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Fracture and repair of bone: a multiscale problem

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Abstract This article reviews current work on the strength and toughness of bone, its mechanisms of fracture and its ability to repair and adapt its structure. These properties are affected at all size levels, from the nano-structure of collagen molecules and mineral crystals, through the microstructure of osteons and trabeculae, up to the macroscopic shape and density variations that occur at the level of a whole bone.

Introduction

The strength and fracture of bone has interested scientists for a very long time. Galileo Galilei, in his pioneering work on mechanics, "*Dialogues Concerning the Two New Sciences*" [1], discusses the shapes of bones in relation to their strength as an example of a problem in scaling. He worked in the University of Padova, and it can be no coincidence that it was there, around the same time, that the first anatomy theatre was built, allowing students to observe the dissection of cadavers. Interdisciplinary research in this field has a long history.

In this article I will discuss the current state of our understanding of fracture in bone, and point out lines of developing research. It is impossible, or at least unwise, to discuss the fracture of this material without also discussing its repair, because our bones are living structures, capable of maintaining their integrity by continual repair of damage and by adapting to changes in their stress environment. These two aspects of bone—its resistance to fracture and its functional adaptation—have evolved hand-in-hand, giving us a material, which is supremely well adapted to its role.

Two themes will run through this article. The first is that the subject is a hierarchical one which must be viewed on different scales: it is convenient to divide these into three, which I will call the *macro*, *micro*, and *nano* scales, though inevitably these divisions are somewhat arbitrary and overlapping. The second theme is that, despite some unique characteristics, bone is a structural material, which can be investigated in the same way, using the same tools and ideas, which we use to investigate other structural materials. Thus the expertise of materials scientists, who understand the relationships between structure and mechanical properties, is vital to our research activities in this field.

The macro scale

In the world of man-made materials it is normal to think of 'the material' and 'the structure' (i.e. the macroscopic structure of the object in question) as two different things, the first being broadly the province of the materials scientist whilst the second is the concern of the engineer. In natural materials, however, there can be no such easy distinction: in structures such as a human bone or tendon or the stem of a plant, the properties of the material vary from place to place within the structure in a smooth, continuous manner which we are only beginning to imitate in, for instance, functionally-graded materials. For example, in the head of the femur (Fig. 1) the material varies from the solid outer shell of cortical bone to the inner network of

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trabecular bone, in which the size and orientation of individual trabeculae is driven by local stress. It is difficult to know where the material stops and the structure begins, so we must start our discussion by considering an entire bone, for example a typical long bone such as the femur. At this scale three factors exert an influence on the mechanical performance of the structure, these are: shape, size and density.

Shape

It is often said that the shapes of our bones have been optimised for their purpose through long ages of evolution. In fact 'optimised' is not quite the right word, because evolution does not act to optimise a structure but rather to make it just good enough to give the organsm a competitive advantage, a better chance of survival. Alexander [3] and Martin [4] considered the various factors involved: crucially, the aim here is not to avoid fracture at all costs, in fact a certain probability of fracture (which, for the individual, may mean death) is essential in order to reduce weight, ensuring a gracile support structure, one which is light and efficient. Nevertheless, the optimisation problem is an interesting one for the student, and gives us some useful insights. Consider the problem of designing a bone—simplified to a regular cylinder of outer radius r and thickness t: what will be the optimum value of the shape factor r/t, assuming that the aim is to minimise weight for a given strength? Long bones are subjected to a mixture of loading types: tension, compression, bending and torsion. It is a simple matter to show that, for the cases of tension, compression and torsion, the factor r/t has no effect—it cannot be optimised. On the other hand, under applied bending the optimum value will be infinity: clearly no sensible solution arises. Pauwels [5] pointed out that there is an extra weight term, because the bone tube is full of marrow, and this leads to a finite optimum value for r/t. Currey and Alexander [6] developed this idea still further, considering different modes of failure (yielding, impact, etc); their results suggested an optimum value of approximately 2 which, despite considerable variation, is a typical value for long bones.

Modern approaches to this problem tend to use computer simulations—usually finite element (FE) analysis—to study the development of the complex shapes of real bones. These will be discussed in the next section since they are also capable of simulating density variations.

