

Review article

The pathobiology of the osteoclast

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SUMMARY This article reviews recent information concerning the origin of osteoclasts and the local and systemic regulation of their activity. It appears that much of the environmental responsiveness of osteoclasts is mediated by cells of the osteoblastic lineage, which exert a major influence on the localisation, induction, stimulation, and inhibition of osteoclastic bone resorption. Some of the mechanisms by which osteoclast function may be disturbed by inflammatory and neoplastic diseases are discussed, and it is suggested that many pathological disturbances of osteoclastic bone resorption may be explicable as mimicry of physiological regulatory mechanisms by local hormones introduced into bone as the local regulators of the diseased tissue.

The osteoclast is the effector of bone resorption. Its activity is normally integrated to the requirements of skeletal morphogenesis and restructuring and to those of calcium homeostasis, but its potential for destruction is shown by the reckless, random resorption which occurs in Paget's disease and in giant cell lesions (in which the multinucleate cells are probably osteoclasts^{1 2}). Less conspicuously, but ultimately with similarly devastating effect, the osteoclast is often a party to the development of osteoporosis, to which it contributes with levels of osteolysis above those found in unaffected individuals;³ the scale of this osteoclastic contribution to disease in an ageing population is emphasised by the observation that 30% of all individuals who reach age 90 have sustained a fractured femoral neck and 50% a collapsed vertebra.⁴ Osteoclasts act in collaboration with pannus in the osteoarticular destruction of rheumatoid arthritis, and osteoclasts effect tooth loosening and loss in periodontal disease. In non-metastatic hypercalcaemia, which commonly mars and shortens survival irrespective of the extent of tumour spread, there is release into the circulation by the tumour of stimulators of osteoclastic bone resorption.^{5 6}

Despite its central role in these pathological processes, and largely due to its inaccessibility, the osteoclast has been a poorly understood cell. In recent years, however, new information has been gleaned concerning the origin of osteoclasts and the

humoral and cellular control of their resorptive activity.

Natural history

Osteoclasts form by fusion of mononuclear precursors. Parabiosis experiments, quail-chick chimaeras, and bone marrow and spleen cell transplantation experiments have established that while osteoblasts derive from local mesenchyme, osteoclasts take origin from a cell which can reach bone via the circulation.^{7 8}

Among circulating cells the mononuclear phagocyte initially seemed the most plausible precursor, similarly specialised for degradation and capable of fusion.⁹ Macrophages, however, are unable to correct the osteoclastic defect, curable by bone marrow, in osteopetrosis (Chambers, unpublished observation; JF Loutit, personal communication);¹⁰ they are also incapable of restoring radiation induced reductions in osteoclast number and function.¹¹ Osteoclasts lack enzymes such as chloroacetate esterase,¹² present in mononuclear phagocytes, and possess enzymes, such as tartrate resistant acid phosphatase,¹³ absent from mononuclear phagocytes. Calcitonin induces cytoplasmic quiescence in osteoclasts but not in mono- or multinucleate macrophages.¹⁴ The primary function of osteoclasts is excavation of bone, and, although mononuclear phagocytes release calcium and hydroxyproline from devitalised bone powder, this may reflect digestion of phagocytosed bone particles,¹⁵ a process

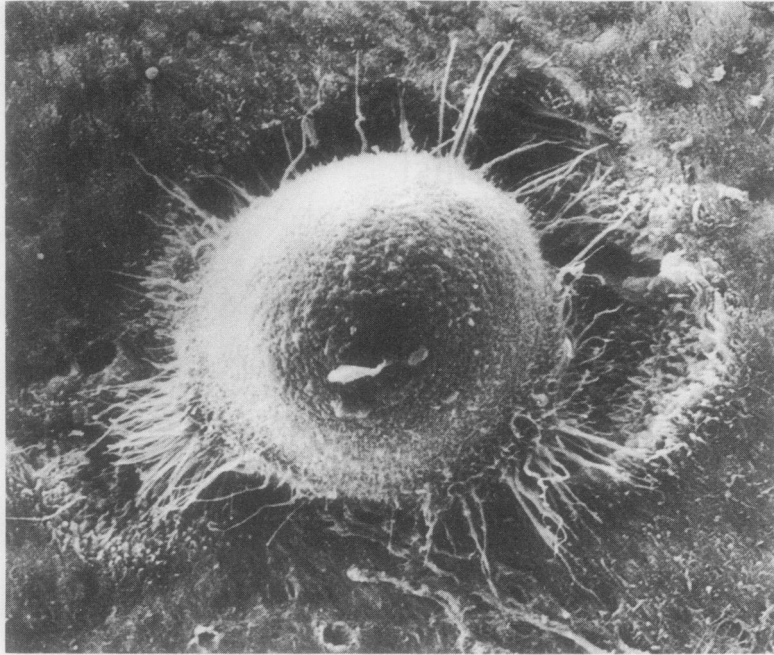


Fig. 1 Scanning electron micrograph of osteoclast after 8 h incubation on a slice of cortical human femoral bone. The osteoclast has formed a resorption cavity, which it still partly obscures. $\times 1200$.

