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BONE REMODELING IN RESPONSE TO *IN VIVO* FATIGUE MICRODAMAGE

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Abstract—It has been suggested that osteonal remodeling is triggered by bone microdamage. The validity of this theory rests on the assumption that loading within the physiological range will produce substantial microdamage with relatively few load cycles. The object of the first experiment was to determine threshold values required to consistently produce fatigue microdamage *in vivo*. The left forelimb of five groups of dogs, characterized by different strain levels and different numbers of load cycles, were loaded in three point bending. The number of microscopic fields which contained some microdamage was calculated as a percentage of the total number of fields. This experiment indicated that loads producing strains as low as 1500 microstrain on the radius and 1400 microstrain on the ulna for 10,000 cycles will produce significant bone microdamage. A second experiment was performed to verify this threshold and to determine whether microcracks are associated with the initiation of bone remodeling. Procedures in this experiment were the same as those in the first, except that all dogs were loaded in such a way as to produce strains on the radius of 1500 microstrain for 10,000 cycles, and the dogs were sacrificed 1–4 days after loading. The loaded limb demonstrated significantly more microdamage than the control limb ($p = 0.03$). Moreover, we observed 44 times as many microcracks in association with resorption spaces as expected by chance alone. These data support the hypothesis that fatigue microdamage is a significant factor in the initiation of intracortical bone remodeling.

INTRODUCTION

A recent paper presented a theory stating that repetitive stress initiates remodelling in compact bone (Martin and Burr, 1982). The theory is based on the observation that the lamellar structure of osteons arrests and traps microcracks in bone produced by cyclic loading (Carter and Hayes, 1977a,b; Dempster and Coleman, 1961; Frost, 1960; Tschantz and Rutishauser, 1967). Typically, the crack, upon reaching an osteon, enters the cement line and follows it for some distance. Alternatively, the crack may pass through the cement line to follow an interface between lamellae within an osteon. In either situation the crack would substantially debond or separate the Haversian canal from the surrounding bone. It was hypothesized that this osteon debonding causes physiologic changes to cells within the Haversian canal which lead to the repair of the damaged regions. The repair is effected by a new osteonal tunneling and refilling process emanating from the wall of the Haversian canal. This repair prevents the accumulation of microdamage due to repetitive loading and increases the fatigue life of compact bone.

The validity of this hypothesis rests in part on the assumption that loads within the physiological range will produce substantial amounts of microdamage with relatively few load cycles. If this were the case, the initiation of osteonal remodelling in response to microdamage accumulation could be a significant mechanism for the stimulation of bone turnover. The correctness of this hypothesis also rests on the demonstration that new osteonal cutting fronts occur in association with microcracks. This paper presents preliminary data which are the first to indicate: (1) the threshold values required to produce fatigue microdamage in bone *in vivo* and (2) that microcracks may be associated with bone resorption, the first step in making a new osteon. The purpose of this paper is solely to demonstrate that microdamage can be produced in a bone subjected to physiological strains, and that damage may be related to the remodelling function of osteons. No attempt is made in this paper to correlate strains with damage in any geographical sense around the bone cortex, although this problem is one which deserves investigation in future studies.

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MATERIALS AND METHODS

Experiment 1

Eleven skeletally mature male mongrel dogs, weighing 12–16 kg, were anesthetized and a uniaxial strain gage (Micromeasurements cat. no. EA-13-125AD-120) was bonded to the cranial (tensile) surface of the midshaft of the left radius. The forelimb bones in the dog are not fused, but are separated by an interosseous membrane for most of their length. The radius and ulna are stacked in the cranio–caudal plane, with the radius most cranial. This makes it possible to apply strain gages to the cranial surfaces of both the radius and ulna. The bones are approximately the same diameter proximally, but the radius expands distally while the ulna becomes smaller.

The left radius and ulna were repetitively loaded at 2 Hz *in vivo* in three point bending using the cam-operated device shown in Fig. 1. This device consisted of proximal and distal contoured and padded supports, each 2.5 cm wide, for the cranial surface of the

limb segment, and a central platen for the caudal surface. The loading platen was applied to the caudal surface of the limb directly below the strain gage. It was wider than the limb and 1.2 cm long. This is important because it caused application of a distributed rather than a concentrated load to the caudal surface of the ulna. The distributed nature of the load was further enhanced by the mass of soft tissues on the flexor surface of the forelimb between the loading platen and the ulna. The bending of the radius and ulna in this way was studied *in vitro* using axial strain gages on the cranial surfaces of both bones. These data indicated that strains on these two surfaces were comparable over a range of applied loads (Fig. 2). Strain magnitudes on the ulna were not significantly different from those on the radius at any of the loads used in our *in vivo* experiments. Only at very high loads, which produced nonphysiological strains, was the strain on the ulna greater than that on the radius. This is consistent with data in walking dogs which demonstrate that strain ranges on the radius and ulna are nearly equal (Caler, personal communication). The orientation of the applied load in our experiment was, necessarily, different than that in walking dogs. This may have produced nonphysiological strain distributions, but the strain magnitudes on both the radius and ulna were physiological. While the loading apparatus could have subjected the ulna to some stress concentrating effects, the mass of soft tissue between the point of load application and the ulna makes large stress concentrations unlikely.

