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Leader

Mechanical stimulus to bone

The skeleton provides support for the body and serves as a reserve of calcium, playing an essential part in calcium homeostasis. In some parts of the body bone is also important to protect vital organs. At times, there are competing requirements that would compromise one or more of these roles were it not for complex and sensitive mechanisms to control the interaction between functional and metabolic demands on the skeleton. Unlike many man made structures, the specification for the skeleton is not constant, in that the loads applied to it change with different activities. Although the mass of skeletal elements could be such that the greatest possible loads would not result in failure, this would have considerable implications in terms of energy expenditure. Perhaps one of the most fascinating aspects of the biology of the skeleton is the process of functional adaptation. The basic form of skeletal elements is determined by genetic factors.[1] The fine detail and adult shape of bones, however, are markedly influenced by the functional environment. In particular, the prevailing mechanical stimuli act as a potent control of modelling and remodelling in bone.

The relation between function and form was noted nearly a century ago by Julius Wolff,[2] who studied the arrangement of trabecular arcades in the proximal human femur. The shape and loading of this bone resemble that of a Fairbairn crane. Furthermore, the stress trajectories in this structure closely resemble the pattern of trabeculae in the proximal femur. Wolff also noted the relation between the level of activity and the size of bones. From his clinical and experimental observations he proposed his classic law of bone remodelling, which postulated that both the mass and distribution of bone within the skeleton were appropriate to withstand best the prevailing mechanical loads. These observations were based upon knowledge of the form of the bone and an assumption of the applied forces. Although even at this time it was evident that bone had the ability to change size and geometry in relation to mechanical stimulus, the control mechanisms were not understood. To determine the nature of this response both the mechanical stimulus and resultant biological response had to be measured.

In the early 1970s a technique pioneered by Evans in 1953[3] was developed to allow direct measurement of surface bone strain in vivo over a period of time during physiological activities.[4–6] This technique was based upon the implantation of rosette strain gauges and allowed the magnitude and orientation of the principal strains to be calculated during physiological loading. Studies on the calcaneus of the sheep confirmed that the trabecular arcades within the bone were aligned with the trajectories of the principal compressive and tensile strains.[7]

Measurements of surface strain at different sites on a number of bones, in a range of species from man to fish during peak activity, showed the level of deformation to be similar despite the variation in anatomical conformation of the limbs and histological arrangement of the tissue.[8] Further studies showed that a remodelling response could be evoked by perturbation of the normal strain environment. A doubling of strain induced by removal of one of the paired bones of the forearm in pigs resulted in an adaptive hypertrophy, restoring both the total cross-sectional area of bone and the customary strain level.[9] This correlated well with observations by Jones *et al*[10] that the humerus in the serving arm of professional tennis players was about 30% greater in mass than the non-serving arm. These data suggest a feedback loop with a displacement control, which is supported by recent observations on astronauts, who after long periods in space show not only a generalised loss of bone mass throughout the skeleton but also a difference in distribution of osteopenia. The arms lose less bone than the legs. This is related to the level of functional use during the time in space.[11] The relation between mechanical stimulation and the activity of bone cells, with associated remodelling, is also of importance at a localised level within bones. For example, it has been suggested that the resorption of bone in the calcar region of the femur after insertion of a prosthesis is a result of induced change in local strain patterns.[12]

Although there is considerable evidence of the acutely sensitive response of bone to functional environment, the transduction paths from mechanical input to cellular activity are poorly understood and the exact mechanical characteristics associated with specific remodelling events require precise definition.

An experimental model has been developed in which a functionally isolated bone can be subjected to quantified strain regimens.[13] In this preparation it has been shown that functional isolation results in bone loss involving both intracortical porosity and endosteal resorption. As isolation must also disturb blood supply the response for intracortical porosity is consistent with that seen following application of fracture plates.[14] An exciting step forward was made using this model when it was shown that very few cycles of deformation were required each day to initiate a hypertrophic response. With a frequency of 0·5 Hz and 36 cycles of an osteogenic strain regimen a maximal increase in bone mass was obtained. Perhaps it should be noted that although the applied strain was physiological in magnitude, it was of

abnormal distribution. The change in distribution of strain may represent a potent osteogenic signal. Experimental data also confirm that the mechanical stimulus must be cyclical—equivalent deformation imposed as a static event fails to evoke a remodelling response.[15]

The difference in sensitivity to strain magnitudes and rates during abnormal modes of loading, in relation to that seen with the usual physiological distribution, may suggest that the response of bone to mechanical influences is an error driven system. This can be used to advantage in attempting to override the drive to reduce bone mass in postmenopausal osteoporosis. In contrast with the usual hormone replacement therapy, some recent studies have shown that short periods of high intensity diverse exercise on a regular basis can arrest the loss of bone and in some instances increase bone mass.[16] While regular daily loading can induce an adaptive response, a single loading episode produces demonstrable changes in both cells and matrix. After about 50 cycles of loading a change in orientation of proteoglycan molecules within the matrix occurs. This is seen in bone from a variety of species, including man. The effect persists with a half life of 24 hours and has been proposed as a strain 'memory' within the matrix.[17 18] Studies using tritiated uridine and also staining for glucose 6-phosphate dehydrogenase indicate cell activity in the osteocyte population within minutes of an applied osteogenic mechanical stimulus.[19] The osteoblasts on the bone surface show an active appearance within a few days of a single period of mechanical stimulation. These data further represent early steps in the adaptive response but are not specifically the transduction mechanism.