quite different from resorption of extracellular bone surfaces. Both mono- and multinucleated macrophages lack the ruffled border characteristic of osteoclasts,^{15,16} and are without perceptible effect on bone slices in which osteoclasts, under identical conditions, rapidly induce deep excavations¹⁷ (Figs. 1–4). Osteoclasts lack Fc and C3 receptors,^{18,19} and all the macrophage specific antigenic markers so far studied are absent from osteoclasts.^{1,20–22}

Mature mononuclear phagocytes are thus clearly quite different from osteoclasts. Nevertheless, special environmental conditions might induce the osteoclastic phenotype in immature mononuclear phagocytes. It has been proposed that 1, 25 dihydroxyvitamin D₃, which stimulates osteoclastic bone resorption, may induce mononuclear phagocytes to become osteoclastic. This view is based on the ability of the hormone to induce maturation in immature mononuclear cells, in which it elicits the expression of Fc and C3 receptors and macrophage specific antigens, enhances phagocytic potential, and engenders a tendency to giant cell formation.^{23,24} But induction of fusion in mononuclear phagocytes is certainly no proof of osteoclastic differentiation; the development of Fc and C3 receptors and macrophage antigens seems to make these cells less, not more, like osteoclasts, and such cells remain incapable of bone excavation.¹⁷ The proposal is also difficult to reconcile with the absence from

osteoclasts of either receptors for²⁵ or direct responsiveness to²⁶ this hormone.

A second proposal is that bone itself induces osteoclastic differentiation in immature mononuclear phagocytes. Osteoclasts develop in viable bone explants, taken from embryos before osteoclasts are present, if the explants are co-cultured with proliferative bone marrow cells composed predominantly of macrophage precursors.^{27,28} Because neither mature macrophages nor dead bone could substitute, it was argued that live bone had induced the immature mononuclear phagocytes to osteoclastic differentiation. An alternative explanation would be the converse: that the marrow cells induced osteoclastic differentiation among explant cells, analogous to the stimulation of osteoclast formation by parathyroid hormone (PTH) in similar bone rudiments²⁹ (and perhaps mediated by prostaglandins or interleukin 1, both of which are produced by mononuclear phagocytes and both of which have PTH like effects on bone (see below)). Thymidine labelling of the marrow cells before co-culture³⁰ yielded equivocal results: 89% of osteoclast nuclei were labelled after co-culture but only 1% were labelled heavily (26% of mononuclear phagocytes were labelled heavily). Osteoclasts may have originated either by proliferation of a subpopulation of heavily prelabelled marrow cells or even a minor population of non-haemopoietic cells contained in the bone

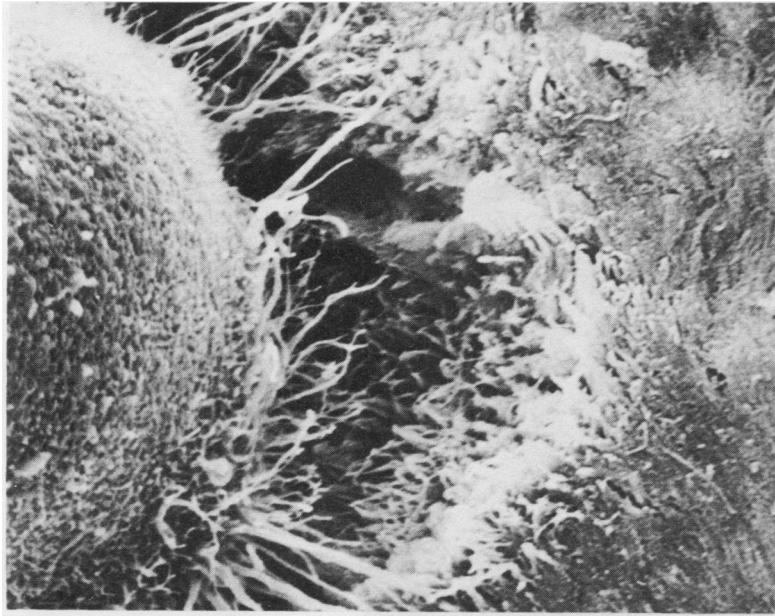


Fig. 2 Higher magnification of Fig. 1, which shows abrupt edge of excavation, the wall consisting of blind ending fibrils. The osteoclastic surface is typically domed and covered by a dense mat of microvilli. $\times 2400$.

marrow cultures (see below) or by proliferation of bone explant cells during (thymidine contaminated) co-culture.