During the *in vivo* treatment of the experimental dogs, strains were recorded on a chart recorder for the entire loading period. Dogs were divided into the five loading groups shown in Table 1. Strain levels were based on *in vivo* physiological levels previously measured by various researchers in dog radii *in vivo* (Carter *et al.*, 1980; Rubin and Lanyon, 1982; Caler *et al.*, 1982). These strain levels were chosen to correspond to the maximum and minimum ranges of tensile strain measured on the cranial surface of the dog radius *in vivo*. The right forelimb of each dog was not loaded and was used as an internal control.

Immediately following the load applications, the dogs were sacrificed and each radius and ulna from loaded and unloaded sides was removed. A 1 cm section of the loaded portion of the left radius and ulna, at the site of the load application and the strain gage, and a section from the same region of the right radius and ulna were cut from the bone using a Buehler Isomet metallurgical saw, and bulk stained in basic fuchsin for 3–4 weeks (Frost, 1960). Undecalcified hand ground sections 150 μm thick were cut from the center of each piece and viewed at 200× magnification. Microstructurally, 30–35% of the bone cortex was occupied by secondary osteons; the remainder of the cortex was occupied by remnants of secondary osteons, primary osteons and primary lamellar bone. This compares favourably with human bone, in which 45% of the cortex is composed of viable secondary osteons (Evans, 1982). A total of 81 cross sections from the three most heavily loaded groups of dogs each were examined in their entirety for the presence of microdamage. Since significant differences in experimental and control limbs were not found at strains below 1500 microstrain or numbers of cycles less than 10,000 animals in the two least heavily loaded groups were not

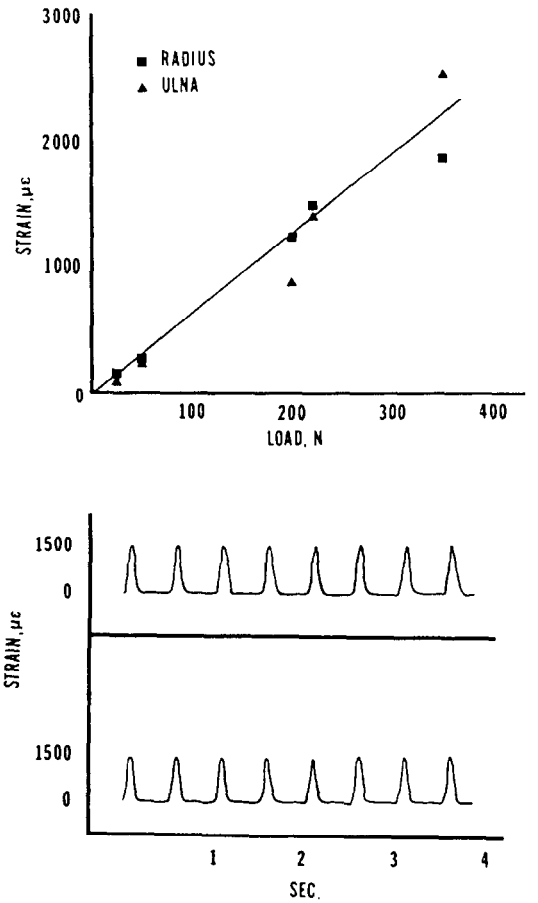

Fig. 2. Load strain curve demonstrating that strains on the radius and ulna are nearly equal at loads used throughout the experiments reported here. Only at high loads which produce nonphysiological strains was strain on the ulna greater than that on the radius. The lower diagrams compare the waveform of the strain on the radius and the ulna when the strain magnitudes on the radius are 1500 microstrain.

Table 1

Group 1	Group 2	Group 3	Group 4	Group 5
no load	625 με 100 cycles	625 με 1000 cycles	625 με 10,000 cycles	1500 με 10,000 cycles

