The Biological Mechanisms of Tooth Eruption and Root Resorption,
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Is tissue resorption and replacement in permanent teeth of mammals caused by stress-induced hypocalcemia?

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Summary

Natural resorption and repair of tissues in permanent teeth of mammals are often attributed to restricted odontoclastic and cementoclastic activity under localized control. I suggest that in addition to the well known local causes, systemic alteration of dental tissues caused by regulation of blood-serum calcium is common also. This newly recognized type of tissue alteration apparently affects teeth internally and externally, and interferes with normal rates of tissue calcification as well. Causal connections between systemic alteration in tooth tissues and stress-induced low serum calcium (hypocalcemia) in mammals are indicated by this study but are not directly demonstrated. Two theoretical models are presented that explain how certain manifestations of stress may produce different responses and results.

Introduction

Localized dental resorption and repair

Many dental scientists view resorption and repair of tissue in permanent teeth as having strictly proximate causes. It is thought that odontoclastic or cementoclastic activity occurs in response to local injury, pressure, disease or malocclusion. Most alteration occurs in external cementum of root bases of single teeth or a few adjacent teeth, although penetration into dentine is not unusual. More importantly, this type of tissue alteration is reportedly not directly influenced by systemic episodes or events. This has led many workers to conclude that in most cases, permanent teeth probably cannot respond to systemic control and that there are no other important factors responsible for resorption and repair of tooth tissues beyond those of exclusively local origin (Fish 1932; Kronfeld 1949; Ferguson and Hartles 1964; Scott and Symons 1964; Jenkins 1966; Jones and Boyde 1971; Rasmussen 1972; Eanes and Termine 1983; Veis and Sabsay 1983).

Systemic dental resorption and repair

There are many reasons for thinking that, although locally induced alteration may be common, it may not be the only major mechanism. Our knowledge of calcium kinetics is already adequate to construct a fairly convincing *prima facie* case for systemic resorption and repair in teeth, and the evidence seems at least plausible, even if the resorption has not been reported before.

1. Calcium is critically important to virtually all of a mammal's physiological processes (Martin 1985; Miller 1987). 2. Teeth are a rich calcium source, with the same percentages of calcium phosphate as bone (Eannes and Termine 1983). 3. Presumably, teeth are affected by the same cells, hormones (Boyde, Ali and Jones 1984, 1985; Thoma 1954; Sullivan and Jolly 1957; Scott and Symons 1964), and processes that build and destroy bone tissue (Symonds *et al.* 1966; Braithwaite, Glascock and Riazuddin 1969; Parfitt 1976). 4. In addition, dental formative surfaces are attended by and exposed to the same circulatory system that delivers calciostatic hormones to bone (Saunders and Röckert 1967).

In mammals, under at least several stressful conditions, including giving birth (parturition), blood serum calcium may temporarily fall below the normal range. Low serum calcium (hypocalcemia) occurs because calcium intake into the blood is exceeded by calcium loss from circulation. Restoration of serum calcium to normal levels is usually brought about when calcium is borrowed from the body's solid, semifluid and fluid calcium compartments, such as bone and extracellular tissues. The resulting calcium debt in non-serum calcium compartments is due to actions of serum parathyroid hormone (PTH) on bone cells and on

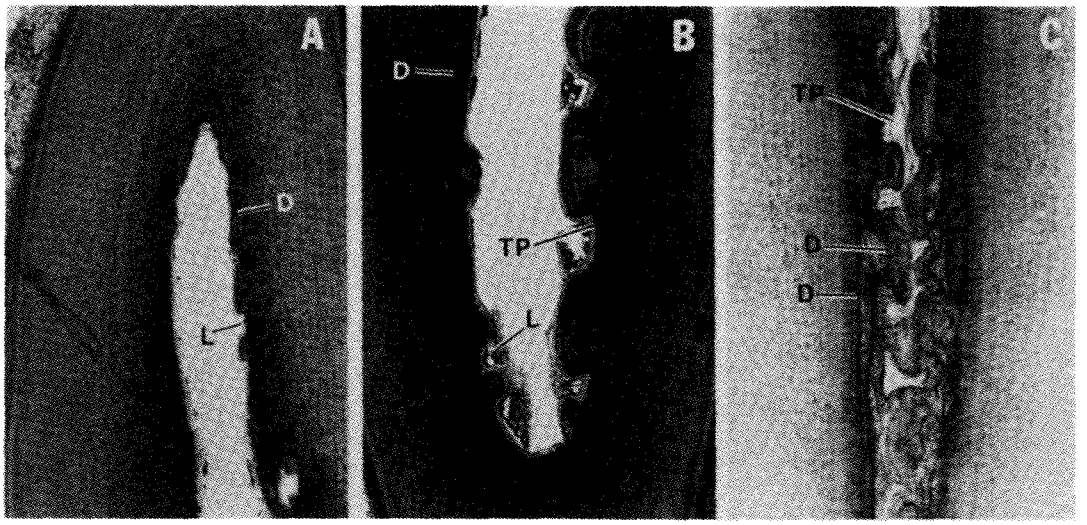

Fig. 1 Progressive stages of mineralization interference in dentine along pulpal margin in dolphin teeth. A. Incipient stage of local interference (L) on right side and regional interference on left side. Usually dark layer (D) of dentine appears to define a break in the regular layering pattern. B. Intermediate stage showing scalloped development typical of localized interference and thickened predentine (TP) within scallops. C. Advanced stage of interference showing convoluted scallops with noticeably thickened predentine.

ionic enzyme pumps that transfer calcium across compartmental membranes to blood (Braithwaite *et al.* 1969; Parfitt 1976; Gorbman *et al.* 1983). The calcium debt is usually repaid after conditions normalize, but during hypocalcemic conditions every accessible calcium source, including teeth, should be affected.

