Mathematical modeling of microdamage in bone remodeling and adaptation

MATHEMATICAL MODELING OF MICRODAMAGE IN BONE REMODELING AND ADAPTATION

P.J. PRENDERGAST[1] and R. HUISKES

Biomechanics Section, Institute of Orthopaedics, University of Nijmegen, PO Box 9101, 6500HB Nijmegen, The Netherlands

ABSTRACT

Some of the arguments for and against microdamage as a signal for remodelling and adaptive remodelling are reviewed. To study the characteristics of damage-driven adaptation, a formalism for prediction of adaptive bone remodelling based on microdamage and repair is presented. In mathematical terms, this formalism requires an integral remodelling law. The consequences of this are analysed. If microdamage is indeed a factor in bone remodelling, then the bone material must have a mechanism for sensing it. To investigate whether or not this would be possible, a finite element model of a cross-section of a unit of cortical bone is generated. The consequence of the presence of microcracks is analysed from the point of view of how it would alter the strain sensed by (a) osteocytes or (b) bone lining cells. It is predicted that both could be sensitive to microdamage. If this prediction is correct, then there would be no either/or situation with regard to strain and microdamage as remodelling stimuli: rather both could act simultaneously to maintain mass and avoid failure.

1. INTRODUCTION

In the frequent citations of the work of Wolff[1], his idea is usually expressed in the following way: bone adapts its internal architecture and external conformation in accordance with mathematical laws.[2] Although Wolff did not derive a mathematical law himself, he did collect evidence that the direction of cancellous bone trabeculae followed the principal stress trajectories. In recent times, a paradigm for understanding mathematical laws relating to tissue adaptation has emerged. It involves a remodelling signal (sensed by a mechanoreceptor or sensor) and a remodelling rule (which transduces the signal into cellular stimulus for remodelling activity).[3] The remodelling signal and the remodelling rule combine to give a mathematical law describing the bone remodelling process. The more of the mechanism of remodelling is captured by the remodelling signal, the less complex the remodelling rule needs to be to complete the mathematical

[1] On leave from the Bioengineering Research Centre, Department of Mechanical Engineering, Trinity College, Dublin 2, Ireland.

law.[4] Therefore, from a mathematical modelling point of view, a signal can only be judged in the context of the remodelling rule used to implement it. An attempt is made to illustrate this concept by listing some possible remodelling signals (Fig. 1).

The case for microdamage as a signal for bone remodelling has been made for many years,[5,6,7] although it has been difficult to produce direct evidence to support it. It is easy to argue against microdamage as a signal by posing questions such as "How does microdamage occur and how is it sensed?", "Can it be formulated into a mathematical law to predict bone adaptations in the sense postulated by Wolff?" and, most obviously, "If microdamage does occur then why can't it be seen?" Clearly it would be confusing to try to answer these questions all at once. This paper aims to consider two arguments against damage driven bone remodelling in particular to see if they can be refuted using mathematical modelling techniques.

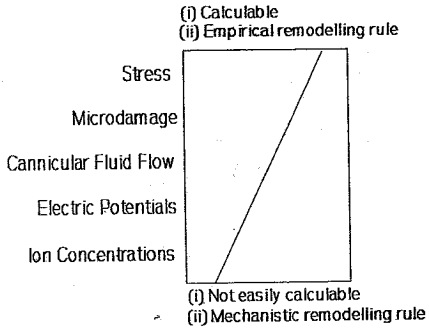

Fig. 1 Mechanistic remodelling signals facilitate predictive remodelling rules. However mechanistic remodelling signals are more difficult to use in computational models and require a knowledge of the micro-anatomy of bone.

The first argument against damage driven remodelling is that it would be costly in metabolic terms for bone to rely on damage as a controlling signal. However, assuming that bone, like all tissues, is in a certain way efficient for its function then some balance must be struck between minimizing the amount of damage to the tissue and minimizing the amount of tissue required to form the bone. The second argument is that the cell population would have to be able to sense proximity to the failure strain,[8] i.e. for a damage control mechanism to operate the presence *and* growth of microdamage would need to be sensed. Furthermore, it is known that many units of bone material are sustained under very low strains. If microdamage were to be the remodelling stimulus then even these low strains would have to induce an appreciable microdamage stimulus and this is considered unlikely.[9]

2 DESCRIPTION OF THE MODEL

In the following section, it is shown that a mathematical law for microdamage-stimulated remodelling can be derived. It is not intended that this be considered as a complete new remodelling theory. Rather it is hoped that, by capturing some of the characteristics of damage-stimulated remodelling in a mathematical model, the biomechanical role of a microdamage remodelling signal can be better understood.