Sensitivity to loading is seen not only in intact bone but also in the repair process following fracture. Two patterns of repair are seen in bone—one is direct or primary healing[20] and occurs in situations of rigid fixation and high interfragmentary stability. Under these mechanical conditions the fracture line is bridged by secondary osteons, and little or no external callus is formed. This type of healing occurs over a relatively long time course and in the early stages may involve a temporary intracortical porosis, which has been attributed to both stress protection and vascular occlusion of periosteal vessels. After application of a fracture fixation plate the loads are shared between the plate and the bone, resulting in a reduction in customary strain and an associated osteopenia. Mechanical influences are not the only cause of the resorptive remodelling associated with internal fixation of fractures as certain types of plate also affect periosteal blood flow, and this has been shown to induce temporary intracortical porosity.[21] Reduction in mechanical stimulus seems to be associated with a reduction in cortical thickness as a result of endosteal bone loss. Modification of the undersurface of the plate to reduce periosteal contact has been shown to prevent the intracortical porosity.

The second type of repair is indirect or secondary fracture healing, which is seen in situations where interfragmentary stabilisation is less rigid and some motion occurs between fragments.[22 23] The pattern of healing involves the formation of external callus to bridge the fracture gap and stabilise the fragments. As the interfragmentary motion is reduced the tissues present in the gap differentiate from the original haematoma through granulation tissue, fibrous tissue, fibrocartilage, and woven bone. The process of remodelling and replacement with lamellar bone then continues over a longer period of time to restore the anatomical form of the bone. To some extent the mechanical environment at the fracture site will determine the ability of this tissue differentiation.

Indirect bone healing occurs in fractures treated with casts, braces, intramedullary nails, and external skeletal fixation. The rate and extent of repair are related to the conditions imposed by the device. When external fixators are used the frame configuration can be adjusted to alter the mechanical environment at the fracture site.[24] Rigid frames reduce interfragmentary motion and inhibit the rate of repair, though pin tract complications are reduced. Flexible frames permit high levels of interfragmentary motion and stimulate prolific external callus, yet have a tendency to lead to a greater incidence of problems related to the pin tracts. This general pattern of repair, however, has been shown to be sensitive to short periods of applied cyclical mechanical stimulation. Furthermore, the characteristics of the mechanical stimulus have also been shown to influence the repair process despite the short duration of application.[25] Both experimentally and in subsequent clinical trials it has been shown that short periods of dynamic mechanical stimulation of appropriate characteristics will enhance fracture repair. The optimum regimen appears to be one of low levels of displacement, rapid rate of movement, and low applied loads.[26] Furthermore, by measurement of increase in fracture stiffness during healing the frame geometry can be adjusted to provide changes in mechnical environment at the fracture site and allow the sensitivity of the repair process to mechanical stimuli to be used to control the repair process. Additional experimental studies indicate that controlled dynamic stimulation should be started in the early stages of healing.[27] Thus applied mechanical stimulation can be used to initiate fracture repair in patients who are non-weight bearing as a result of concomitant injuries.

Indirectly, mechanical stimulation will also influence the integration of prosthetic replacements with skeletal elements. The long term aseptic loosening of femoral components in total hip replacement may be attributed to the changes induced in the functional strain environment of the proximal femur. Experimental studies have indicated that the presence of a prosthesis results in a significant change in the magnitude and distribution of strains, particularly in the calcar region. An understanding of the relations between strain distribution and bone remodelling is essential if a new generation of functionally compatible prostheses is to be developed. New materials currently under investigation may also play a part in the ability to design prostheses that will engender osteogenic strain environments to encourage bone formation in areas that support the prosthetic device.

The ultimate goal must be in the elucidation of the transduction pathways that link mechanical stimulus to an integrated cellular remodelling response. Ultimately this will lead to a more convenient method of controlling bone remodelling, possibly using pharmacological agents, in relation to repair, replacement, and treatment of degenerative diseases of the skeleton.