This report has three major objectives. The first is to describe a previously unrecognized mechanism for dental-tissue alteration in mammals that apparently responds to systemic calcium regulation. The second is to consider the yet unproven likelihood that stressors, changes in serum calcium and tooth-tissue alteration are causally related. The third objective is to illustrate some effects of stress on serum calcium by proposing two theoretical models involving cases of hypocalcemia, in this study and in reports by others.

Methods and materials

Dental-tissue-alteration samples

The present study came about serendipitously. I first recognized resorption and reparation features in decalcified and stained thin sections of dolphin teeth during age estimation studies (Myrick *et al.* 1983). Initial examination of a few hundred teeth indicated the need for a thorough study of dental tissue alteration in dolphins. I concluded the study on dolphins after having microscopically examined teeth from more than 2500 individuals.

The samples included teeth from spinner *(Stenella longirostris)*, spotted *(Stenella attenuata)* and common *(Delphinus delphis)* dolphins, killed in an eastern Pacific commercial purse-seine fishery in which dolphins are chased and netted to catch the yellowfin tuna that follow the dolphin schools (Perrin 1969; Perrin, Coe and Zweifel 1976). The samples also included teeth from bottlenose dolphins *(Tursiops truncatus)*, which are not affected by a fishery; these were collected primarily from carcasses beached along the coasts of California and Baja California.

Each sample contained specimens of all ages and both sexes, except common dolphins of which only males were available. In about 300 of the more than 2500 specimens, from two to six teeth of single individuals had been prepared. These permitted me to compare features in two or more teeth from the same animal in slightly more than 10% of the specimens examined.

In addition, to determine whether similar dental-tissue alteration occurred in other mammals, I examined thin sections of teeth from 9 Montana black bears *(Ursus americanus)*, 10 Rocky Mountain elk *(Cervus elaphus)* and 1 bobcat *(Felis rufus)* from New Mexico. I also studied photographs of teeth from other mammals, including humans.

Results

Dolphin teeth

The dolphin teeth showed the effects of alteration in various stages, in various combinations, with and without repair and with and without evidence of repetition of resorption and repair. I recognized three basic forms of alteration. Each form showed one or more types of physical expression (types). All three forms apparently originated at the for-

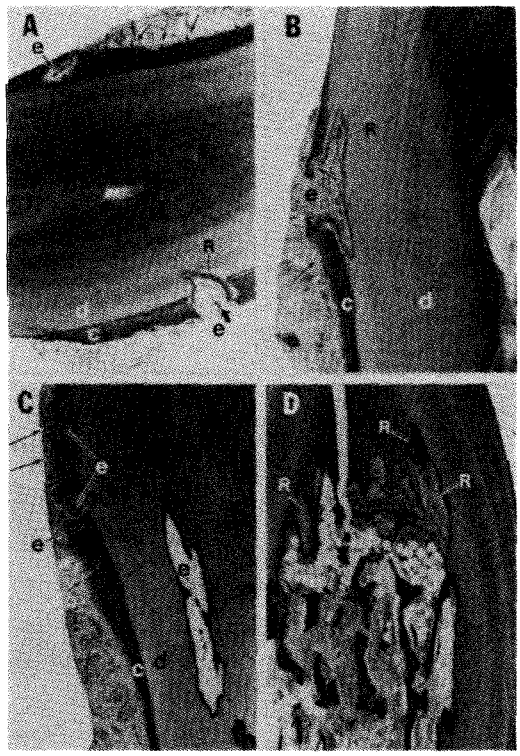

Fig. 2 Stages of excavational resorption in cementum (c) and dentine (d) of dolphin teeth. A. Earlier resorption of tooth is marked by partially repaired (R) excavations (e) on each border. Arrows indicate possibly new resorption activity. B. Example of more extensive excavational resorption which has been lined with reparative material (R). Arrows indicate possible second cycle of resorption. C. Advanced stage with arrested activity within cementum (e) and apparently active unrepaired areas in dentine (e). Arrows show areas of possible impending second cycle of cemental resorption. D. Severe resorption features indicating, by crosscutting lines, activity has been repeated. Fibrous tissue fills lower portion of resorption cavity. (R indicates areas repaired by bone- or cementum-like materials.)