Efficiency of mechanical function . . .

Bone is a highly heterogenous composite, consisting of both solid and liquid phases. The solid phase has mainly two constituents both of which are crystalline:[10] collagen organic constituents and hydroxyapatite inorganic constituents. Both constituents have very different elastic properties[10] and so it is not surprising that many studies have shown diffuse microstructural damage under *in vitro* mechanical loading. Of course, it is possible that bones have sufficient mass (i.e. are sufficiently large) so that this kind of diffuse microdamage does not occur under functional loads. Such damage-free bones might not be optimal biologic structures because they would be metabolically expensive to form (because they require more bone tissue) and to transport (because they are heavier).[11] Therefore, an alternative and equally plausible possibility is that bone material accepts a physiological level of microdamage under functional loading—the payback being that less osseous tissue would be required for the bone to carry out its mechanical function. This begs the question "If bone can build-up microdamage, or 'accumulate' microdamage, then what is to stop it from completely fracturing in the course of time ?"

. . . a repair process.

Following the foregoing discussion, let us assume that bone is mechanically efficient when it has an amount of diffuse microdamage which gives the tissue giving a residual strength lower than the maximum strength of the collagen/hydroxyapatite composite. If this is true, then a repair process must exist which ensures that damage does not accumulate. This implies that there is a *dynamic* equilibrium between damage formation and damage repair under physiological loading conditions: i.e. some damage entities are being generated at the same time as others are being repaired. Therefore, at remodelling equilibrium,

$$\frac{d\omega}{dt} = k \qquad (1)$$

where ω denotes an amount of microdamage per unit volume and k is the remodelling repair rate. If the load changes sufficiently, then it is possible that the dynamic equilibrium between damage formation and damage repair is disturbed.[12]

The model can be verbally described as follows: when the load is reduced on a bone, it becomes too strong to fulfil its task efficiently and therefore it must adapt to remain functionally efficient. Alternatively, when the load is increased, damage will accumulate and the bone tissue will be too close to failure (have too low a factor of safety) and bone mass must be increased in response to this.

Oftentimes complex concepts are best understood by analogy. Consider that many structures are designed with preventive maintenance in mind.[13] Rather than designing to prevent failure altogether, the structure is designed to facilitate testing and repair. For example, the designers of aircraft components do not make them so big that they will never fail, because this would create higher material costs and higher running costs. Instead, damage is allowed to accumulate in a controlled manner. After a certain time the

aircraft is brought in for maintenance, the components are scanned, and cracks are repaired as necessary.

3. A MATHEMATICAL LAW (Remodeling stimulus and Remodeling rule)

A remodelling rule relates the remodelling signal to a change in bone mass. This causes a geometrical change in the bone, such as changes of porosity or external shape of bone. To have predictive value, the remodelling signal in the bone must be calculable from a knowledge of the applied load, the continuum properties of the bone tissue and the geometry of a bone.

3.1. Continuum Damage Remodeling Signal

The continuum damage assumption implies that microscopic damage is distributed continuously in a differential element. This allows the effect of the microscopic damage, or microdamage, to be accounted for via the constitutive law of the material. As the damage entity gets large relative to the dimensions of interest, the continuum damage model is no longer adequate and the damage entity is considered as a crack and is analysed using fracture mechanics. The applicability of continuum damage mechanics for cortical bone was discussed by Krajcinovic and Trafimow.[14]

To solve a problem using continuum damage mechanics, one must chose a damage variable which describes the state of microcracking in an infinitismal volume of the material. To analyse the consequences of microdamage stimulated remodelling (section 5.1 below), the remaining life variable is chosen, based on the fatigue data for cortical bone.[15] The remaining life damage variable measures the damage as the ratio of the expended life of the material at a given stress to the total life of the material at that stress. In the case of damage accumulation during fatigue loading of many different stress levels (denoted σ_i), the accumulated damage is given by

$$\omega = \sum_{i=1}^{n} \frac{n_i}{N(\sigma_i)} \tag{2}$$

where n_i is the number of accumulated cycles at σ_i and $N(\sigma_i)$ is the fatigue life at σ_i.