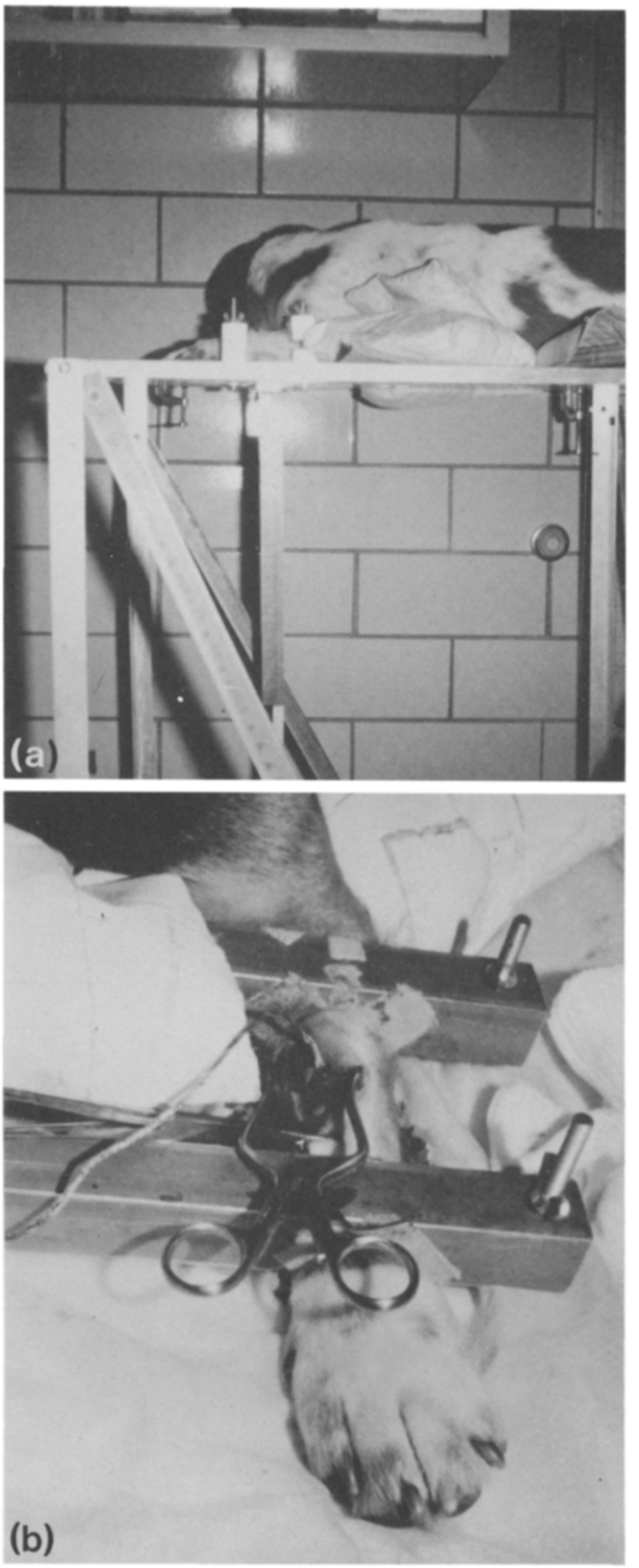

Fig. 1. (a) The cam-operated device used to load the dog *in vivo* in three point bending. (b) The limb was clamped and a uniaxial strain gage bonded to the radial midshaft.

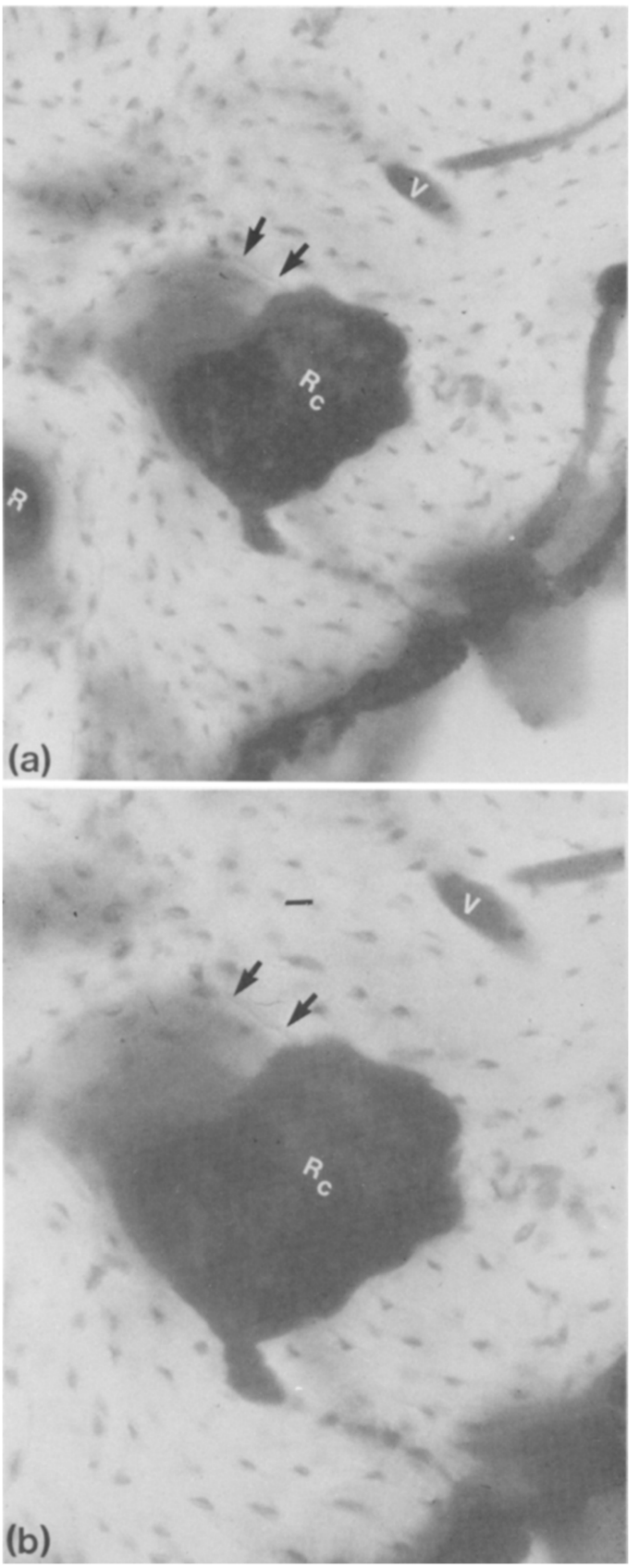

Fig. 5. (a) and (b)