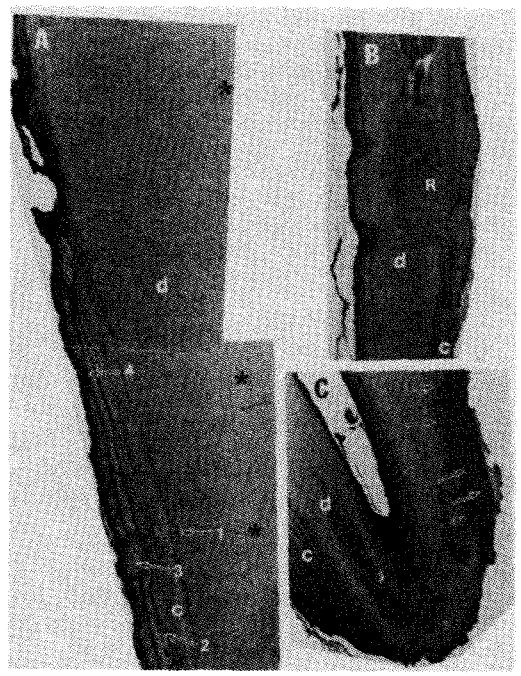

Fig. 3 Resorption in dental tissues of black bears. A. Numbered arrows indicate series of resorption episodes in cementum. Number 1 indicates areal resorption with repair that crosscuts the dentinal (d) layers. Other numbers indicate combinations of areal and excavational resorption with repair. Asterisks indicate possible local mineralization interference along dark line that may represent regional interference. B. Opposite side of tooth shown in 3A. Wide, irregular reversal line caused by areal resorption apparently done in second winter with repair (R) completed before third winter. C. View of tooth of bear older than that represented by 3A and B. Cycle-like minor areal resorption (arrows) in cementum (c) with repair indicating activity was concurrent with dark layer formation.

mative surfaces of dentine (along the pulpal margin) and cementum (along the external surface of the root).

1. Mineralization interference (develops continuously). This was so-named because the affected tissues appeared either never to have been properly mineralized or because mineralization was delayed while the protein matrix continued to form.

Interference was recognizable by some abrupt change in the pattern of layers (Fig. 1), usually a strong discontinuity in pattern or a layer that was especially dark, followed by a gap in layering (similarly stained layers were interpreted by Klevezal and Myrick [1984] as indicating parturition in mature female dolphins). The layering hiatus was followed in turn by a noticeably thickened unmineralized predentine or precementum.

This form of alteration was of two types: 1) regional, which occurred along extensive portions of a formative surface, and 2) local, which occurred at regularly spaced sites along a formative surface. Regional interference in cementum often showed unusually thin mineralized cemental tissue. Local interference was identifiable by wavy (early stage) to scalloped (advanced stage) tissue margins with layers usually evenly spaced in the convex portion and squeezed together (but not truncated) in the concave portion (Figs. 1B and C). Neither of the two types of *mineralization interference showed repair.* Because of the absence of replacement materials and because the alteration evidence was parallel to the formative surfaces, regional interference was the most difficult to detect. Presumably many cases of this type of alteration escaped my notice.

2. Areal Resorption (develops continuously). Areal resorption showed massive removal of tissue sub-parallel to the layering plane, such that resorptive edges (or reversal lines) cut incongruently as a wide front across layers next to resorption areas (Fig. 3). Areal resorption was not ac-

companied by thickened predentine or precementum. Additionally, in some specimens partial repair of resorbed areas by cementum- or bone-like material occurred.

3. Excavational Resportion (known also as "dissection resorption" or "tunneling resorption" when found in bone [Grech *et al.* 1985]). This form of alteration was easily defined because it occurred in many stages of development. Reversal lines were almost always without any particular orientation. I recognized nine stages from incipient to advanced, which I define below:

Stages

A. formative margins with slight depressions which tend to truncate tissue layers;
B. depressions deepened, becoming pit-like;
C. pits tend to be elongated, forming short tunnels;
D. C stage with replacement bony tissue;
E. long tunnels, directed inwardly toward dentine if originated from cementum, but coincide with orientation layers if from dentine;
F. E stage with replacement bone or other repair tissue;
G. expanded and elongated tunnels, usually penetrating dentine if from cementum, tending to obliterate large areas of dentine and pulpal margin if internal in origin;
H. G stage with replacement bone or other tissue;
I. G, H and earlier stages with crosscutting tissues indicative of separate, repeated alteration reactions.

Of the stages of excavational resorption, I regarded C through E as intermediate, and F through I as advanced (Figs. 2A-D).

Replacement of resorbed areas in dolphin teeth usually was with cementum-like or bone-like materials. Reparation with dentine was never observed. In most of the specimens that had undergone replacement activity, the repair materials usually only lined or partially filled (i.e., they rarely were completely filled) the resorbed region (Figs. 2B-D). To a noticeable extent reparation materials included fibrotic tissue (Fig. 2D) similar to that described in cases of human idiopathic resorption of teeth (Thoma 1954; Goldman 1954; Sullivan and Jolly 1957).

Nearly all specimens in the dolphin-tooth samples revealed at least incipient stages of one or more alteration forms. In approximately 90% of the more than 300 specimens in which more than one tooth was available from an individual, each of its teeth showed the same alteration form(s) and at least similar stages of alteration.