Density

Bone can vary its density by changing its porosity. The solid material (cortical bone) that makes up the outer shells of our bones has typically 5% porosity. This can increase under conditions of disuse or disease, forming osteoporotic bone; further increases in porosity give rise to a spongy, open structure known as cancellous or trabecular bone, which is found near joints where it provides a low-weight solution to the problem of transferring compressive stresses from the joints down into the bone tube, as we saw above (Fig. 1).

The prediction of bone shape (in practice largely confined to predicting the local thickness of the cortex) and the distribution of density (or, in some cases the local structure of the trabecular bone), has been extensively studied using FE simulations. These features are not only determined by evolutionary pressures, but can also change within the lifetime of an individual, as a result of changes in the stress environment as caused by, for example, the adoption of a more active lifestyle or the implantation of an artificial joint [7]. The most successful simulations are those, which take account of the development of damage over time, its continual repair and the functional adaptation, which will occur if the rates of damage and repair are not equal [8].

This work will not be discussed in detail here, as it takes us out of the realm of materials science, being largely concerned with continuum-mechanics techniques such as damage mechanics, using control variables such as strain-energy density. Some workers have achieved considerable predictive success (see for example [9]), though their work is hampered by the limited amount of experimental data available and the large degree of scatter inevitable in such data.

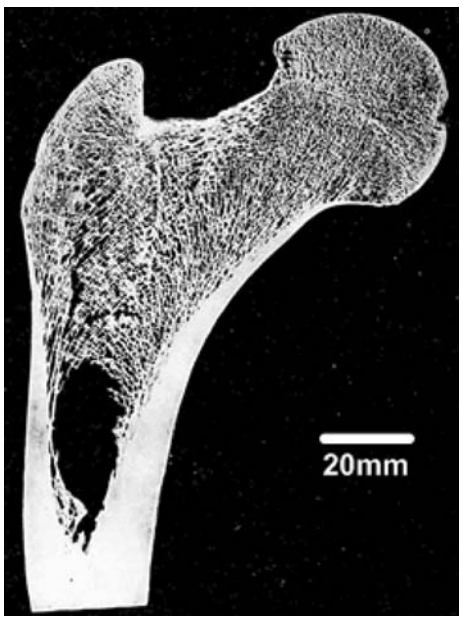

Fig. 1 Cross section through the head of a femur, showing the outer shell of compact cortical bone and the open network of trabecular bone [2]

Size

The stress to cause failure in a sample of bone will decrease with increasing size of the sample. This is a well-known phenomenon, apparent when failure occurs by a 'weakest-link' mechanism, as in the strength of brittle materials such as ceramics and the fatigue strength of metals. It is a major issue for bone because of the enormous changes in scale that occur: the bones of a mouse and those of an elephant are essentially the same shape, but vary in volume by many orders of magnitude. Such problems are traditionally addressed using a probabilistic technique: we showed that a Weibull analysis is capable of predicting scaling factors in the fatigue strength of cortical bone, and that the approach can be extended to discuss size effects in different animals and, with the addition of terms to describe repair and adaptation, can be used to predict the probability of stress fractures (i.e. fatigue failures) in athletes, military personnel and other vulnerable groups [10; 11].

The micro scale

Fracture

The work described above was essentially in the realm of continuum mechanics, though the introduction of probabilistic terms hints at the existence of local material variations and therefore of a microstructure. Various pieces of evidence give us clues as to the relevant size scale on which fracture mechanisms operate. For example, cracks and sharp notches have almost no effect when they are as small as 0.37 mm [12] and even circular holes as large as 10 mm diameter do not reduce the strength of the specimen by as much as the elastic stress-concentration factor [13]. Systematic studies by Nalla et al. [14] and Malik et al. [15] have shown that the measured fracture toughness, K_c, increases with crack length for cracks up to several millimetres long. This behaviour, described by the so-called R-curve (resistance curve, see Fig. 2), is expected to persist until the crack is at least an order of magnitude larger than those microstructural features which affect toughness. A final clue comes from the theoretical analysis, commonly used in process zone and critical distance approaches [17; 18], which derives a critical length scale, L, as a function of the fracture toughness and static strength (σ_o) of the material, as:

$$L = \frac{1}{\pi}\left(\frac{K_c}{\sigma_o}\right)^2 \quad (1)$$

Strength and toughness vary considerably in bone, but if we use typical values (K_c = 4 MPa(m)$^{1/2}$, σ_o = 160 MPa) we obtain L = 0.2 mm. All of these pieces of evidence suggest that the fracture of bone, and therefore its toughness, is controlled by mechanisms operating at the 0.1–1 mm scale.