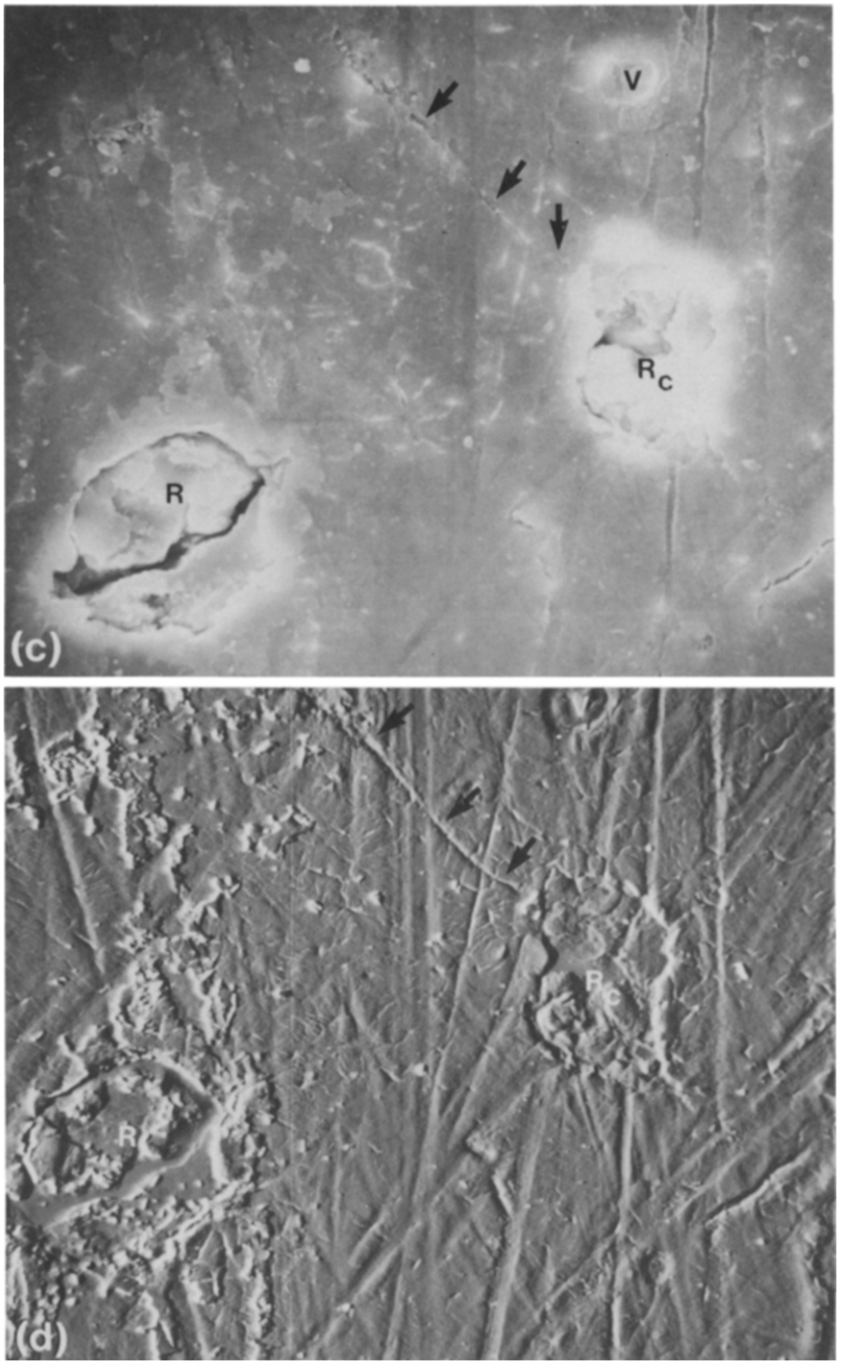

Fig. 5. (a) Photomicrograph of microcrack (arrows) in direct association with a resorption space. *V*, vascular channel; *Rc*, resorption space with associated crack; *R*, resorption space with no crack. 270 × (b) Higher power photomicrograph of (a). Since the crack is stained with basic fuschsin, it was present prior to preparation of the histological section. 370 × . (c) SEM image of (a). Although some preparation artifact can be seen, the crack demonstrated histologically is clearly present. The full extent of the crack was not observed histologically; the actual size of the crack seen on the scanning electron micrograph is much larger. Observation of microcracks from histological preparations in this study may have been a conservative measure of microdamage production. 200 × (d) Backscattered image of microcrack and resorption space in (a). The depth of the crack can be seen and easily distinguished from artifactual cracking not present on the histological section. 200 × .

examined. The number of 0.05 mm^2 fields in which some microdamage was observed was calculated as a percentage of the total number of fields. All counts were made blind.

The size of the groups in this first experiment did not permit a matched pairs statistical design, so loaded and unloaded limbs were treated as independent samples and compared using the Mann–Whitney U test. Since no difference could be demonstrated between strain magnitudes on the radius and ulna during loading, the radius and ulna were pooled to increase the sample size. Right and left sides for the pooled data were compared using the Student's *t*-test.