Although individual antigens commonly disappear, emergence of a subpopulation does not gener-

ally result in the complete loss of lineage specific antigenic markers mentioned above.^{1 21 22} Especially surprising, if osteoclasts were derived from immature mononuclear phagocytes, is the absence of common leucocyte antigens from osteoclasts.^{1 21 22}

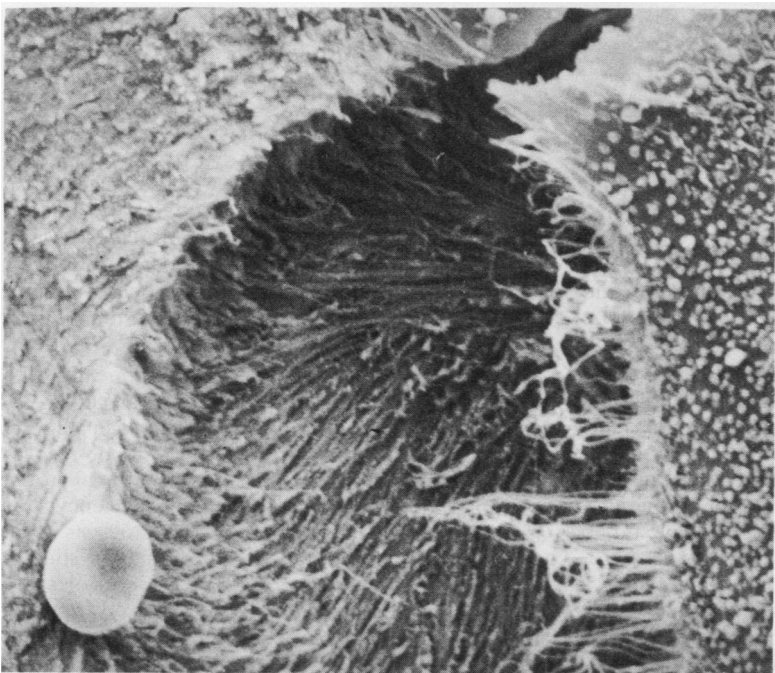


Fig. 3 Part of an osteoclast with associated resorption lacuna. The pit base consists of partially demineralised organic fibrils. In the pit wall are seen blind ending organic fibrils, the continuity of which has clearly been interrupted during resorption. Osteoclasts resorb both mineral and organic components of bone unaided by other cell types. $\times 3000$.



Fig. 4 *If osteoclasts are removed with detergent after incubation the entire excavation can be visualised. Note sharp edge between unresorbed and resorbed bone. Debris marks the peripheral extent of osteoclast cytoplasm. The clear zone thus occupied the band between the peripheral debris and the excavation margin. Bone beneath the osteoclastic peripheral clear zone has remained completely unaffected, while inside this, bone has been resorbed. This appearance strongly suggests that the clear zone represents a non-resorptive circumferential seal which could enable the formation of an inner micro-environment in which lysosomal enzymes act at an unusually low (for an extracellular space) pH. $\times 3500$.*

These are expressed on all the known nucleated progeny of the haemopoietic stem cell, irrespective of degree or direction of differentiation, and their absence from osteoclasts implies that osteoclasts derive from a transplantable cell distinct from the haemopoietic stem cell, a possibility favoured by bone marrow transplantation experiments.³¹ Osteoclasts may derive not from haemopoietic cells at all, but from the stromal cells of the haemopoietic microenvironment recently shown to accompany marrow transplants.^{32, 33}

Osteoclasts are reliably recognised on bone surfaces only by their multinuclear state, but mononuclear equivalents also probably exist. We have noted that a proportion of the mononuclear cells disaggregated with osteoclasts from neonatal bone show a hormonal response to calcitonin indistinguishable from that of (multinucleate) osteoclasts.¹⁴ Kaye³⁴ found that 45% of acid phosphatase positive cells,

mononuclear on serial section, were associated with resorption lacunae and that lacunae were equally common beneath mono- and multinucleate acid phosphatase positive cells. Bone resorption by mononuclear cells, suggested by these results, implies that the mononuclear cells are functionally competent osteoclasts.