3.2. An Integral Remodeling Rule

Unlike strain, microdamage accumulates as a function of loading histories. If an excess or deficit of microdamage has been generated due to an increase or decrease of load, then this signal will be 'remembered' even if the strain were to return to its homeostatic value. If the change in damage within the bone from its homeostatic value is denoted $\Delta\omega$, then a linear remodelling rule can be written to relate the surface position (denoted X) to the amount of microdamage as

$$\frac{dX}{dt} = C\Delta\omega \tag{3}$$

where C is a remodelling rate constant. The remodelling stimulus (i.e. $\Delta\omega$) can be calculated by integrating the mismatch between the damage formation rate and the damage repair rate occurring after some functional load change to give

$$\frac{dX}{dt} = C\int_{t_o}^{t} (\dot{\omega} - k)dt \tag{4}$$

where the superimposed dot denotes a time derivative. Therefore, it is only necessary to calculate the damage formation rate and the repair rate to use the above equation—it is not necessary to explicitly calculate the amount of remodelling equilibrium damage. Assuming that the damage formation rate is independent of the amount of damage (i.e. a linear damage growth law), then the damage formation rate is the inverse of the fatigue life. An expression for the repair rate as a function of the homeostatic load and the microstructure of the bone has been derived.[16] For the purposes of the analysis presented in the following section, it is assumed that the repair rate [denoted k in equation (4) above] stays constant after a load change, although the formalism presented here does not require this assumption.

4. CONSEQUENCES OF MICROCRACKING STIMULATED REMODELING

In the first part of this section, the mathematical model is used to investigate the mechanical consequences of microdamage-driven adaptation. In section 5.2, a finite element model is used to investigate whether or not the cell population in the bone would be able to sense the presence and growth of microscopic damage in Haversian bone. In the final section, some of the results of these models are used to reconsider the arguments against microdamage-driven remodelling from the mechanobiologic perspective.

4.1. Mechanical Consequences of a Damage Stimulus

The mathematical consequences of using damage as a remodelling stimulus have been analysed using finite element simulations.[17,18] In this chapter, a simple two-unit model is used for a more fundamental analysis. The results can be compared to those of Weinans *et al.*[19] who used a two unit model to investigate the dynamic behaviour of strain-adaptive remodelling. A remaining life damage variable and a linear damage growth law are used to give an expression for the

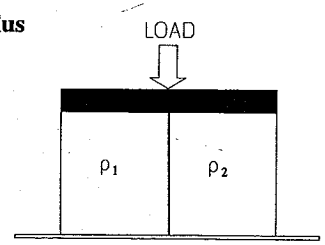

Fig. 2. Two bone units of density ρ_1 and ρ_2 loaded in parallel.[19]

damage formation rate in equation (4). Two uncoupled bone units respond simultaneously but independently to a load applied in parallel, as illustrated in Fig. 2. A change in the

$$\dot{\omega} = \frac{1}{N_f(\sigma)} \tag{4}$$

applied load generates a response in the two units as they change their density (and thus their elastic modulus according to the relationship $E = C\rho^{\gamma}$) in order to achieve a new remodelling equilibrium. If both units have the same initial density then they will adapt together. If they have slightly different initial densities then the unit with the higher density will take more load because it is stiffer and the unit with the lower density will bear correspondingly less load. It has been shown for strain-adaptive remodelling that, for realistic values of γ (i.e. between 2 and 3), one unit achieves maximal density and the other unit disappears.[19] If the same simulation is carried out using the integral remodelling rule required for damage-adaptive remodelling, then direct convergence to a homeostatic equilibrium is not achieved. Instead of a direct convergence to homeostatic equilibrium found for strain-adaptive remodelling, an oscillatory behaviour exists for damage-adaptive remodelling where the surviving unit remains active, Fig. 3. If the repair rate were to eventually adjust to the new load, then this oscillation would reduce over time.[20] Nonetheless, the mathematical model does predict that, if microdamage is a remodelling signal, monotonic convergence to a homeostatic structural geometry would not occur.