In order to standardize our observations as much as possible, microcracks were defined as having certain characteristics. Because in some cases microcracks were difficult to differentiate from cement lines, microcracks present in the bone were required to have sharp edges and some depth of field; cement lines have neither of these characteristics in our preparations. In addition, we required that the crack must involve more than one osteon, or have arisen from outside the osteonal cement line and have propagated into the osteon. This convention produced a bias for counting cracks larger than a certain length. All microcracks observed at 200 × magnification were verified at 400 × magnification. Because of the size bias and the magnification level used to examine the bone sections, many smaller microcracks were inevitably overlooked. This was unavoidable, but should present only a systematic error, and should not affect the comparison of loaded and unloaded extremities.

Experiment 2

A second experiment was performed both to verify the threshold found in our first experiment, and to determine whether microcracks could be found associated with bone resorption. Eight 12–16 kg skeletally mature male mongrel dogs were used. All procedures were the same as those in the first experiment, except that the radii of all dogs were treated at 1500 microstrain for 10,000 cycles; the dogs were not sacrificed immediately, but were killed 1, 2 or 4 days after loading to allow time for resorption to begin. Data were collected on microcracks cm^{-2}, porosity, resorption spaces cm^{-2}, and the number of microcracks directly associated with the cutting fronts of resorption spaces. Direct association in this context means that both the crack and cutting front were present in the same or in adjacent osteons. The data for this experiment were analyzed using a correlated *t*-test.

We attempted to verify that the cracks defined histologically were indeed microcracks by comparing our histological preparations with a scanning electron microscopic image of the structure. Regions of the bone cross section in which microcracks had been identified were photographed and mapped under the light microscope. These regions of the cross section were then cut out, mounted and sputter coated with gold. The mapped region was identified under SEM and then viewed at increasing magnification.

RESULTS

Experiment 1

Figure 3 shows the percentage of microscopic fields in which some microdamage was observed for experimental and control limbs of the dogs in the three most heavily loaded groups. Differences were found between loaded and unloaded radii of dogs in the 1500 microstrain group, but statistical significance could not be demonstrated. Statistically significant differences ($p < 0.025$) were found between loaded and unloaded ulnae of dogs in this group and, when the sample size was increased by pooling data from radius

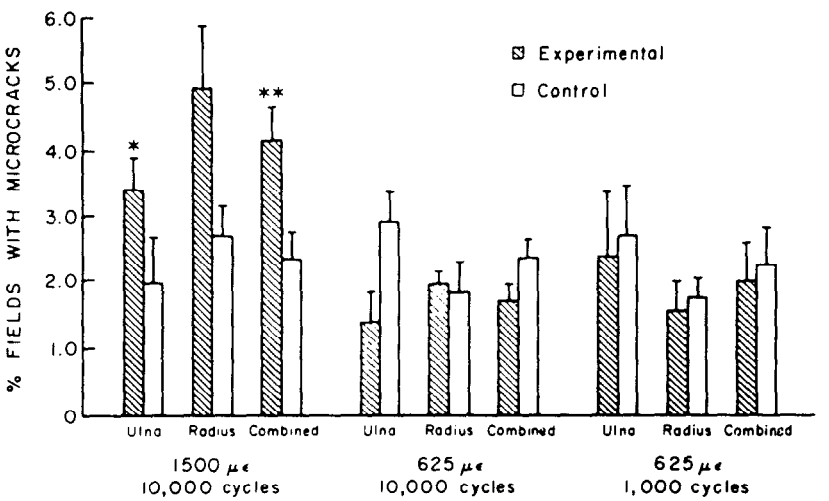

Fig. 3. The effects of strain magnitude and number of cycles on microdamage production. Significant differences in microdamage between experimental and control limbs were found after 10,000 cycles for strains at the upper limit of the physiological range (1500 microstrain).

and ulna, highly significant differences ($p < 0.005$) were found between loaded and unloaded limbs of this group. Every cross-section was studied over its entire surface, and there was no indication of regional concentrations of microdamage in any of the dogs, either directly over the area of contact with the loading platen, or elsewhere.

No significant differences were found between loaded and unloaded limbs of either of the 625 microstrain groups, even for pooled data. There were no significant differences between groups in microdamage accumulation in the unloaded limbs, as would be expected. Finally, the loaded limb of the 1500 microstrain group demonstrated significantly more microdamage than the loaded limbs of the other two groups.

Experiment 2

Figure 4 shows the number of microcracks cm^{-2} found in the loaded and non-loaded limbs of each dog sacrificed 1, 2 or 4 days after the loading applications. Differences between experimental and control sides were fairly consistent, but because of the small sample size statistical significance could not be demonstrated when the radii or ulnae were analyzed separately. When the radii and ulnae were pooled to increase the sample size, the loaded limb demonstrated significantly ($p = 0.03$) more microdamage than the non-loaded limb. The differences between experimental and control limbs are quite subtle, and perhaps could be better demonstrated with a larger sample of experimental animals. Nevertheless, the significant differences between experimental and control limbs verifies the results of our initial experiment which suggested that microdamage can be produced at 1500 microstrain with only 10,000 cycles.