The life span of osteoclasts *in vivo* appears to be up to seven weeks, with a half life of around 6–10 days.^{35–37} There is little information concerning the fate of these cells *in vivo*. Cessation of bone resorption, either during remodelling,³⁸ after calcitonin administration,³⁹ or after calcium deficiency,⁴⁰ is associated with disappearance of osteoclasts from endosteal surfaces. Individual nuclei may be shed to resume a mononuclear existence.³⁹ Centrioles are pooled in osteoclasts as a group distanced from the nuclei,⁸ and separation would be a complex affair. During bone repletion abrupt cessation of bone

resorption is associated with migration of osteoclasts from endosteal surfaces into adjacent marrow spaces, where they do not transform into mononuclear cells but degenerate and disintegrate.⁴⁰ We have never seen a nucleocytoplasmic unit separate from an osteoclast *in vitro*: each polykaryon survives for hours or days before an abrupt demise.

Systemic regulation

The bone apposed surface of osteoclasts actively engaged in resorption reveals a distinctive appearance. The central area is elaborately folded (ruffled border) and interdigitates with bone crystals and with frayed collagen fibrils. This is surrounded by a clear zone, rich in actin filaments and free from organelles, of close apposition of osteoclast to the bone, which probably serves as a peripheral seal confining an inner micro-environment into which lysosomal enzymes are extruded.⁴¹⁻⁴³

Administration of PTH *in vivo* is followed within minutes by an increase in the proportion of osteoclasts which show a ruffled border, in the extent of the ruffled border on each cell, and within a few hours, in the overall number of osteoclasts.⁴⁴⁻⁴⁷ Calcitonin has the opposite effects.^{48,49} The advent of techniques for organ culture of bone^{50,51} has enabled identification of these hormonal effects as direct actions on bone.⁵²

Calcitonin appears to act directly on osteoclasts; these cells possess calcitonin receptors^{14,53,54} and calcitonin inhibits disaggregated osteoclasts from bone resorption.^{2,26} The exquisite sensitivity of osteoclastic bone resorption to inhibition by calcitonin,²⁶ the rapidity with which osteoclastic resorption is altered by both PTH and calcitonin, and the observation that animals with defective osteoclasts have a severely restricted ability to respond to PTH with a rise in plasma calcium,⁴¹ suggest that changes in osteoclastic resorptive activity may largely account for the contribution of bone to the hormonal regulation of plasma calcium concentrations.

The mechanism by which calcitonin inhibits bone resorption may be through inhibition of cytoplasmic motility, presumably essential for enzyme exocytosis and endocytosis: motility is abolished by picomolar concentrations of calcitonin, and reduced within the physiological range;⁵⁵ and cytochalasin B, an inhibitor of microfilament assembly, induces an identical state of cytoplasmic quiescence in osteoclasts and similarly inhibits osteoclastic bone resorption.⁵⁶ Cyclic AMP has been implicated as a second messenger in calcitonin responsiveness: analogues of cyclic AMP inhibit both motility and bone resorption in isolated osteoclasts.^{26,57} Furthermore, agents which reduce cyclic AMP degradation enhance cal-

citonin responsiveness,⁵⁷ and calcitonin is known to increase cyclic AMP concentrations in bone.^{58,59}

Although PTH stimulates osteoclastic resorption in intact bone, several studies have failed to show PTH receptors on osteoclasts.^{60,61} PTH is also without influence on either the motility of or bone resorption by isolated osteoclasts.^{2,26,62} This implies that PTH stimulates osteoclastic resorption through a primary effect on another cell type. The most likely candidate for this role is the osteoblast (see footnote).^{*} These cells possess PTH receptors and are induced to a variety of functional changes, including cyclic AMP production, by the hormone.⁶³

One mechanism by which osteoblasts stimulate osteoclastic bone resorption appears to be through mineral exposure.⁷ All bone surfaces, except in areas of osteoclastic resorption, are lined by a layer of unmineralised osteoid.⁶⁴⁻⁶⁶ This is readily visible by light microscopy during bone formation. When formation ceases mineralisation continues for a while but is arrested within a few hundred nanometers of the bone surface, at the level of the lamina limitans; this is a zone of altered staining properties, the specific function of which may be to inhibit progression of the mineralising front to the bone surface.⁶⁷

