effect might evoke tertiary reactions from other determinants, and further and less direct effects could ensue. To complicate matters further, the agent might act simultaneously on two or more of the system's five determinants (as growth hormone affects muscle growth, body weight, and longitudinal bone growth).

In addition, intermittent administration of parathyroid hormone and prostaglandin E_2 make new bone formation modeling drifts arise and increase bone mass [20–27]. This may stem from an effect on mediator mechanisms (prediction #3-4). Then BMU-based remodeling increases and begins removing the added bone, which one could explain as a secondary reaction of the mechanostat (prediction #2) to unneeded extra bone. As already noted, the mechanostat idea would require increased remodeling to continue even after the treatments stop until the added bone is removed, and that happens [25]. If nonmechanical factors dominate bone modeling and remodeling, one would predict that the increased remodeling should stop when the treatment did, since only the above agents supposedly increased it.

An inability of osteoclasts to resorb mineralized cartilage and bone at normal rates provides the primary cause of osteopetrosis. It stems from genetic effects on those cells or their precursors, or on prediction #5 [46]. The histology and development of affected skeletons plus clinical facts about affected patients show that the other determinants do seem to try to compensate for the effects of the disturbed one, to create a mechanically useful skeleton even if not a normal one (Note 1, Appendix). These situations also depend on some feedback, described elsewhere [1, 2].

Comments

Status of the Above Predictions

Although varied evidence supports or in some cases merely fits the predictions, we know of no evidence that would negate them (ideas, yes, but not evidence). If nonmechanical factors dominate mechanical influences on skeletal physiology, six of the above predictions should be false. Yet none is false. This does not yet verify the proposal and the paradigm it comes from, but it would seem to make them worthy of consideration.

"Targeted" Research

The above analogy suggests that many nonmechanical factors viewed formerly as causing osteoporoses by acting on effector cells (as an example) (Table 1) could instead work more in the sense of more gas in a car's tank or bigger or smaller engines or wheels, and not the car's driver. Bone physiology certainly needs both the factors and the effector cells, but neither separately nor collectively could they alone determine its direction and end points (Note 5, Appendix). The proposal suggests only the mechanostat and anything that affects it could do that (of course nonmechanical factors might affect the mechanostat too, as in Note 7). If true, this suggests some things skeletal research might do to obtain much-needed information.

To find the *in vivo* roles of nonmechanical agents (or factors) in healthy and diseased bones study how the agents help or hinder the ways that bone modeling, remodeling, architecture, mass, and strength normally respond to mechanical usage challenges in intact subjects. Acute and chronic disuse, and acute and chronic hypervigorous MU (as in weight lifting, not long distance running [31]) provide the chief challenges. That idea should also apply to collagenous tissue structures (fascia, tendon, ligament), cartilage, growth plates and joints [33]. Such studies should distinguish transient from steady state effects of agents.

Learning how to control the mechanostat (or mechanostats if bone, cartilage, and fibrous tissue each has its own version) could become an important task for targeted research in the sense suggested in the paragraph above).

Such targeted research has begun; material in the following citations suggests some ways to do it [47–52]. Much more is needed. It takes little imagination to see numerous problems and questions cited in predictions #1-#8 that targeted research could resolve. Besides bone problems, others would concern fascis, ligament and tendon, cartilage and joints [33]. This article's proposal concerns many things not usually associated with applications of Wolff's law to bone, but that seems to relate to it in an operational sense.

Conclusion

This article offers a glimpse of a new paradigm [31, 33] that supplements predecessors with equally essential tissue-level and vital-biomechanical roles in skeletal physiology and disease. Some of its insights suggest that some current ideas about skeletal physiology, pharmacology, and disease might benefit from reexamination. If that causes some controversies, resolving them in the past always improved knowledge and understanding, and few sciences make much basic progress without them ("Where everyone thinks alike, is much real thinking done?"). Ergo, discussion of the above ideas and the paradigm is welcomed. James R. Lowell once said "only fools and the dead never change their opinions." Who would not wish to postpone both those states as long as possible?

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Appendix

Note 1: A car's driver and its controls can compensate for some malfunctions, such as a wheel that pulls to one side, weak brakes, stiff steering, misfiring cylinders in the engine, bad shock absorbers, a partly deflated tire, a burned out headlight, a loose bearing, a leaking radiator, etc. In the same sense the skeleton's mechanostat might compensate for some natural or iatrogenic malfunctions of ''ancillaries,'' mediator mechanisms, and/or effector cells.