We observed many microcracks in association with the cutting fronts of resorption spaces. Figure 5 shows light microscopic, SEM and backscattered images of one example found in a 1 day dog. The microcrack was

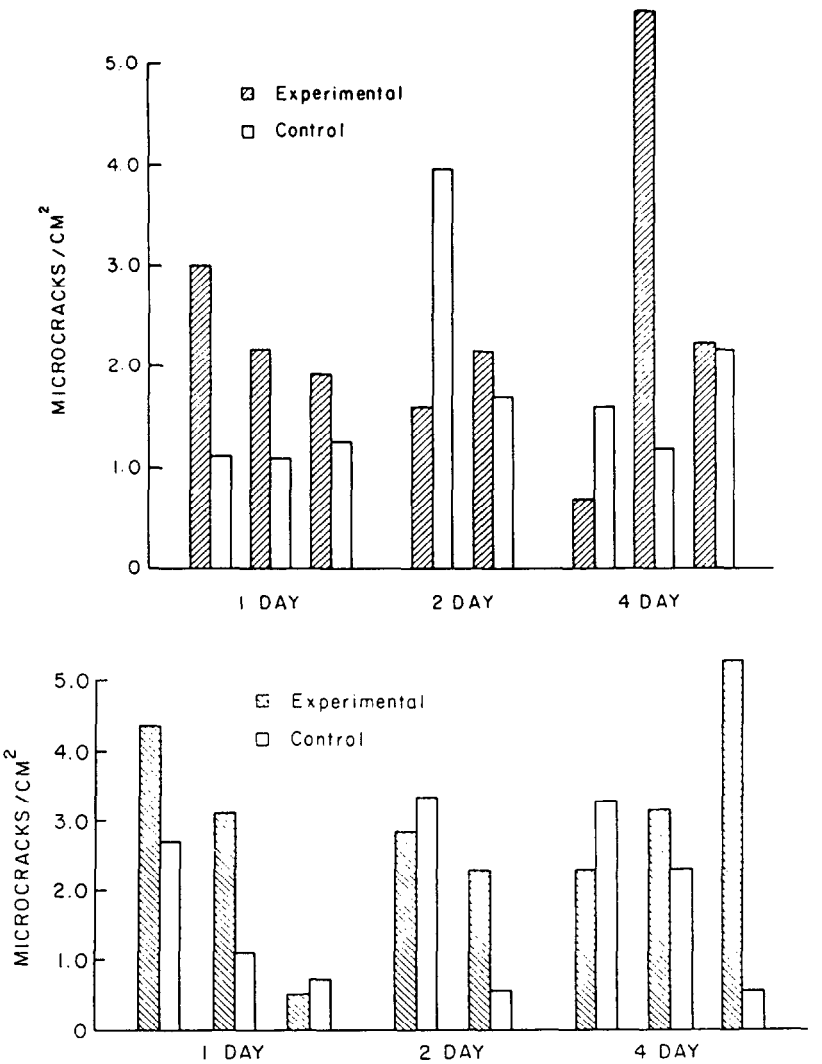

Fig. 4. The number of microcracks cm^{-2} found in experimental and control (a) radius and (b) ulna of each dog sacrificed 1 to 4 days after load application. Each pair of bars represents a single animal.

histologically stained so that it must have been present prior to cutting and grinding. The scalloped edges of the resorption space are characteristic of Howship's lacunae, and suggest that resorption was occurring in the direction of the damaged region of bone at the time the dog was sacrificed. Since the sample specimens were not prepared initially for viewing with the scanning electron microscope, there is some surface scratching of the SEM images caused by the grinding and processing of the specimen for histological analysis. However, the crack identified histologically can be clearly distinguished both from the diffuse shrinkage artifact and from grinding artifact. This demonstrates the value of using both histological preparations and electron microscopy, since histologically the microcrack was stained and must have been present prior to cutting and grinding. The use of the backscattered image appears to be the best method for distinguishing microcracks.

An important question is whether or not the observed frequency of association between resorption cavities and microcracks was significantly higher than that to be expected from a purely random process. If higher, the argument that microcracks are the stimulus for cellular differentiation leading to bone resorption and subsequent osteon formation is strengthened.

To answer this question, the following analysis was done. Let the following independent probabilities be defined:

R = the probability that an osteon contains a resorption cavity

C = the probability that an osteon contains a crack

C' = the probability that an osteon either contains a crack or shares a cracked cement line with an adjacent osteon.