Several different mechanisms operate, and there is considerable debate as to their relative importance. A useful distinction here is between so-called 'intrinsinc toughening' mechanisms, which operate in front of the crack tip, and 'extrinsic toughening' mechanisms which operate behind the tip, in the crack wake; the latter are responsible for the increase in measured toughness with crack length as shown in Fig. 2. Nalla et al. studied these using a number of techniques, including three-dimensional imaging by tomography [19; 16]. They concluded that a major contribution to toughening comes from the bridging of the crack faces by unbroken ligaments of material, an extrinsic mechanism illustrated in Fig. 2. Much smaller contributions were predicted to come from other mechanisms such as crack deflection, bridging by collagen and the consumption of energy in the zone of microdamage ahead of the crack. Vashishth et al. [20] on the other hand, predicted a major role for microdamage, which takes the form of a cloud of small cracks ahead of the main crack, whilst Yeni and Fyhrie argued that collagen-fibre bridging across microcracks has a significant effect on bone's strength [21]. Another important factor is plasticity. Bone exhibits non-linear stress/strain behaviour: taking some typical figures (Young's modulus = 15 GPa; tensile strength = 160 MPa; strain to failure = 0.02) we see that about half of the strain to failure is due to non-linear deformation, some caused by microdamage, some by viscoelasticity and some by plastic deformation, which occurs in the collagen phase (see below concerning bone's chemical make-up). Testing at high strain rates, where collagen has less time to deform, reduces the strain to failure [22] and also the toughness [23]. It seems likely that plasticity is responsible for a large proportion of the intrinsic toughness of bone, though further work is certainly needed to clarify the relative contributions of these different mechanisms.

Individual microstructural features begin to make themselves apparent as the crack length gets smaller. The principal features of interest in cortical bone are osteons; these are long, cylindrical structures, typically 200 μm in diameter and many millimetres long, which run along the length of the bone (Fig. 3). In the centre of each osteon is a blood vessel, supplying nutrients to living cells, which reside in small cavities nearby, connected by thin cellular processes (Fig. 4).

Discontinuous crack growth is observed under constant load for sub-millimetre cracks (see Fig. 5) [25], in contrast to the smoother growth behaviour of longer cracks [26]. Cracks are temporarily arrested by features such as osteons and Volkman's canals. For crack lengths less than about 100 μm