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1 Fell H B. Skeletal development in tissue culture. In: Bourne G H, ed. *The biochemistry and physiology of bone* 1st ed. New York and London: Academic Press, 1956: 401–40.
2 Wolff J. (1892) *Das Gesetz der Transformation der Knochen*. Berlin: von August Hirschwald. Berlin. Translated by Maquet P, Furlong R. *The law of bone remodelling*. Berlin: Springer, 1986.
3 Evans F G. Methods of studying the biomechanical significance of bone form. *Am J Phys Anthropol* 1953; **11**: 413–35.
4 Lanyon L E, Smith R N. Bone strain in the tibia during normal quadrupedal locomotion. *Acta Orthop Scand* 1970; **41**: 238–48.
5 Lanyon L E. In vivo bone strain recorded from thoracic vertebrae in sheep. *J Biomech* 1972; **5**: 277–81.
6 Cochran G V B. Implantation of strain gauges in vivo. *J Biomech* 1972; **5**: 119–23.
7 Lanyon L E. Experimental support for the trajectorial theory of bone structure. *J Bone Joint Surg [Br]* 1974; **56**: 160–6.
8 Rubin C T, Lanyon L E. Dynamical strain similarity in vertebrates: an alternative to allometric limb bone scaling. *J Theor Biol* 1984; **107**: 321–7.
9 Goodship A E, Lanyon L E, McFie H. Functional adaptation of bone to increased stress. *J Bone Joint Surg [Am]* 1979; **61**: 539–46.

10 Jones H H, Priest J D, Hayes W C, Tichenor C C, Nagel D A. Humeral hypertrophy in response to exercise. *J Bone Joint Surg [Am]* 1977; **59**: 204–8.
11 Stupakov G P, Kazekin V S, Koslovskiy A P, Korolev V V. Evaluation of changes in human axial skeletal bone structures during long term spaceflights. *Kosm Biol Aviakosm Med* 1984; **18**: 33–7.
12 Lanyon L E, Paul I L, Rubin C T, *et al*. In vivo strain measurements from bone and prosthesis following total hip replacement. *J Bone Joint Surg [Am]* 1981; **63**: 989–1001.
13 Rubin C T, Lanyon L E. Osteoregulatory nature of mechanical stimuli: function as a determinant for adaptive remodelling in bone. *J Orthop Res* 1987; **5**: 300–10.
14 Matter P, Brennwald J, Perren S M. Biologische reaktion des knochens auf osteosynthese platten. *Helv Chir Acta* 1974; **12** (suppl): 1–44.
15 Lanyon L E, Rubin C T. Static versus dynamic loads as an influence on bone remodelling. *J Biomech* 1984; **17**: 141–54.
16 Smith E L, Gilligan C, McAdam M, Ensign C P, Smith P E. Deterring bone loss by exercise prevention in premenopausal and postmenopausal women. *Calcif Tissue Int* 1989; **44**: 312–21.
17 Skerry T M, Bitensky L, Chayen J, Lanyon L E. Loading related reorientation of bone proteoglycans in vivo. Strain memory in bone tissue? *J Orthop Res* 1988; **6**: 547–51.
18 Skerry T M, Suswillo R, El Haj A J, Ali N N, Dodds R A, Lanyon L E. Load-induced proteoglycan orientation in bone tissue in vivo and in vitro. *Calcif Tissue Int* 1990; **46**: 318–26.
19 Skerry T M, Bitensky L, Chayen J, Lanyon L E. Early strain-related changes in enzyme activity in osteocytes following bone loading in vivo. *J Bone Min Res* 1989; **45**: 783–8.
20 Schenk R, Willenegger H. Zur histologie der primaren knockenheilung. *Langenbecks Arch Klin Chir* 1964; **308**: 440.
21 Perren S M, Cordey J, Rahn B A, Goutier E, Schneider E. Early temporary porosis of bone induced by internal fixation implants: a reaction to necrosis, not to stress protection. *Clin Orthop* 1988; **232**: 137–51.
22 Sarmiento A, Schaeffer J F, Beckerman L, Latta L L, Enis J E. Fracture healing in rat femora as affected by functional weight bearing. *J Bone Joint Surg [Am]* 1977; **59**: 369–75.
23 McKibbin B. The biology of fracture healing in long bones. *J Bone Joint Surg [Br]* 1978; **60**: 150–62.
24 Wu J J, Shyr H S, Chao E Y S, Kelly P J. Comparison of osteotomy healing under external fixation devices with different stiffness characteristics. *J Bone Joint Surg [Am]* 1984; **66**: 1258–64.
25 Goodship A E, Kenwright J. The influence of induced micromovement upon the healing of experimental tibial fractures. *J Bone Joint Surg [Br]* 1985; **67**: 650–5.
26 Kenwright J, Goodship A E. Mechanical stimulation of tibial fractures. *Clin Orthop* 1989; **241**: 36–47.
27 Goodship A E, Adams M A, Kenwright J. The influence of mechanical stimulation on different stages of fracture healing. *Transactions of the 35th annual meeting, Orthopaedic Research Society, February 6–9, Las Vegas, Nevada*. 1989.