Given the size of osteons in dogs, it is difficult for an osteon to be adjacent to more than seven other osteons. It is assumed, therefore, that

$$C' < 7C. \tag{1}$$

If d is the density of osteons (no. cm^{-2}) on a cross section, and c is the number of microcracks cm^{-2}, one has

$$c = Cd. \tag{2}$$

Similarly, if r is the number of resorption spaces cm^{-2}, one has

$$r = Rd. \tag{3}$$

The probability that an osteon containing a resorption cavity will also contain a crack, or share a cracked cement line with an adjacent osteon, is

$$C'' = RC'. \tag{4}$$

Then the expected number of such osteons cm^{-2} is

$$n = C''d \tag{5}$$

and

$$n < 7(RC)d. \tag{6}$$

Substituting from equations (2) and (3), the expected fraction of microcracks associated with resorption spaces in a purely random situation, would be

$$n < 7(rc)/d. \tag{7}$$

In the animals examined one day after loading at 1500 microstrain for 10,000 cycles, the following means were obtained for the loaded side:

$$r = 0.093\ cm^{-2}.$$
$$c = 0.0132\ cm^{-2}.$$

The osteon density was not counted for the analyzed sections, but examination of adjacent sections from these same dogs shows that this variable ranges from 5 to $15\ cm^{-2}$. Choosing the middle of this range and substituting these values into equation (7), one obtains

$$n < (0.093)(0.0132)/10$$
$$< 0.000123\ cm^{-2}.$$

The actual mean value of n for these dogs was $0.00537\ cm^{-2}$. The observed value is 44 times larger than that expected by chance. Even allowing considerable margins for error in this analysis, the result strongly supports the conclusion that the association between microcracks and resorption cavities in these experiments was not simply fortuitous, but based on a physiologic response.

DISCUSSION

Microcracks, probably caused by fatigue, are normally present in Haversian bone (Frost, 1960; Tschantz and Rutishauser, 1967; Devas, 1975), and accumulated microdamage caused by repetitive loads will eventually lead to catastrophic failure (Kenny and Campbell, 1966). Fatigue failure of bone is resisted as much by the efficiency of the repair process in bone as by its ability to arrest crack propagation (Wainwright *et al.*, 1976). It is important that mechanisms exist not only for stopping crack propagation, but also for the repair and remodelling of the damaged region. Previous investigators who have reported that Haversian bone is mechanically weaker in bending and tension than primary bone (Currey, 1959, 1962, 1975; Walmsley and Smith, 1957; Hert *et al.*, 1965; Evans and Vincentelli, 1969; Evans, 1976; Saha, 1974; Saha and Hayes, 1974, 1977; Cartwright, 1975; Wright and Hayes, 1976; Reilly *et al.*, 1974; Carter *et al.*, 1976; Carter and Hayes, 1976, 1977a, b), or is less able than primary bone to withstand fatigue (Carter *et al.*, 1976; Carter and Hayes, 1976, 1977a, b) were primarily concerned with the properties of bone *in vitro* and did not consider the effects of bone remodelling *in vivo* on fatigue life. Frost (1966) and others (Tschantz and Rutishauser, 1967; Chamay, 1970; Chamay and Tschantz, 1972; Swanson *et al.*, 1971; Baker *et al.*, 1972; Enlow, 1977; Hylander, 1979) have suggested a cause and effect relationship between the accumulation of fatigue damage *in vivo* and the stimulation of bone remodelling in the damaged areas. The data of Carter

and Hayes (1977a) are particularly consistent with this hypothesis.

It is well known that osteons act as crack arrestors in bone through a concentric lamellar structure which arrests and traps cracks. Failure at weak interfaces by delamination at the cement lines deflects and traps the crack, increasing fracture toughness and extending the bone's fatigue life (Piekarski, 1970; Ascenzi and Bonucci, 1967; Dempster and Coleman, 1961; Currey, 1962; McElhaney and Byars, 1965; Sweeney *et al.*, 1965; Cooke *et al.*, 1973; Margel-Robertson, 1973; Pope and Murphy, 1974; Simkin and Robin, 1974; Saha, 1974a, b, 1975; Saha and Hayes, 1977; Bonfield and Li, 1966).

Martin and Burr (1982) recently extended these observations by suggesting specific mechanisms through which osteonal remodeling could occur as a reparative reaction in response to microdamage accumulation. *In vivo* fatigue experiments to verify such a cause and effect relationship between microdamage and osteonal remodelling have never shown unequivocally that bone remodelling occurs preferentially in fatigue damaged regions. However, data from the present study supports such a cause and effect relationship, and emphasizes that neither the loads nor the duration of loading required to produce damage is beyond reasonable physiologic limits. This study indicates that loads at the upper limit of the physiological range can produce significant amounts of microdamage within 10,000 cycles. Only 11 miles of running will produce 10,000 load cycles on the forelimb of a 14 kg dog at strains close to 1500 microstrain. This may be equivalent to only one or two days activity.