To estimate the extent of some of the different forms of alteration among the samples, I made some preliminary counts, by sex and species, of several forms and stages of alteration (Table 1). To test for significance of results, I used variance tests for homogeneity in proportions (Snedecor and Cochran 1973). A tally of male and female spinner dolphins significantly showed that the presence of regional mineralization interference in cementum was detected in females more than twice as often as in males (64% vs. 28%). Female spinner dolphins showed almost no (1%) detectable sign of regional and local mineralization interference in dentine whereas 28% of female spotted dolphins exhibited both types of interference alteration; this difference was significant. Of the four dolphin species, my counts of specimens showing intermediate or advanced excavational resorption for cementum indicated a significantly higher incidence in spinner dolphins than any other species. For excavational resorption, female spinner dolphins showed nearly twice the detectable frequency as male spinner dolphins. Bottlenose dolphins, the one sample not collected in the purse-seine fishery, had the lowest incidence of this alteration form. However, two other species samples that were from the fishery (common dolphin males and spotted dolphin males and females) did not have significantly higher percentages than the bottlenose dolphins for this form. These preliminary comparisons indicated that activity in such alteration forms differed by species and sex, and at least for cementum of spinner dolphins, females showed substantially more alteration than males.

Table 1. Sex and species differences in degree and frequency of some types of dental tissue alteration in mature dolphins.

Species	Sex	Number in Subsample	Tissue and Alteration Form			
			CEMENTUM: Regional Mineralization Interference			
			%	(N)		
1. *S.longirostris*	female	*200	64	(128)		
2. *S.longirostris*	male	150	28	(42)		
			DENTINE: Regional and Local Mineralization Interference			
			%	(N)		
1. *S.longirostris*	female	*420	1	(4)		
2. *S.attenuata*	female	*316	28	(90)		
			CEMENTUM: Excavational Resorption			
			Intermediate and Advanced		Advanced Only	
			%	(N)	%	(N)
1. *S.longirostris*	female	782	30	(235)	15	(112)
2. *S.longirostris*	male	710	17	(120)	8	(57)
3. *D.delphis*	male	59	3	(2)	3	(2)
4. *T.truncatus*	male & female	141	1	(2)	1	(1)
5. *S.attenuata*	male & female	*335	3	(10)	1	(5)

*Indicates that some of the same specimens of a subsample were used to evaluate two or more types of alteration.

Human teeth: idiopathic resorption

Dolphin teeth showing intermediate and advanced stages of excavational resorption were identical in almost every detail to photographs of human teeth depicting "idiopathic resorption" (hereafter referred to as I.R.) (Sullivan

and Jolly 1957; Stanley 1965). Published photographs and descriptions indicated that I.R. invasion starts either from within the pulp cavity, so-called "internal resorption," or along the outside surface of the root, "external resorption" (Thoma 1954; Stanley 1965; Fullmer 1984). Both patterns of invasion were in dolphin-tooth samples also. As in excavational resorption seen in dolphins, most tunneling in I.R. examples is without specific orientation.

Because I could detect no important differences between dolphin excavational resorption and human I.R., I suggest that they were derived by similar processes. In advanced I.R., large amounts of original tissue were absent and pulpal margins were obliterated. Repeated crosscutting of resorption and repair structures (Sullivan and Jolly 1957; Stanley 1965) was similar to that in advanced stages of excavational resorption in the dolphin teeth. Like much of the reparation in the dolphin teeth, I.R. cases (Thoma 1954; Stanley 1965) indicate that repair material is of bony, cemental and fibrotic tissue, which often incompletely fills the resorption cavities.

Teeth of other mammals

Seven black bear specimens, the bobcat specimen and all ten elk teeth showed features of dental-tissue alteration. Photographs of teeth of racoons, a badger, river otters, coyotes, domestic sheep, mule deer and moose (provided at random by G. Matson) revealed alteration and repair features as well.

Black bears

Dentine of most black bear specimens showed only a few thin layers with some waviness, which I interpreted as minor regional and localized mineralization interference. However, all three forms of alteration in cementum, resembling those in dolphin specimens, occurred in several bear specimens. Especially obvious were repeated excavational resorption features alternating with repair materials and areal resorption structures.

The tooth of a five-year-old bear showed three forms of alteration in cementum and two in dentine (Fig. 3). The cementum contained a succession of reversal lines that delimited repeated local excavational resorption of tissue formed earlier. Peripheral to the sites of resorption, each reversal line was continuous with a corresponding thin, straight, dark-stained, cemental layer that marks the end of a year's deposition, i.e., formed just before hibernation (Stoneberg and Jonkel 1966). This indicated to me that resorption activity began during or shortly after deposition of a dark layer. Based on the sequence of crosscutting reversal lines, at least four such resorption periods must have occurred in this animal's lifetime, each separated by about a year (i.e., an annual layer) (Figs. 3A and B). The most severe response apparently was in the second annual resorption period, interpreted from cemental layers as the second winter of life. This was indicated by extensive areal resorption along a broad front that transgressed the dentine at an angle to its layers on both sides of the tooth. Despite the presumed severity of the resorption, complete repair was accomplished by the early part of the following year, well before the formation of the third dark layer.

Thus, most detectable alteration in the black-bear sample occurred in winter and was usually fully repaired before the following winter. Several specimens showed it to have occurred on a regular basis (i.e., every year or so).

Elk

The elk specimens revealed a variety of alteration features, although repeated cemental excavational resorption and local mineralization interference in the dentine occurred in all specimens. As in black bears, dark-stained winter cemental layers in the elk specimens (Keiss 1969) were associated with irregular reversal lines of excavational resorption showing usually (but not always) complete cycle-like repair. In some specimens, replacement materials of excavational resorption included fibrotic tissue, which resembled the advanced stages in human I.R. and dolphin excavational resorption. Scalloping of the pulpal margins as a result of local mineralization interference was in an advanced stage in the dentine of some of the elk. However, the scalloping was not as regularly spaced and had thinner marginal predentine than advanced examples in dolphins.