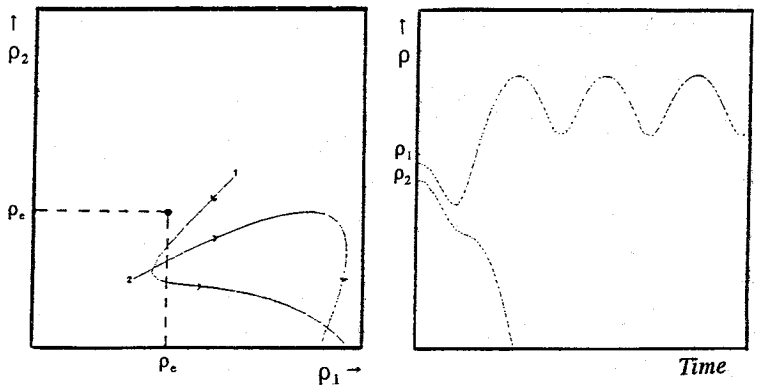

Fig. 3. (a) A phase plot showing the change in density of the two units after a change in load. Paths denoted 1 and 2 represent the solutions obtained with different perturbations of (ρ_1,ρ_2). Path 1 denotes a perturbation to a higher density and path 2 denotes a perturbation to a lower density. In both cases, the unit which has the lower initial mass goes to zero and the unit with the higher initial density survives; (b) The time-course of the mass change showing that the surviving unit continues to remodel and "turn over" mass.

4.2. Biological Consequences of a Response to Microdamage

The primary biological question is whether or not microdamage can be sensed as a control stimulus by the cell population ordinarily resident in the bone tissue. Not only must the presence of microdamage be sensed, but also the extent of it must be gauged if it is to act in controlling the stimulus. Recently, Mori and Burr[21] established experimentally that damage activates bone remodelling by stimulating resorption. However, so far no mechanism for damage stimulated remodelling has been fully established, although certain hypotheses have been advanced. One possibility is that osteocytes act as sensors of strain,[22,23] and that they are therefore sensitive to the alteration in the strain field caused by microdamage or microcracking.[5,9,24] A change in the homeostatic microdamage 'burden' would then activate surface resorption and adaptive remodelling. An alternative mechanism could be that the mechanical environment of bone lining cells are altered after microcracking, to initiate a remodelling response.[25] In this way old and deteriorated bone would be preferentially remodelled during bone turnover.[7,26] To investigate these hypotheses, a generalised plane strain finite element model of a section through a piece of cortical bone was generated, as described in detail elsewhere.[27] The geometrical representation includes the Haversian canal and lacunae and other microstructural features, Fig. 4. A load was applied in the axial direction (i.e. along the axis of the osteon) and in the plane of the osteon. Various types of microdamage were applied and lacunae were sampled to see if their cross-sectional area would alter as microdamage progressed. Considering just one kind of microdamage, namely micro-cracks in the cement-line,[5,28] it is seen that Haversian canal wall stresses are highly changed, Fig.5(a). Similarly the osteocytes (which are contained in most lacunae[29]) could be affected, depending on how sensitive they are to deformation, see Fig. 5(b).

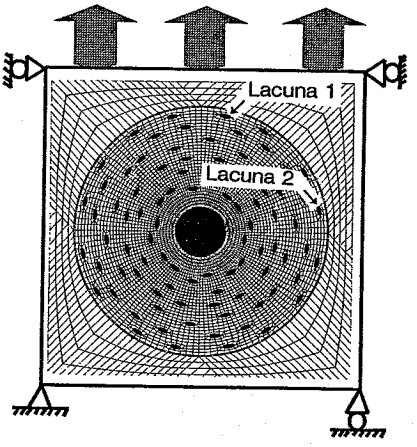

Fig. 4. The 2D finite element model of a section of Haversian bone. Loads and restraints are shown. It is a generalised plane-strain finite element model, therefore ε_z can be specified as 2000$\mu\varepsilon$.

4.3. Mechanobiological Conclusions

It is, of course, still possible that bone remodelling and adaptation may have nothing to do with microdamage, but it should be clear that microdamage activated remodelling cannot be dismissed for the reasons that (a) microdamage cannot be a controlling stimulus and (b) the extent of microdamage cannot be sensed by the bone.