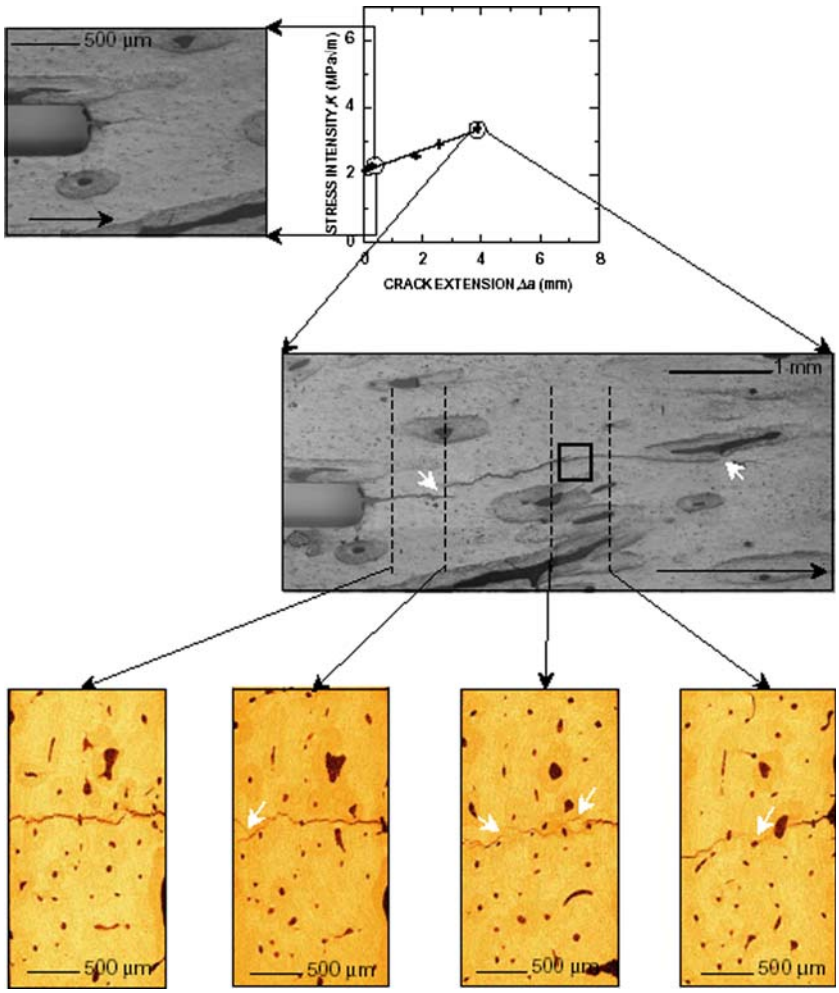

Fig. 2 Cracks in bone show increasing toughness with crack length, as the graph here demonstrates for a crack growing from a notch. The photographs, taken at early and late stages in the test, show how the increasing toughness is correlated to the presence of unbroken ligaments which span the crack faces [16]

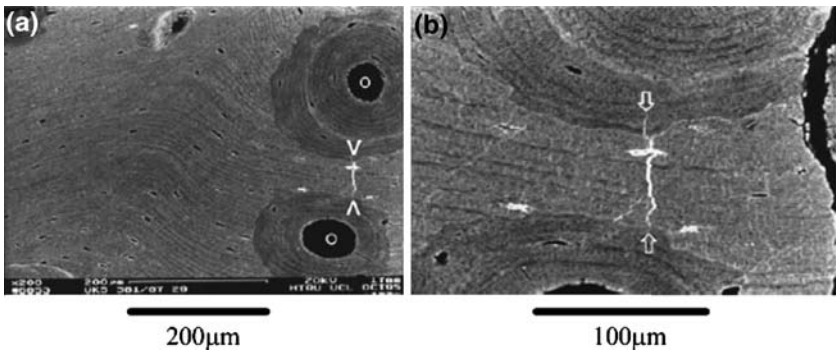

Fig. 3 A transverse section through a human femur, showing (on the left) two osteons with a crack running between them. At higher magnification (on the right) the crack is seen to be white, indicating that it has been filled in by subsequent mineralization [24]

crack growth behaviour becomes completely dominated by these features and this is especially apparent under cyclic loading [27; 28]. Small fatigue cracks initiate in the interstitial bone between osteons (Fig. 3). Much work has gone into the detection and measurement of these cracks, using penetrant dyes [29]. Unlike metallic materials (but very

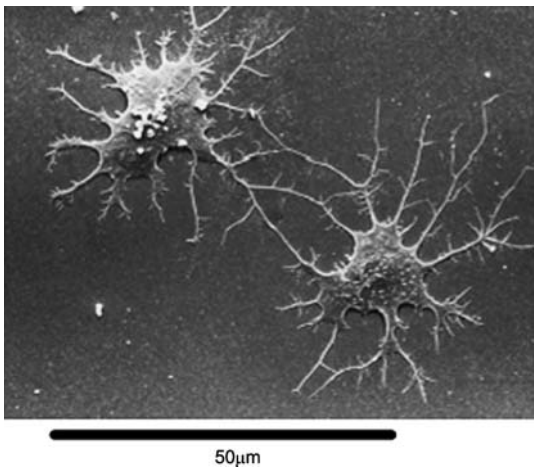

Fig. 4 Two bone cells (osteocytes): note the long thin processes through which the cells communicate; these run in narrow channels (canaliculi) within the bone matrix

much like fibre composites), bone develops cracks not only on its surface but internally, so the majority of the damage is not immediately visible. Dyes of different colours can be introduced to stain cracks at different stages during a test, providing a picture of the development of damage over time [30]. In shape these cracks are typically elliptical planes, about 400 μm by 100 μm, oriented with their major axes approximately (but not exactly) parallel to the bone's longitudinal axis: Fig. 6 shows an image of a typical crack, obtained using laser scanning confocal microscopy [31]. Again this is very different from the behaviour of fatigue cracks in metals, which orient themselves perpendicular to the principal stress axis, but not unlike some forms of delamination damage in composite laminates.