Thus for elk, detectable alteration activity occurred during the formation of the winter layer. Repeated patterns of such structural associations indicated that alteration tended to occur with regularity. Advanced stages of resorption and interference and occasionally incomplete repair, sometimes with fibrotic tissues, suggested severe responses with little recovery.

Bobcat

After a 30-pound male bobcat was killed in a trap near White Sands, New Mexico, on 28 January, 1986, one of its teeth was prepared for age determination. Its layered cementum indicated an age of about six years. A reversal line occurred in the cementum after the fifth dark annual layer had been deposited (i.e., in winter 1984-85). The reversal line showed excavational resorption through all previously formed cemental tissue, penetrating almost into the dentine. Before the bobcat died, a sixth dark layer had formed over an extensive resorption area that was incompletely repaired (Fig. 4).

After examining the bobcat specimen, I studied recent historical climatological data of the trap area. The data suggested possible connections between resorption and abnormally severe climate before and during the presumed time of resorption. Conditions were quite dry locally in 1983, with a winter (1983-84) of prolonged cold. Precipitation was only somewhat more than normal (14.88" vs. 12.35") in 1984-85 but all of it fell as snow. (The winter of

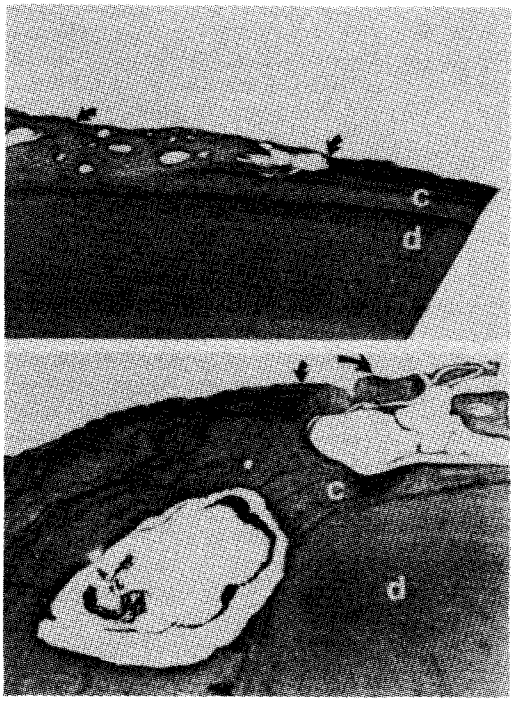

Fig. 4 Unrepaired cemental excavation in tooth of six-year-old bobcat (d = dentine, c = cementum). Five dark layers are truncated and damage is partially roofed over by a sixth dark layer (arrows). This is interpreted as resorption that occurred during the animal's fifth winter, which was relatively severe. Possibly, lingering ill health prevented repair of resorption damage.

1984-85 had a period of extreme cold with almost 15 inches of snow compared to a normal annual snowfall of zero inches.)

Thus, based on the position of the reversal line, resorption occurred after a year of abnormally cold temperatures and during the 1984-85 winter of record high snowfall. The evidence in this example was not strong; the bobcat's physical condition was unknown and its geographical position during the severe climate was only presumed to be near the trap site.

Discussion

Systemic control of tissue alteration

The study of the samples yielded strong evidence that the features of dental-tissue alteration observed were products of systemic—not local—control. Several of the most important points follow:

In the dolphin samples, when more than one tooth (up to six teeth) was available from an individual, each tooth usually showed the same forms and stages of alteration. Such a situation should be rare in localized alteration. In jaw samples from which dolphin teeth showing alteration had been removed, there were no signs of tumor, infection, or mechanical injury; such signs should be obvious in many cases of localized alteration. Usually the sites of resorption were not near root bases. Root-base resorption is common in locally induced resorption. In some dolphin species, features of alteration originating from within the pulp cavity were frequent, whereas local resorption usually originates externally. Frequency data indicated that females tended to have detectable alteration features twice as often as males of the same species; this could not be easily explained by localized control. Excavational resorption and fibrotic repair of dolphin teeth are evidence for hyperparathyroidism when it occurs in bone (Gaillard 1959; Rasmussen 1961; McLean and Urist 1968; Raisz 1976; Martin 1985; Grech *et al.* 1985). Repeated alteration and replacement were indicated within the same resorption site. Repetitious internal resorption and repair at the same site would be difficult to explain without invoking systemic processes.