We have found that osteoclasts do not resorb bone if the osteoid layer is intact (nor do they resorb demineralised slices of cortical bone) but do so if the osteoid is first removed by collagenase.⁶⁸ Since osteoclasts are clearly capable of destruction of all the components of bone⁵⁶ (Figs. 1-4), this indicates that contact with bone mineral, but not osteoid, induces osteoclasts to resorptive activity. We also found⁶⁹ that osteoblasts are able to remove the surface osteoid layer *in vitro*, to expose (but seem incapable of resorption of) adjacent mineral; that

*Footnote

Osteoblasts are strictly the cells which synthesise osteoid. During bone formation some cease osteoid production and become interred in bone as osteocytes. When bone formation ceases osteoblasts take up an inactive appearance and become flattened "resting osteoblasts" or "surface osteocytes". The extent to which these processes are reversible, and to which osteoblasts, resting osteoblasts, and osteocytes share properties and potentialities in common, is not known. *In vivo*, bone resorption is generally seen in areas adjacent to resting osteoblasts and, accordingly, these cells are generally the candidates as osteoclast stimulators. When environmental circumstances change, however, osteoclastic resorption may be initiated in areas where osteoblasts are actively forming bone.⁷⁰ The cells of the (osteoblastic) lineage which line bone surfaces may represent a population of flexible phenotype and similar potentialities, each member of which can either form bone, induce osteoclastic resorption, or do neither as appropriate to systemic and local stimuli. Despite this possibility, when a property is ascribed to osteoblasts in this review, this should be taken to mean only that at least some cells of the lineage defined above possess that property, and does not necessarily imply that all members, or any particular member, possess the stated property.

PTH accelerates this process; that bone so modified has an increased susceptibility to osteoclastic resorption; and that this susceptibility is abrogated by demineralisation.

Do these experimental results reflect physiological processes? They would certainly account for the otherwise unexplained apparently universal presence of osteoid on non-resorptive surfaces; mineral exposed surfaces have been described only in association with osteoclastic resorption *in vivo*, presumably because osteoclastic resorption rapidly succeeds osteoid removal. In an *in vivo* system, however, in which many osteoclasts can be induced to resorb bone in a well defined temporospatial sequence, the earliest observation, immediately preceding the appearances of multinucleate cells, is exposure of mineral on to the bone surface.⁷⁰ Also consistent with a role for mineral contact as a stimulus to osteoclastic resorption *in vivo* is the well recognised preference of osteoclasts for mineralised compared with poorly mineralised bone in osteomalacia, and the failure of osteoclasts to resorb demineralised, but not mineralised, bone implants.⁷¹ This model could also explain the finding that PTH causes collagen destruction in bone despite inhibition of osteoclastic resorption by acetazolamide, or incompetence of osteoclasts in osteopetrosis: in such circumstances collagen but not mineral is dissolved.^{72,73} Osteoblasts produce collagenase and tissue plasminogen activator and secrete increased amounts in response to PTH.⁷⁴⁻⁷⁷ I strongly suspect that this proteolytic enzyme secretion does not represent the ability of osteoblasts to act as alternative bone resorbing cells, but rather represents the mechanism by which these cells initiate osteoclastic bone resorption.

Osteoblasts may induce osteoclastic resorption not only through mineral exposure but also through an independent mechanism. If disaggregated osteoclasts are incubated on slices of devitalised cortical bone (in which mineral is artificially exposed during cutting) PTH is without effect; but if osteoblasts and osteoclasts are cultured together on the same slice PTH increases osteoclastic resorption of the substrate (McSheehy JAP, Chambers TJ; unpublished observations). PTH similarly enhances osteoclastic motility and spreading, in the absence of bone, only in the simultaneous presence of osteoblasts.⁷⁸ Osteoclastic stimulation occurred only if the two cell types were in contact and could not be transferred by supernatants of osteoblast cultures; it was unimpaired by indomethacin, a prostaglandin synthetase inhibitor. Stimulation seemed to depend on either a short range/unstable transmitter or osteoblast osteoclast contact.

Among the actions of PTH on osteoblasts, one of

the most hormonally sensitive is the rapid induction of a stellate configuration in the normally cuboidal cells.⁷⁹ The small diameter of the cytoplasmic processes so formed may facilitate close approach to osteoclasts, an event which may alter membrane properties such as permeability⁸⁰ and induce electrostatic displacements of membrane calcium⁸¹ in the osteoclast. Alternatively, the shape change may be associated with the exposure of cell surface effector molecules, as occurs during the platelet shape change (which exposes platelet factor 3, to catalyse the critical initial step of the clotting cascade⁸²). The osteoblastic shape change may, however, reflect other functions, unrelated to osteoclastic stimulation. Fibre forming cells exert traction on their substrate, which induces newly formed collagen fibres to align parallel to the long axis of the cell;⁸³ collagen traction requires cytoplasmic motility and is suppressed by cytochalasin B.⁸⁴ Cytochalasin B induces an identical change in osteoblastic shape to that caused by PTH.⁷⁹ Since PTH acutely inhibits new bone formation, the shape change may merely reflect cessation of collagen deposition and alignment.