These cracks grow relatively quickly until they reach barriers in the microstructure such as the cement lines, which surround osteons (Fig. 3). At this point the great majority of cracks cease growing altogether. A few continue, usually growing around their first osteon but breaking through osteons as they become longer and more energetic. Thus the osteon structure (or, in some other animals, a different microstructure on a similar scale, known as plexiform bone) is crucial in determining the material's resistance to fatigue failure. Recently a lot of work has been done in this field, measuring the length and number-density of microcracks (and also regions of so-called 'diffuse damage' which will be discussed below). Correlations have been found between the amount of damage and the applied load, the age of the subject, the density of bone cells, the existence of osteoporosis and other factors [32–35]. Further theoretical work is needed to make sense of all this data.

Repair

The repair process in cortical bone is ideally suited to deal with cracks of this size. First described by Frost [36], repair uses two different types of cells, working together: osteoclasts—cells, which dissolve bone—are followed by osteoblasts, which make new bone. The result is a so-called Basic Multicellular Unit (BMU) taking the form of a cavity approximately 200 μm across which moves along the length of the bone, removing old material containing microcracks and replacing it with new material, forming an osteon. It has taken a lot of careful research to demonstrate that BMUs do not occur randomly but are targeted towards microcracks [37–39] (see Fig. 7). The actual mechanisms by which this happens are still being investigated and this is a very exciting area of current research, involving elements of materials science, fracture mechanics, biochemistry and genetics. For example, Klein-Nulend and co-workers [41; 42] have suggested a mechanism to control the movement of BMUs. A crucial feature of this model is fluid flow, which is relatively stagnant in the region just ahead of the BMU cavity; osteoclast activity here is envisaged to be stimulated by altered levels of nitric oxide emitted by cells, causing the BMU to move along paths of maximum principal stress. Hazenberg et al. [43] have proposed a mechanism, which considers how cracks can be detected. The main step in this model is the fracture of cellular processes, which pass across crack faces; these are envisaged to be cut in a scissor-like action due to local

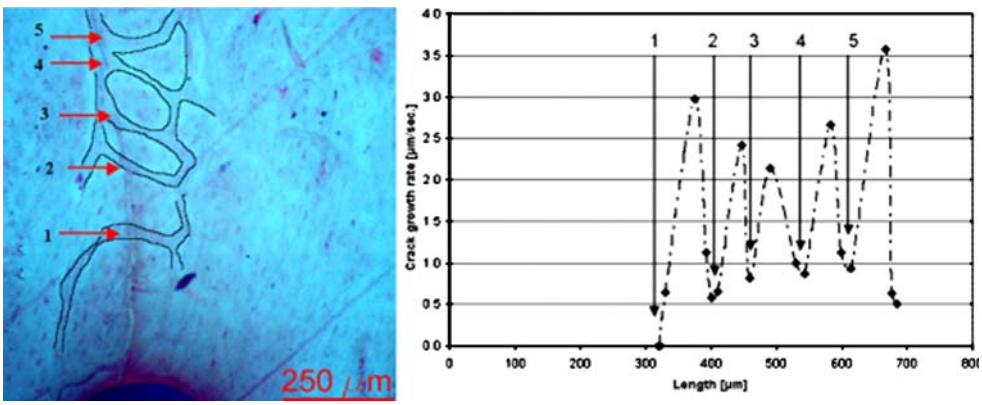

Fig. 5 Crack growth rate as a function of length for a small crack growing in cortical bone. Growth is discontinuous: minima in the graph (numbered) correspond to periods of temporary arrest when the crack encountered features in the microstructure, in this case Volkman's canals (enhanced on the photograph)

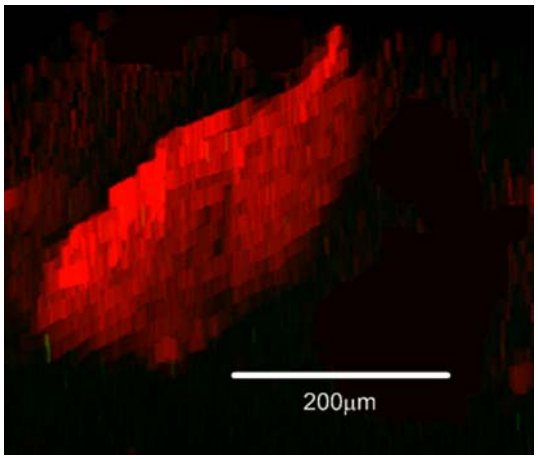

Fig. 6 An image of a typical crack inside a specimen of bone, obtained using laser scanning confocal microscopy [31]

shearing motions. Once broken, these cells release a substance, which stimulates the formation of osteoclasts, creating a BMU. Other work has suggested mechanisms by which cells might be affected by the presence of a nearby crack and signal to other cells to initiate the repair process [44; 45].