In the cases of I.R. in human teeth (which I studied from descriptions and photographs in other reports), those features in dolphin teeth characteristic of hyperparathyroidism in bone, including dissection resorption (Gretch *et al.* 1985) and fibrotic replacement materials, occurred also in human teeth with I.R. (Thoma 1954; Goldman 1954; Sullivan and Jolly 1957). When I.R. is discovered, several teeth from adjacent or diverse positions are found, with some frequency, to be affected once or repeatedly over a short period in the same individual (Thoma 1954; Stanley 1965). The presence of damage in several teeth in otherwise apparently healthy humans is evidence for non-localized resorption factors. The unknown cause or causes of I.R. (Mummery 1920; Sullivan and Jolly 1957; Fullmer 1984) was taken as additional evidence of non-localized alteration. Symptoms have not been sufficiently consistent to identify ultimate cause because most cases have been discovered after the condition has reached advanced stages and caused pain (Sullivan and Jolly 1957; Stanley 1965). Patients in these cases reported no local pressure and experienced no local tumor, injury, infection or malocclusion, while the I.R. condition developed into advanced stages identical to those in excavational resorption seen in dolphin teeth.

Evidence from the bobcat study is weak because data were lacking concerning the bobcat's condition and whether the animal was a long-standing resident of the area in which it was trapped. Nevertheless, circumstantial evidence supports a (systemic) connection between cemental alteration and environmental conditions. The otherwise neatly layered cementum was presumably excavated suddenly in 1984-85, at about the time of the unusually harsh weather in the area.

Evidence was clear that dental alteration in the black bears and elk was under systemic control. Alteration features were repeatedly connected to winter periods. Of

striking importance was that activity resulting in complete replacement almost always occurred between winter resorption bouts. Cyclic control of such well-timed alteration in so many individuals could be most easily explained by systemic controlling factors.

Implications of systemic control

In this report I have marshaled evidence that a previously unrecognized type of dental-tissue alteration may commonly affect distantly related mammals and that this alteration is under systemic control. If this is correct, then the proximate controller is serum calcium, just as it is in bone-calcium turnover.

Under hypocalcemia, calcium-borrowing is initiated by actions of increased serum PTH. I presume that when calcium is borrowed from tissues or fluids near the teeth, tooth tissues would be resorbed by activity of clastic cells, or mineralization interference would occur as calcium ions are drawn away from mineralization sites. In normocalcemia, PTH activity is suppressed, calcium is deposited at normal rates and any calcium debt accrued by the tissues may be repaid. In teeth, this should initiate repair activity.

It seems likely that the longer calcium-borrowing occurs, the more time and calcium are required to complete repair or repayment after stabilized normocalcemia suppresses PTH. If normocalcemia is only intermittent, interspersed for short periods by repeated periods of hypocalcemia, PTH release would increase intermittently and calcium deposition would tend to be inhibited. Repair of dental tissues would not occur at all or would occur only sporadically and incompletely, perhaps with non-calcified tissues such as fibrotic tissue (as in the dolphin specimens). Intermittent hypocalcemia (and hyperparathyroidism) might also result in repeating (crosscutting) structures of resorption and repair, as I have described in dolphins, bears, elk, and which has been reported in humans.

Conversely, if periods of normocalcemia are sufficiently long, tissue should become fully repaired (as in the bears and most of the elk specimens). However, crosscutting resorption structures with repeated incomplete repair (as in human I.R. cases and dolphin specimens) should indicate that periods of normocalcemia were too short or interrupted too often by periods of hypocalcemia.

Thus, one may begin to infer, by reversing the terms in the argument, that members of a mammal population are likely to be chronically hypocalcemic if the occurrence of poorly repaired systemic resorption damage is found to be common. Further, hypocalcemia of population members would be expected to be seasonal or to occur in some sort of cycle if fully repaired and repeated damage from systemic resorption is found to be common.

Causes and symptoms of hypocalcemia

In most mammals the serum calcium value usually falls within a narrow range of 9.0 to 11.0 mg/100 ml (Berkow 1982; Martin 1985; Porat and Sherwood 1986). A mammal is hypocalcemic when its serum calcium falls to levels below about 9.0 mg/100 ml. If serum calcium continues to fall to 7.0 mg/100 ml or less, hypocalcemia is regarded as already severe and PTH secretion is quickly elevated to its highest rate and calcium recruitment activity is maximized (Gorbman *et al.* 1983).

One result of hypocalcemia is resorption of dental-tissue and presumably even greater bone resorption. In severe hypocalcemia or at least in more severe responses, symptoms of tetany begin to occur in many mammals. Susceptible animals show depression, dullness, ataxia and neuromuscular hyperexcitability. These signs may be followed by twitching, convulsion, regional paralysis and death.

How is it then that PTH actions do not normalize serum calcium before symptoms of tetany progress or before extensive resorption occurs?

There is no general agreement as to major causes of hypocalcemia in apparently healthy mammals. However, there is growing recognition among endocrinologists that in healthy, susceptible mammals low serum calcium results from responses to stress stimuli of various sorts, including temperature extremes, exhaustive exercise, starvation, injury and fear (Martin 1985; Gorbman *et al.* 1983; Viru 1985). Noxious stimuli are received via the hypothalamic-pituitary-adrenal pathway. Stimuli of sufficient strength, duration, or frequency evoke hypersecretion of glucocorticoids (principally cortisol). Depending on the stressor, cortisol is released into the blood in concentrations of up to 10 times normal amounts (Gorbman *et al.* 1983; Martin 1985), and secretion and release can continue or recur for days or weeks (Martin 1985; Viru 1985).