The actions of vitamin D metabolites on bone and bone cells are complex.⁸⁵⁻⁸⁷ Production of the most active metabolite, 1, 25 dihydroxyvitamin D, is under hormonal control. This compound assists mineralisation of osteoid, probably through its effect on plasma calcium and phosphate concentrations.⁸⁸ It also has a direct effect on bone in organ culture as a stimulator of osteoclastic bone resorption.⁸⁹ While osteoclasts possess neither receptors for²⁵ nor direct responsiveness to²⁶ the hormone, osteoblasts do possess receptors⁹⁰ and, like PTH, the hormone stimulates tissue plasminogen activator activity in osteoblasts.⁷⁶

LOCAL REGULATION

While the overall activity of osteoclasts is regulated in accordance with the role of bone as a reservoir of mineral for plasma calcium homeostasis, local osteoclastic activity is determined by the function of bone as a mechanical support. The shapes and structures on which this function depends are the result of complex and dynamic patterns of osteoclastic bone resorption during morphogenesis and remodeling. It is difficult to envisage how osteoclasts, derived from an immigrant cell, could achieve such intricate patterns without some form of instruction from locally resident bone cells. Bone lining cells (active and resting osteoblasts) make junctional communications with each other and through canaliculi contact underlying osteocytes to form a three dimensional network of cells, which seems well placed to sense the shape of bone and its reac-

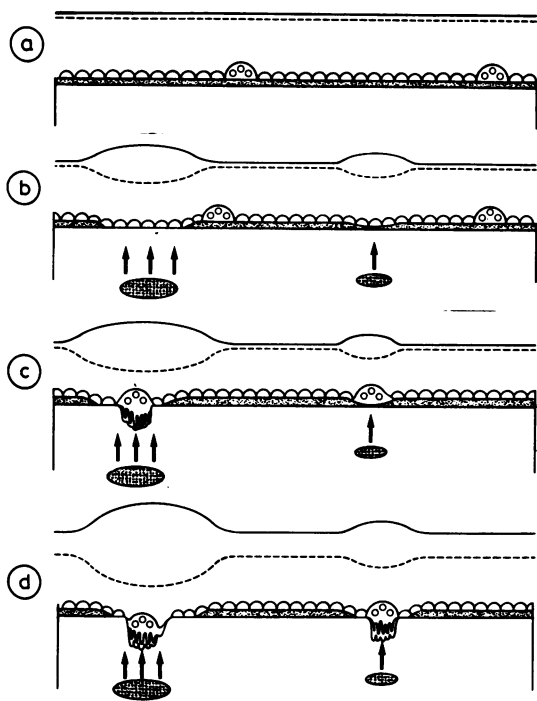


Fig. 5 Diagrammatic representation of working hypothesis for the local and systemic regulation of bone resorption. Local concentrations of prostaglandins (broken line) and osteoclastic stimulation (continuous line) are represented as lines above bone surface; unmineralised osteoid is shown hatched (resting seam). Under circumstances in which neither bone formation nor resorption is occurring (a) levels of stimulator and inhibitor are equivalent and the osteoid seam remains intact. Osteoblastic homeostasis is perturbed (b) by large and small local stimuli (morphogenetic, or generated as a response of bone to physical stress and strain) (represented as subjacent oval shapes). Such stimuli may be transmitted from underlying osteocytes or detected directly by bone lining cells, and induce deviation of osteoblast homeostasis from a neutral and towards a bone resorption inductive state (osteoid destruction, reduced prostaglandin production) (prostaglandin E_2 production by the underlying osteocytes would have this effect on surface lining osteoblastic cells and may represent the signal to the surface cells -cf the interesting but unexplained inverse sensitivities of osteoclasts and osteoblasts to prostaglandin E_2 and prostacyclin^{57,143}). This signal might alternatively be a cytokine—see last paragraph). This results in gradients of osteokinetic agents and zones of net stimulation into which osteoclasts would tend to localise (chemotaxis). Small net stimuli may result in non-resorptive localisation, while larger stimuli may be sufficient to expose bone mineral and initiate osteoclastic resorption(c). The effect of systemic hormones—for example, parathyroid hormone (PTH) is superimposed on these local patterns, such that (d) the general osteoblastic setting is modified. Without changing the gradients which determine localisation of osteoclastic

resorption, PTH increases the divergence of osteokinetic agents over the whole bone surface, causing enhanced stimulation of those osteoclasts already resorbing bone, and recruitment of osteolytic activity in previously non-resorptive osteoclasts.

tion to stress and strain and to transmit these sensations as signals to the bone surface, where new bone formation or resorption is possible.