Some theoretical models have attempted to reproduce these damage and repair processes in computer simulations. Martin [46; 47] has incorporated the behaviour of BMUs, creating an equilibrium crack density in which cracks are continually being created and removed. This equilibrium can be disturbed in various ways, leading to adaptation or stress fractures. One interesting feature is the fact that the BMUs themselves tend to increase stress because they increase the level of porosity, creating a potential instability. We have developed a model in which the growth behaviour of each individual microcrack and BMU is described, using stochastic variables [48]. Such models have the advantage that they can predict many parameters, which can be directly measured, such as the number density of cracks and BMUs, and so can be tuned in the light of experimental data.

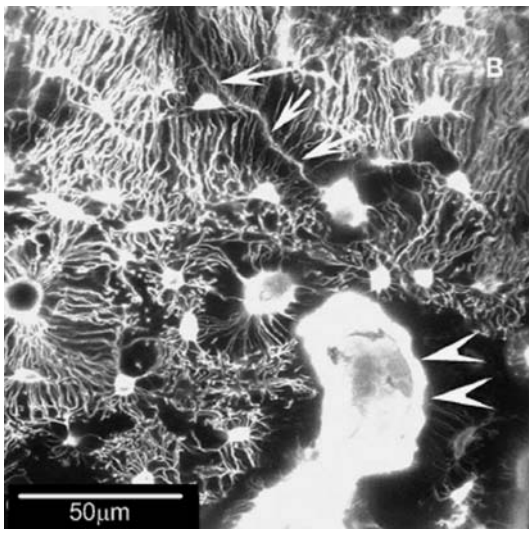

Fig. 7 The resorption cavity of a BMU (white object indicated by large arrowheads) moves towards a microcrack (indicated by the smaller arrows). The surrounding structure shows bone cells and their processes [40]

Trabecular Bone

Trabecular bone can be thought of as a network structure of rods and plates of thickness typically in the 10–100 μm range. Its failure characteristics are very different from those of solid cortical bone. As might be expected for a foam-like material, failures of individual trabeculae (by cracking, tensile snapping or compressive buckling) contribute to a gradual deterioration in the material's integrity. Partially broken trabeculae can be repaired by BMU's, though in this case they operate by scouring the material surface, rather than by tunnelling. Completely fractured trabeculae can be repaired in much the same way as a broken bone, by the formation of a microscopic callus [24], as shown in Fig. 8. Sometimes this cannot happen and then the surrounding network structure must adapt to the loss. There is evidence for a gradual deterioration in the structure of this type of bone over long periods of time, due to random fracture events, which may contribute to the onset of osteoporosis.

The nano scale

This final section considers structure on the scale reaching from 1 μm down to molecular dimensions. The processes of damage and repair on this scale are less well understood than at the larger size levels, though some recent work has begun to shed light on the effects of structure and composition on material strength and toughness.

Bone is a composite material, made up of two fibrous components, closely interwoven. These are collagen, a biological polymer with a triple helix, and a mineral phase based on calcium, which is traditionally called hydroxyapatite (though recent work suggests may be better described as a carbonated apatite [49]). In the formation of bone, long fibres of collagen (typically 0.2 μm in diameter) are laid down first; hydroxyapatite is subsequently precipitated amongst the fibres, forming elongated crystals, each typically 5 nm diameter and 40 nm long, joined in a continuous network. Layers of this material are built up, very much like the process of making fibre-composite laminate sheets, though the laminar thickness in this case is of the order of a few microns. Mechanical properties can be