The elevation of serum steroids reportedly decreases serum calcium in at least two ways: 1. it increases excretion of calcium by the kidneys and so net calcium loss is accelerated, and 2. it transfers ionic calcium into mitochondria of soft tissues where it is sequestered in amorphous combination with phosphate, and so its availability to other tissues is remote. Presumably, if strong stimuli, steroid-cascading and hypocalcemia continue, PTH activity in recruiting calcium from tissues would be ineffectual. I conjecture that this is because calcium removed from tissues would be swiftly lost from the blood through the actions of elevated serum cortisol.

Tetany might be caused in sensitive individuals and those already encumbered by extra serum-calcium demands (e.g., pregnant or nursing females). This would be a likely result if ionic pumps began to transfer calcium rapidly from the semifluid and fluid compartments—where non-bone calcium is most plentiful—to the blood. Because of the effects of increased serum steroid concentration, the blood would act as a calcium sink.

The richest source of such calcium is the sarcoplasmic reticulum of the muscle fibers. Removal of calcium from these containers would bring on tetany because their ionic

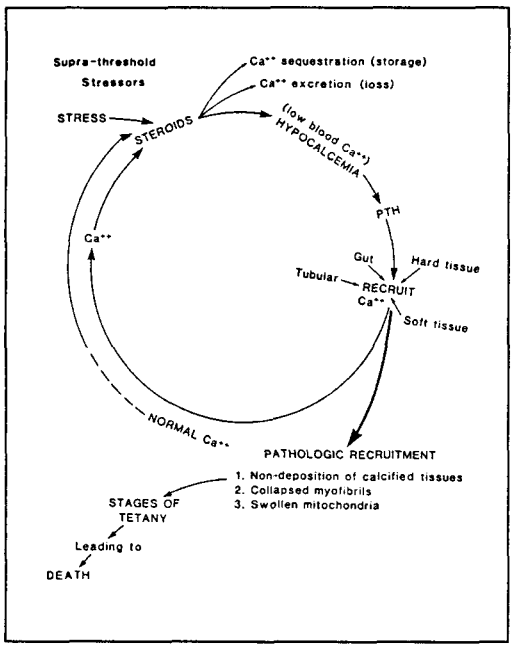

Fig. 5 Theoretical model showing systemic calcium ion flow in hypothetical cases of supra-threshold stressors which generate a glucocorticoid flood, hypocalcemia and ineffectual recruitment of body calcium.

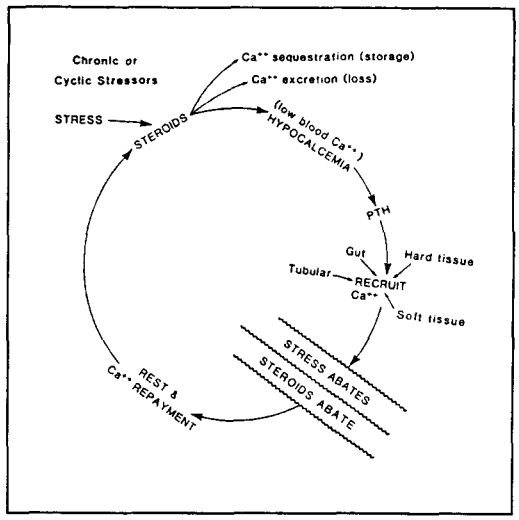

Fig. 6 Theoretical model showing systemic calcium ion flow in hypothetical cases of chronic sub-threshold or cyclic threshold stressors. In the case of chronic stressors, rest and Ca^{++} repayment is impaired. In the case of cyclic stressors, stress regularly abates, decreasing steroid secretion and promoting Ca^{++} repayment.

calcium is required for muscle contraction. Large-scale removal would invoke paralysis and probable death. Figure 5 represents a theoretical model for such hypothetical cases.

I conjecture further that a less severe situation may occur as in the model in Figure 6. Here, the noxious stimuli would be temporary or cyclic, or perhaps mild and chronic. Presumably this would cause less cortisol to be secreted and released. Marginal or intermittent hypocalcemia would promote low but above-basal secretions of PTH. If cyclic, the stressors would ultimately produce repetitious resorption with full repair in teeth. Chronic stressors, which allowed little recovery time, would ultimately produce large-scale dental resorption with inadequate reparation.

Stress-induced hypocalcemia

If stressors cause the hypersecretion of cortisol into the blood and the elevated serum steroids cause hypocalcemia, then some evidence of these relationships should be found in data related to results in this study and in data reported in accounts by others.

Black bears

Evidence from the black bears suggests that resorption may be due to stresses of winter cold, fasting and cubbing. The bear teeth showed resorption associated with dark-stained annual layers usually followed by complete repair. Montana black bears begin forming the thin, dark cemental layer just before the onset of hibernation (Stoneberg and Jonkel 1966). For these bears, hibernation is a dormant period during which the bear eats nothing and yet it does not conserve body stores by becoming torpid (Pelton 1982) as do true hibernators. In addition to fasting, mature female black bears regularly give birth and begin to suckle (up to four) cubs during hibernation (Pelton 1982). Presumably, resorption is associated with fasting in all individuals except the neonatal cubs (who nurse) and with late pregnancy, parturition and early lactation in mature females.

All specimens with cyclic resorption features show damage, presumably sustained during hibernations. It is completely repaired between winter seasons, just as healthy females of other species fully repay borrowed bone calcium between pregnancies (Braithwaite *et al.* 1970; Toverud and Boass 1979).