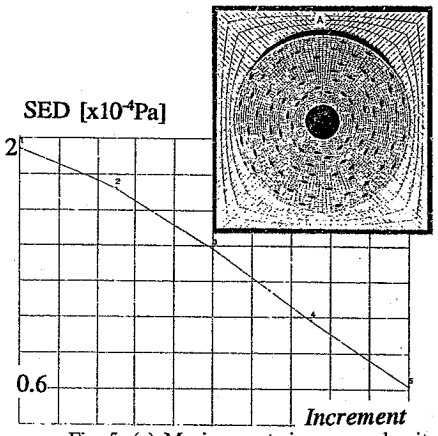

Fig. 5. (a) Maximum strain energy density change on the Haversian canal wall during growth of a cement-line microcrack. The crack begins at point A and grows, in five iterations, to the final dimensions shown in the inset.

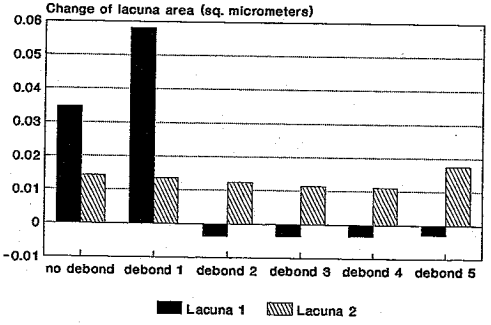

Fig. 5 (b) Cross-sectional area changes of the two lacunae chosen for sampling [indicated in Fig. 4. above].

In the case of (a), the formalism presented above shows that a mathematical model to predict bone adaptations can be developed using microdamage as a remodelling stimulus. This required first that there be an amount of microdamage in the bone at homeostasis (i.e. remodelling equilibrium) and second that the repair rate can either lag or exceed the damage formation rate. Such a controlling mechanism would generate bone remodelling activity that does not necessarily converge directly to the homeostatic structure after an alteration in load. Indeed, it is possible that normal homeostatic bone turnover is driven by a process whereby damaged bone (being less stiff) is shielded from the load, and this initiates resorption and subsequent repair.[30]

In the case of (b), the results of the microstructural finite element model suggest, though they do not prove it conclusively, that the growth of microdamage might be sensed by the population of cells in the bone tissue, i.e. either the osteocytes or the bone lining cells. Ultimately the role of microdamage as a contributing factor to the adaptation of tissues will require, not only evidence that a microdamage burden is continuously borne by the bone during normal functional loading[31] and is a causative factor in remodelling,[21] but also that the dynamics of remodelling and repair constitutes the essential metabolic equilibrium of bone which, if lost, drives a series of structural changes that have consequences for the external and internal structure of bone.

5. DISCUSSION

The introduction to this chapter evoked Wolff because he is held responsible for many of our views on bone adaptation. However, there were many opinions regarding the function-form relationship in bone emerging from other places at this time. As an example, Ward[32] writes "bone consists of numerous slender columns . . . adapted . . . to sustain concussion or pressure from below". The use of the word "concussion" is

interesting because it shows that, whatever may be attributed to Wolff[1], other thinkers had not made up their minds about a failure prevention objective or a strain/stress maintenance objective at this time. More recent commentators have kept their options open on this point as well.[2,3,33]

It has sometimes been suggested that more than one control system may be operative in bone mass regulation.[34] The mathematical models presented above suggest that the remodelling stimulus is not exclusively microdamage or strain but rather that both operate together in a process of maintaining mass and simultaneously avoiding failure. Consider the scheme in Fig. 6. The alteration in load is responsible for an unphysiological strain distribution and unphysiological amounts of microdamage will be generated depending on the responsiveness of the repair rate. Therefore, after a change in load both strain equilibrium (which is static in nature) and damage equilibrium (which is dynamic in nature) will be lost. Microdamage may activate remodelling itself by the release of growth factors embedded in the bone[35] or disruption of the canalicular network. It may also change the local strains to initiate a strain adaptive response. Simultaneously, the altered strains may initiate a process of remodelling and adaptation independently of damage.