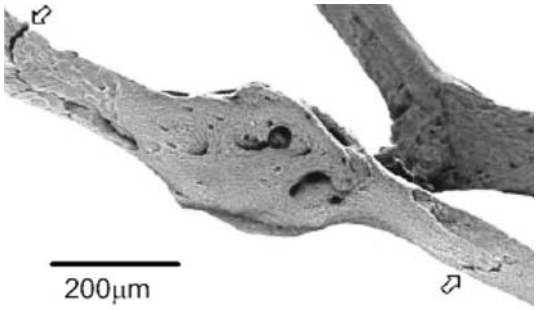

Fig. 8 An individual trabecula containing a callus, which has formed to repair a fracture [24]. Note that subsequent cracks have initiated (arrowed) indicating an imminent re-fracture

adjusted by varying fibre orientations; for example, osteons are built with laminae encircling the blood vessel as tubes: varying the proportions of fibres in different orientations creates osteons with different mechanical properties [50].

In addition to the microcracks mentioned above, damage can occur on a smaller scale. Areas of material stained by the penetrant dye (Fig. 9) are seen, at higher magnification, to consist of many small cracks, each typically 1 μm in length; this has been termed 'diffuse damage' [51]. Other kinds of damage presumably exist at smaller size scales—one can imagine, for example, fracture of the hydroxyapatite crystal network and the breakdown of the interface between it and the collagen fibres, but to my knowledge these damage modes have yet to be observed, partly due to the difficulty of preparing specimens for high-magnification work without creating damage in the process.

Some recent pieces of work have investigated the effect that changes at the molecular level have on bone's strength and toughness: a good review on toughness effects at the nano scale has been provided by Nyman et al. [49]. As yet no clear, consistent picture has emerged but there are some themes developing which merit further attention. Firstly, we cannot forget a third constituent of bone, which is

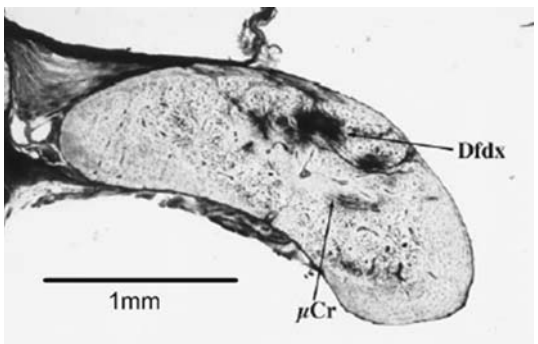

Fig. 9 Cross section of a rat ulna after extensive fatigue loading [45]: microcracks can be seen (labelled μCr) along with a region which has become stained due to the presence of diffuse damage (labelled Dfdx)

water; it occupies about 25% by volume of compact bone. It is well known that if a bone sample is allowed to dry out before testing it becomes much more brittle as well as containing more damage, created by shrinkage. The removal of even small amounts of water has been correlated to reductions in toughness and plastic strain [52]. Water is found both in the collagen phase, where it stabilises collagen fibres via hydrogen bonding, and in the mineral phase, where it alters the crystallographic structure.

A second factor is the quality of the collagen phase, whose deterioration has been correlated to age-related changes in bone toughness and strength [53; 54]. An important parameter here is the degree of crosslinking. Like many polymers, collagen undergoes crosslinking, which tends to make its structure stronger, but also perhaps more brittle. The degree and type of crosslinking changes with the age of the tissue [55; 56] and is affected by several other factors [57]. Gamma radiation, which denatures collagen, causes reductions in bone strength and toughness [58]. Changes in the mineral phase also affect mechanical properties [59; 60], and cracks tend to accumulate preferentially in regions of high mineral content [61].

Almost nothing is known about any repair processes that may be operating at the sub-micron level, though Boyd [24] has pointed out that macroscopic cracks can sometimes be filled in with mineralised material (Fig. 3) suggesting an alternative to repair by BMUs.

Concluding remarks

The fracture and repair of bone is a subject for which we have to take a hierarchical perspective, a fact, which has not been lost on some researchers [62; 63]. Changes at the sub-micron level, which affect the chemistry and structure of collagen fibres and mineral crystals, determine the nature of the basic material, the material within which cracks will grow. But significant elements of the control of toughness occur at the microstructural scale, where features such as osteons in cortical bone, and the geometry and arrangement of trabeculae in cancellous bone, strongly affect the ease of crack growth and local fracture events. At the macroscopic scale, bone's ability to vary its material properties—properties such as density and fibre orientation—allow the best use to be made of the material to create a strong, light, efficient skeletal structure.

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