This is consistent with the *in vitro* data of Carter and Hayes (1977a) and Carter *et al.* (1981a, b). They observed an almost immediate loss of bone stiffness and increased hysteresis in uniaxial fatigue loading of human femoral cortical bone *in vitro*. This is similar to the fatigue behaviour of other composite materials, in which these changes are attributed to the production and accumulation of diffuse microstructural damage. Carter *et al.* (1981a, p. 469) state, 'This extremely low value for fatigue strength would indicate that human cortical bone is constantly accumulating fatigue damage during normal daily activities. The normal process of bone remodelling would thus be a prerequisite to the long-term structural integrity of the skeletal system.' This is also consistent with the *in vivo* data of Rubin and Lanyon (1984) and O'Connor *et al.* (1982) which suggest that bone remodelling can be induced with only a few load cycles. Our finding that substantial microdamage can accumulate in bone with only a few days activity suggests that physiological repair of this damage is indeed necessary to maintain the mechanical integrity of bone over rather short periods of time. The implication of this is that some mechanism of preferential microdamage repair must occur in regions with moderate microdamage accumulation. If this were true, we should expect to see the initiation of bone remodelling—i.e. bone resorption—within a few days after the production of the damage. In our study, the frequency with which microcracks were observed in direct association with bone resorption was 44 times higher than expected by chance alone. This argues against the concept (Lanyon *et al.*, 1982) that sufficient microdamage to cause bone remodelling cannot be produced in relatively short periods of time, and supports the hypothesis that microcracks may be a direct and significant stimulus to osteonal remodelling. In this sense, we support the statements of Carter *et al.* (1981a) that fatigue damage accumulated during everyday activities would need to be repaired immediately to maintain the structural integrity of the skeletal system.

Intermittent loading is known to be a more significant stimulus to intracortical remodelling than is continuous stress (Hert *et al.*, 1969; 1972; Liskova, 1965; Liskova and Hert, 1971; Chamay and Tschantz, 1972; Punjabi *et al.*, 1979; Churches *et al.*, 1979). Without repair repetitive cyclic loads can cause bone to fail at stress levels that are only 25–30 % of the ultimate bending strength (Lafferty *et al.*, 1977; Carter and Hayes, 1977b). Increased remodelling rates in cyclically loaded bone highly vulnerable to fatigue damage suggests a nonrandom process of remodelling in which replacement of bone is intensified by some factor in the fatigue process. This is supported by the work of Bouvier and Hylander (1981) who examined the effects of hard and soft diets on the internal morphology of the macaque mandible. They found greater bone remodelling in monkeys eating a hard diet than in monkeys fed a soft diet, and a greater percentage of secondary osteonal bone at sites subjected to the greatest fatigue. They suggested that this was an adaptive mechanism to repair mandibular bone fatigued by the higher strains and/or increased number of load cycles. These data support the view that Haversian remodelling is preferentially stimulated by cyclic loading in areas where fatigue damage is most severe.

The replacement of fatigued bone was demonstrated by Tschantz and Rutishauser (1967), who overloaded dog ulnae by resecting a portion of the radius. They found osteoclasia and osteogenesis occurring in fatigue damaged regions of the dog ulnar cortex. The remodelling response was more marked in regions in which fatigue microdamage was most extensive. While a relationship between the damage and the remodelling is implied in this work, a definite association between specific lesions and the remodelling process was not sought. Furthermore, the study is hindered by the surgical intervention, which in itself could have produced damage or accelerated remodelling. The present experiments, on the other hand, demonstrate that bone resorption occurs in direct association with microcracks, and that the cutting front of the resorption space often appears to be directed towards the area of damage (Fig. 5).

It is likely that the strain environment is an integral part of the stimulus for bone remodelling (Lanyon and

Baggot, 1976; Lanyon and Bourn, 1979; Lanyon *et al.*, 1979, 1982; Goodship *et al.*, 1979; O'Connor *et al.*, 1982). It is now clear that fatigue processes in bone are controlled by cyclic strain range rather than by stress range (Carter *et al.*, 1981b). Fatigue failure of bone *in vivo* generally occurs from repetitive loads generated by daily activities such as walking and running which involve no strain overload and frequencies on the order of 1–3 Hz. Thus it may be that microdamage alone, rather than stress or strain levels *per se*, stimulates intracortical repair and remodelling of bone.

A recent article presents compelling evidence that intracortical osteonal remodelling is not directly influenced by change in strain, although surface formation may be. O'Conner *et al.* (1982) reported that the maximum strain rate ratio (the ratio between the maximum rate of strain during artificial loading and that during normal locomotion) accounted for 68–81% of the total variance in surface bone formation, but accounted for only 43% of the variance in secondary osteonal remodelling. The addition of another strain related variable (maximum strain rate imposed on the cranial surface of the radius) accounted for only an additional 13% of the total variance in osteonal remodelling. This is intriguing evidence that surface and intracortical remodelling may be initiated, influenced or controlled by different factors. The large proportion of variance in periosteal new bone formation accounted for by the maximum strain rate ratio suggests that surface bone formation acts to equilibrate stress and strain, a suggestion which is supported by other research (Martin and Atkinson, 1977). Thus, the low correlation between maximum strain rate ratio and Haversian remodelling further argues against any direct association between the strain regime and intracortical remodelling, but does not rule out the possibility that strain-induced microdamage is closely associated with the adaptive remodelling response.

CONCLUSIONS

The results of this study demonstrate that neither the loads nor the duration of loading required to produce significant microdamage to cortical bone is beyond reasonable physiological limits. The demonstration that substantial microdamage can accumulate in bone with only a few days activity suggests that physiological repair of this damage is an important mechanism for maintenance of the mechanical integrity of bone over short periods of time. The demonstration that microcracks were associated with bone resorption spaces 44 times more often than expected by chance alone suggests a direct cause and effect relationship between microdamage production and intracortical remodelling, and emphasizes the capacity of bone to preferentially repair microdamaged areas of bone cortex.

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