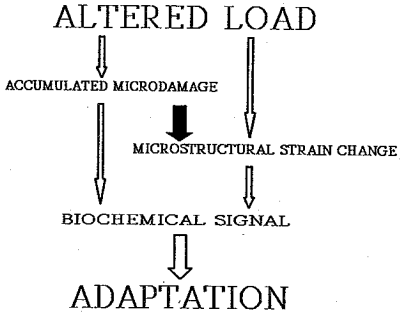

Fig. 6. Possible pathways for transducing mechanical load changes into adaptive response to both damage and strain.

Pursuing this line of argument would suggest an 'asymmetry' in the remodelling rule used to translate remodelling stimulus to adaptation. Since it is known from *in vitro* fatigue studies[15] that microdamage accumulates much quicker at higher cyclic strains, then damage-driven remodelling would accelerate strain-adaptive remodelling at high stresses. On the other hand, much less microdamage than normal would be generated for even slight reductions in stress indicating a decreased remodelling rate at low stresses. An asymmetric remodelling rule as would result if such a hypothesis were true is shown in Fig. 7 below. In this way the influence of microdamage would be to speed up deposition on an increase in load and prevent rapid structural decay on a decrease in load. It is noteworthy that asymmetric remodelling rules have been proposed and applied to prosthetic design-analysis.[36,37]

We must all recognise how easy it is to loose contact with reality. This is particularly true when one carries out mathematical modelling of tissue because we are trying to find the objective for which an organ has been designed by *a priori* assumptions about tissue stimuli. Several questions remain unanswered from the biomechanical point of view. Why is so much of the bone material of the skeleton maintained under very low strain? Does this not raise doubts about a strain maintenance being the only structural objective?

The move away from empiricism toward cell-based mechanistic models will challenge us to answer some of these intriguing questions in the very near future.

6. Acknowledgements

The first author would like to gratefully acknowledge the many discussions he has had with Mr. Clive Lee of the Royal College of Surgeons in Ireland, and Mr. Brian McNamara and Prof.Dr. David Taylor of the Bioengineering Research Centre, Trinity College Dublin. This work is partly supported by The Irish Science and Technology Agency, and by the Commission of the European Communities (Directorate-General for Science and Technology).

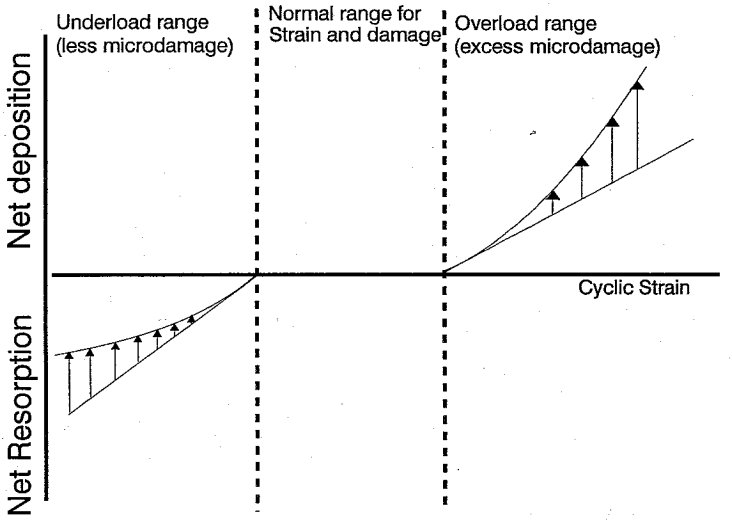

Fig. 7. A hypothetical asymmetric remodelling rule could be the result of combining a microdamage remodelling stimulus with a strain maintenance objective for bone. [Arrows indicate the hypothesised influence of microdamage].

7. References

1. Wolff, J., *Das Gesetz der Transformation der Knochen.* Hirchwald: Berlin (1892). Translated as: *The Law of Bone Remodelling.* (Manquet, P. and Furlong, R.), Springer: Berlin (1986)
2. Treharne, R.W. *Orthop. Rev.* **10,** 35 (1981)
3. Huiskes, R. and Hollister, S.J., *A.S.M.E. J. Biomech. Engng.* **115,** 520 (1993)
4. Prendergast, P.J., McNamara, B.P. and Taylor, D., In *Computer Methods in Biomechanics and Biomedical Engineering.* (Middleton, J., Pande, G.N. and Williams, K.R., Eds.), pp. 40–49, Books and Journals International: Swansea (1993)
5. Frost, H.M., *Henry Ford Hospital Medical Bulletin.* **8,** 25 (1960)