Osteoblasts respond to mechanical forces and electric potentials (known to be generated by mechanical forces acting on bone^{91,92}) with increased cyclic AMP concentrations and prostaglandin production.⁹³⁻⁹⁵ We have found that prostaglandin E_1 , prostaglandin E_2 , and prostacyclin have an effect on osteoclastic motility indistinguishable from that of calcitonin; osteoclastic responsiveness is receptor mediated, with relatively rapid tachyphylaxis, and seems, like calcitonin, to involve cyclic AMP.⁵⁷ The same prostaglandins inhibit bone resorption by disaggregated osteoclasts.²⁶ The low concentrations of prostaglandins required suggests that prostaglandins produced by osteoblasts^{96,97} may play a physiological role as agents of local inhibition of osteoclastic bone resorption. Osteoblasts thus have the capacity to either suppress (though prostaglandin production) or stimulate (through mineral exposure and enhancement of osteoclastic motility) osteoclastic resorption.

Paradoxically, addition of prostaglandins to bone tissue in organ culture stimulates osteoclasts.⁹⁸⁻¹⁰⁰ This implies that the prostaglandins increase resorption in intact bone indirectly, through a cell type effectively absent from cultures of disaggregated osteoclasts, which is induced by prostaglandins to stimulate osteoclasts. Osteoblasts may be responsible: prostaglandins have several actions on osteoblasts in common with PTH—for example, they increase osteoblastic cyclic AMP¹⁰¹⁻¹⁰³ and collagenase and tissue plasminogen activator secretion^{76,77} and cause osteoblasts to stimulate osteoclastic motility.¹⁰⁴ One hypothesis consistent with the above data is that the PTH like effects of prostaglandins represent attempted homeostasis by osteoblasts: the homeostatic response appropriate to the perceived (via osteoblastic cyclic AMP) production of osteoclast inhibitor is a tendency towards osteoclast stimulation and away from prostaglandin production. Endothelial cells may show analogous cyclic AMP mediated negative feedback regulation of prostacyclin production.¹⁰⁵ Such a homeostatic system would be disturbed when prostaglandins reach bone from an external (non-osseous) source (as occurs with prostaglandin addition to organ cultures and when prostaglandins are produced by neoplastic or inflammatory cells in bone): osteo-

clasts would be both directly inhibited (by extraneous prostaglandins) and indirectly stimulated (through osteoblasts). Because osteoclasts become refractory to prostaglandin inhibition,⁵⁷ the net effect of such abnormal conditions would be increased bone resorption.

A working model for the local and systemic physiological regulation of bone resorption, consistent with the above observations, is shown in fig. 5.

DISORDERED REGULATION

The vast majority of tumour metastases elicit both formation and resorption in adjacent bone.¹⁰⁶ Bone resorption generally predominates and the lesion appears osteolytic. The propensity of tumours to metastasise to bone seems unlikely to be related to their osteolytic potential: metastasis is to the medullary cavity, particularly to haemopoietic marrow, where the loose tissue affords ample opportunity for metastatic establishment and considerable expansion without obvious requirement for osteolysis. Nor is there any relation between metastatic osteolysis and hypercalcaemia. Hypercalcaemia is equally common in patients with and without bony metastases,¹⁰⁷ presumably because physiological mechanisms of calcium homeostasis are capable of maintaining normal plasma calcium despite tumour osteolysis. The major clinical significance of the osteolytic potential of tumour metastases is predisposition of bone to fracture.

Local osteolysis by tumours is associated with increased osteoclastic resorption of bone trabeculae beyond the advancing tumour front, often with intervening stroma.¹⁰⁸⁻¹¹⁰ Later, residual spicules of bone may find themselves surrounded by tumour cells, with osteoclasts apparently absent. It has been suggested, on the basis of morphological observations, that these spicules are resorbed by the tumour cells themselves.^{109 111 112} Direct evidence that tumour cells are able to resorb bone without osteoclasts is scarce: as indirect evidence, many tumours are known to produce proteolytic enzymes, and supernatants of cultures of tumour cell lines cause hydroxyproline and calcium release from devitalised bone.^{113 114}

The osteoclastic activity found beyond the advancing front of the tumour indicates that tumour cells in some way stimulate osteoclastic resorption. It is conceivable that this may at least in part reflect initiation of remodelling consequent on mechanical deformation by the tumour of bone trabeculae, with subsequent reformation impaired by the advancing tumour cells. Tumour cells, however, are known to produce several substances which are capable of inducing osteoclastic bone resorption.