Elk

Dental alteration in Rocky Mountain elk may be associated with cyclic stress due to cold, starvation and perhaps exhaustion. Dark-stained layers in cementum and dentine form in winter in the elk (Keiss 1969). Although elk do not hibernate, they do store nutrients for overwintering and normally remain active despite inadequate winter intake of food. Bulls, already predisposed to malnutrition from an active rutting season, and females, increasingly encumbered

by pregnancy, may further draw on limited reserves in populations that migrate yearly to and from winter grounds. Yearling cows and bulls entering their second fall may be involved in reproductive activities. Mortality may be high, depending on severity of the winter season, adequacy of stored fats, reproductive state, general state of individual health, and whether the elk are migratory (Peek 1982).

Dolphins

Except for susceptible reproductive females, most tropical dolphins probably have few strong natural stressors, such as starvation, extreme temperatures, inordinate fear and routine physical exhaustion. If that is correct, then repetitious resorption with token repair, as seen in some of the dolphins in the eastern tropical Pacific, may be ultimately caused by unnatural stressors, particularly those associated with the purse-seine fishery. In the fishing operation, chases and sets on dolphins may be of long duration (two to four hours per set) but frequency of sets on the same schools is not known. Myrick *et al.* (1987) have recently shown that spotted dolphins chased and set upon by purse seiners are hypocalcemic, but that captive dolphins acclimated to conditions of captivity and wild dolphins that are slowly captured and handled with a minimum of disturbance to the animals, have serum calcium values that are normal for other mammals. Myrick *et al.* (1987) also noted that if capture is somewhat rushed or awkward, a dolphin may easily and quickly experience a drop in serum calcium to below normal levels.

Other cases

Apparent confusion abounds regarding ultimate causes of dozens of nominal diseases or conditions in susceptible mammals, which share in common suites of symptoms indicating hypocalcemic tetany. These fall into four categories including myopathies or paralyses associated with parturition in mammals including humans (parturient paresis), capture of wild animals (capture myopathy), transport of domestic and wild animals (shipping disease) and exhaustion exercises.

In capture and transport myopathy cases where data have been given, I have noticed a consistency of rising cortisols (Franzmann and Thorne 1970) and declining calciums (McAllum 1985; Haigh *et al.* 1977; Chalmers and Barrett 1977; Brannian *et al.* 1981). This is also true for cases describing serum steroid or serum calcium changes in heavily exercised horses (Snow 1982; Snow *et al.* 1983). in endurance race horses (Grosskopf *et al.* 1983; Rose *et al.* 1983; Grosskopf and Van Rensburg 1983; Lucke and Hall 1978; Lucke and Hall 1980; Rose *et al.* 1980), in competing ponies in polo matches (Craig *et al.* 1985) and in laboratory animals and humans in exhaustion-exercise studies (Viru 1985).

In capture myopathy, animals are chased and netted or darted. Depending on the individual and species, this may result in paralysis or death after the animal passes through a series of symptoms that usually include those of early and intermediate tetany. A large percentage of these reports have suggested that metabolic acidosis is a major cause of this condition, but often the condition occurs without acidemic signs. I suggest that an alternative explanation for all such conditions may be in order.

In reports that detail the muscle damage in such lethal myopathies, obliterated z-lines of the sarcomeres and loss of skeletal-muscle striations have been described or illustrated a number of times (Lewis *et al.* 1977; Chalmers and Barrett 1977; Brannian *et al.* 1981). The sarcoplasmic reticula attach near and branch from the z-line areas of sarcomeres. If, as one of the conjectural models indicates (Fig. 5), calcium ions were rapidly removed from the sarcoplasmic reticula by recruitment actions of PTH, it would surely disrupt and rupture muscle cells in the regions of the z-lines in a way much like that described for lethal capture myopathy.

Parturient paresis and related conditions occur in mammals at about the time of parturition. Hypocalcemia is the known cause of this potentially lethal myopathy. However, these conditions have often been explained by suggesting that the calcium needs for the developing fetus, for colostrum formation and to prepare for the onset of normal nursing, suddenly overcome the maternal ability to maintain normocalcemia (Brown *et al.* 1979). In fact, serum cortisol suddenly rises immediately before parturition in many animals (Challis *et al.* 1979; Ellendorff *et al.* 1979; Stone *et al.* 1987). This may be more suggestive that hypocalcemia is caused by the stress of periparturient fear and pain or discomfort rather than any sudden demands made on maternal calcium reserves. This would be especially likely for large mammals in which the calcium burden of pregnancy and lactation are relatively small (Simkiss 1967).

To summarize, I agree with Basson and Hofmeyer (1973) who, in considering only myopathic diseases, suggested that many of the nominal conditions are various species- or stress-specific expressions of the same phenomenon. The present study has developed considerable circumstantial evidence indicating that many of the conditions considered above may result from stress-induced hypercortisolism, hypocalcemia and hyperparathyroidism. It has also strengthened the likelihood that natural and unnatural stressors are ultimate causes of systemic alteration of tooth tissues. Nevertheless, firm data are lacking and direct experimentation and directed study will be necessary before it is possible to fully answer the question: Is tissue resorption and replacement in permanent teeth of mammals caused by stress-induced hypocalcemia?

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