6. Radin, E.L., *International Congress Series No. 291. Orthopaedic Surgery and Traumatology.* pp. 59-65, Excerpta Medica: Amsterdam (1972)
7. Martin, R.B. and Burr, D.B., *Structure and Function of Compact Bone.* Raven Press: New York (1989)
8. Rubin, C.T. and Mcleod, K.J., In *Biomechanics of Diarthrodial Joints.* (Mow, V.C., Ratcliffe, A. and Woo, S.L.-Y., Eds.), Vol. II, pp. 97-118 (1990)
9. Lanyon, L.E., *J. Biomechanics* **20,** 1083 (1987)
10. Piekarski, K.R., *Int. J. Engng. Sci.* **11,** 557 (1973)
11. Alexander, R. McN., *J. Theoret. Biol.* **109,** 621 (1984)
12. Prendergast, P.J. and Taylor, D., *J. Biomechanics* **27,** 1067 (1994)
13. Taylor, D. and Prendergast, P.J., In *Fatigue 93.* (Bailon, J.-P. and Dickson, J.I., Eds.), Vol. 3, pp.1435-1440, EMAS Publishers: Birmingham (1993)
14. Krajcinovic, D. and Trafimow, J., In *Advances in Bioengineering.* (Langrana, N.A., Ed.), pp. 41-42, American Society of Mechanical Engineers: New York (1985)
15. Carter, D.R., Hayes, W.C. and Schurman, D.J., *J. Biomechanics* **9,** 211 (1976)
16. Martin, R.B., *J. Orthop. Res.* **10,** 818 (1992)
17. Prendergast, P.J. and Taylor, D., *J. Biomed. Engng.* **14,** 499 (1992)
18. McNamara, B.P., Prendergast, P.J. and Taylor, D., *J. Biomed. Engng.* **14,** 209 (1992)
19. Weinans, H., Huiskes, R. and Grootenboer, H.J., *J. Biomechanics* **25,** 1425 (1992)
20. Levenston, M.E., Beaupré, G.S., Jacobs, C.R. and Carter, D.R., *Bone* **15,** 177 (1994)
21. Mori, S. and Burr, D.B., *Bone* **14,** 103 (1993)
22. Cowin, S.C., Moss-Salentijn, L. and Moss, M.L., *A.S.M.E. J. Biomech. Engng.* **113,** 191 (1991)
23. Mullender, M.G. and Huiskes, R., *J. Orthop. Res.* (in press)
24. Currey, J.D., *Quarterly J. Microscopial Science* **103,** 111 (1962)
25. Martin, R.B. and Burr, D. B., *J. Biomechanics* **15,** 137 (1982)
26. Olivo, O.M., *Bolletino della Società Italiana di Biologia Sperimentale* (Napoli) **12,** 67 (1937)
27. Prendergast, P.J. and Huiskes, R., *A.S.M.E. J. Biomech. Engng.* (accepted)
28. Prendergast, P.J. and Huiskes, R., *Advances in Bioengineering* (Askew, M.J., Ed.), pp. 261-262, American Society of Mechanical Engineers: New York (1994)
29. Frost, H.M., *J. Bone Jt. Surg.* **41A,** 138 (1960)
30. Prendergast, P.J., Weinans, H., Huiskes, R. and Taylor, D., *Key Engineered Materials* **86-87,** 187 (1993)
31. Burr, D.B. and Stafford, T., *Clin. Orthop. Rel. Res.* **260,** 305 (1990)
32. Ward, F.O., *Outlines of Human Osteology.* 3rd Edition, Henry Radshaw: London (1876)
33. Carter, D.R., Fyhrie, D.P. and Whalen, R.T., *J. Biomechanics* **20,** 785 (1987)
34. Carter, D.R., *Calcif. Tissue Int.* **36,** S19 (1984)
35. Eriksen, E.F. and Kassem, M., *Sandoz J. Medical Science* **31,** 45 (1992)
36. Beaupré, G.S., Orr, T.E. and Carter, D.R., *J. Orthop. Res.* **8,** 651 (1990)
37. Weinans, H., Huiskes, R. and Grootenboer, H.J., *J. Orthop. Res.* **10,** 845 (1992)