One such substance is prostaglandin E₂, a local

hormone and one known to stimulate bone resorption (see above), produced in a variety of tumours.¹¹⁵⁻¹¹⁸ Inhibitors of prostaglandin synthesis reduce bone resorption by some tumours,^{110 115 119 120} although this might be the result of an effect on tumour growth.¹²¹

A second potential mediator of local osteoclastis is osteoclast activating factor (OAF),¹²² a lymphokine produced by mitogen stimulated lymphocytes (probably T helper cells) in the presence of macrophages,¹²³ which stimulates bone resorption in organ culture. Similar material is produced in some solid tumours¹²⁴ and in myeloma,^{125 126} where it may explain the increased osteoclast mediated osteolysis found adjacent to myeloma cells in bone.^{125 127} Like prostaglandin E₂ it may act as a bone resorption stimulator through a primary action on osteoblasts¹²⁸ (but see reference 126).

In addition to their potential for local osteolysis, some human tumours produce a combination of systemic osteolysis with hypercalcaemia, which is unrelated to the presence of metastases in bone.^{5 6 107 129} Prostaglandin E₂ has been invoked as a possible mediator:¹³⁰ it stimulates resorption; infusion into laboratory animals causes hypercalcaemia;¹¹⁹ and it is implicated in some animal models of non-metastatic hypercalcaemia.¹¹⁹ The experience of most workers, however, is that a response in man to drugs which inhibit prostaglandin synthetase is unusual.^{131 132}

OAF and related substances may underly the hypercalcaemia which occurs in some haematological malignancies, including T cell lymphomas, in which hypercalcaemia is a common feature.¹³³

Most cases of non-metastatic hypercalcaemia occur in patients with renal and urothelial tumours and squamous carcinomas of the head, neck, and bronchus. These patients form a group in whom hypercalcaemia is associated with systemic osteolysis and changes in renal physiology similar to, but not identical with, those caused by PTH.^{5 134} Ectopic PTH synthesis was once thought to be responsible for this syndrome, but the different renal physiology and low-normal circulating PTH concentrations detected by improved PTH assays in these patients is taken as evidence for the presence of a PTH like humoral mediator of unknown identity. The consensus based on currently available evidence is that neither PTH, vitamin D metabolites, nor prostaglandins are involved in non-metastatic humoral hypercalcaemia in other than rare cases.^{135 136}

Little is known of the mechanisms by which osteolysis occurs in inflammatory lesions such as rheumatoid arthritis and periodontal disease, although several potential mediators have been

identified.¹³⁷⁻¹³⁹ Prostaglandins are present in inflammatory tissue; macrophages may represent the source. A second group of agents which may mediate inflammatory osteolysis are the cytokines, a group of polypeptide hormones which regulate the behaviour of cells in inflammation.¹⁴⁰ The cytokines probably represent a family of local hormones, each of which may be produced by a variety of cells for local action on a range of target cells: as with prostaglandins, their specificity may depend more on localisation of secretion than on uniqueness of structure: cytokines are produced by bone cells and have actions on bone cells.¹⁴¹ Among this generally as yet poorly characterised group of factors OAF and interleukin 1 have been shown to stimulate osteoclastic bone resorption¹⁴² (interleukin 1 acts, like PTH and prostaglandins, through a primary effect on osteoblasts (Thomson BM, Chambers TC; unpublished observations)). Because macrophages produce interleukin 1, and lymphocytes produce OAF, these factors have been implicated in inflammatory osteolysis. It is difficult to discern a clear adaptive role for osteolysis in inflammation; it also seems unlikely that wandering inflammatory cells direct physiological skeletal remodelling through production of these local hormones. More likely, stimulation of bone resorption by OAF and interleukin 1 suggests that these factors, produced by non-inflammatory cells, play a part in the physiological control of local bone resorption and also emphasises a general rule, that many disturbances of bone resorption may represent mimicry of the local hormonal mechanisms of skeletal remodelling by local hormones introduced into bone as the local regulators of the diseased tissue.

I am grateful to Dr JAS Pringle and Dr MJ Wilkinson for allowing me to use Fig. 4.

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