Note 2: Of the numerous animals of three species of varied ages and both sexes/studied in Buenos Aires [9–13], Figures 1 and 2 concern a subset of 103 growing and adult male and female rats, some treated long enough to achieve steady state bone effects with three different doses of aluminum, some with three different doses of an adrenalcorticosteroid analog, and others serving as control groups. Given that ''mixed bag,'' the correlation shown in Figure 1 between the BSI_f and breaking strength seems impressive. Called a ''tomographic bone strength index'' at the time, that BSI_f was calculated as the rectangular moment of inertia multiplied by the grams of bone per cubic centimeter (bone mineral density) at the femoral midshaft.

Note 3: The 40 humans studied in Pforzheim, Germany and plotted in Figures 3 and 4 were also a ''mixed bag.'' They included tall and short, thin and obese, males and females (pre- and postmenopausal), most of them healthy but others with medical problems (diabetes, hypertension, emphysema). They ranged from 16 to 75 years of age. Schiessl called his BSI_s a ''strength-strain index'' or SSI. The pQCT software calculated it as the polar moment of inertia divided by the mean radius of the cross section.

Note 4: In statistics a group of data with a P value of <0.05 would mean less than one chance out of 20 that the mean value of the group differed from the null hypothesis. A P value of <0.001 would mean less than one chance out of 1000 of that happening. On the other hand, the correlation coefficient, r, suggests what fraction of the above value could be explained by the variable under study. A correlation coefficient of $r = 0.94$ would suggest that over 85% of the variable's value could be explained by the thing it was compared to, a strong correlation. When $r = 0.3$, that suggests that 10% of the variable's value could be explained by the thing it was compared to. The more subjects or data points involved in calculating a correlation coefficient, the more reliable it is. Though desirable, determinations of P values were not available for the data shown in Figures 3–5, but in Figures 1 and 2, $P < 0.0001$.

Note 5: Numerous examples of this happended in all developed nations before vaccines made anterior poliomyelitis uncommon. The argument in this part of the text, as in the rest of it, emphasizes that something that is *essential* for physiology need also be *sufficient.* For example, mammalian life depends on both hearts and lungs, and cannot exist without either. Each is essential; neither is sufficient. This means that understanding mammalian general physiology requires understanding (among other things) the functions, roles and connections between skeletal physiology and the relationships among all five items in Predictions, which include effector cells, mediator mechanisms, the mechanostat, and MU. Each is essential; none is sufficient.

Note 6: Hence an explanation for observations that effector cells in many such conditions seem quite normal in kind and function, but still do their ''thing'' in unusual locations, circumstances and/or amounts.

Note 7: It is unusual for a text to refer, as a fact, to some mechanism that has not yet been seen, photographed, weighed, or measured. The mechanostat fits that description. It comprises one or more mechanisms that orchestrate the biologic activities that determine and maintain a skeleton's postnatal architecture and strength. Evidence for its existence is abundant. To explain: (1) It is an old observation that the architecture and strength of bones, joints, tendons, ligaments, and fascia normally fit their mechanical usage in ways that let them endure it for life. This happens in males and females alike, growing and adult subjects, small and large ones, in all known mammals from the shrew to the elephant, and in birds, reptiles, and amphibians. Since some mechanism or mechanisms must achieve those things, ''mechanostat'' was chosen to name and discuss it or them [2]. (2) Proof lies in ''natural experiments.'' For example, bones, joints, ligaments, tendons, and fascia in a limb paralyzed or otherwise made amyotonic at or shortly after birth develop abnormal architectures, masses, and strength during subsequent growth. Yet they all develop normally in the contralateral limb with normal muscle forces. Since the same blood-borne ''messengers'' distribute to both limbs and their cells have the same genome, some MU effect must explain the differences between the involved and normal limbs. It must be inherent in the cells and tissues, and it dominates the effects of most blood-borne hormones and other agents. (3) We do not know yet which cells and other mechanisms comprise or participate in the mechanostat, but it seems clear they do not include osteoblasts or osteoclasts. (4) The genome should determine the mechanostat's properties, and nonmechanical factors like those in Table 1 might modify them.