after treatment with nitrogen-containing bisphosphonates. Our data indicate that although the number of normal-appearing osteoclasts is significantly increased in patients receiving bisphosphonate therapy, as compared with those receiving placebo, the decrease in biochemical markers and increase in bone density suggest that even normal-appearing osteoclasts may resorb bone poorly. Jobke's micrograph of an osteoclast in a shallow resorption lacuna could represent a cell that has just begun to erode or one that has no current resorptive capability at all. Only in diseases involving very high rates of bone turnover can the rate of resorption be revealed by means of dynamic histomorphometry. For example, in Paget's disease, direct measurement of the rate of bone erosion in individual osteoclasts is possible when pagetic osteoclasts bore through the double-tetracycline-labeled cancellous perimeter while excavating a cavity. From the mean depth of the erosion cavity, dates of tetracycline administration, and time of the biopsy procedure, the minimum initial rate of bone erosion can be calculated in micrometers per day just as precisely as the mineral appositional rate.[2] Such an opportunity did not arise in our study.

We believe that Roos and Cox have misunderstood our statements about the production of multinuclear osteoclasts by the fusion of mononuclear precursors to form polykaryons. We did not suggest that this fusion occurred between existing multinuclear osteoclasts. Considerable evidence indicates that osteoclasts are formed by fusion of mononuclear precursors. These findings are from studies that use quail–chick chimeras with some osteoclasts containing nuclei with morphologic features of both quail and chicks,[3] as well as from experiments using ^{3}H-thymidine and autoradiography to show that osteoclasts form by the fusion of mononuclear precursors,[4,5] not by nuclear replication. The fate of all cells that originate in the hematopoietic environment is to leave, do their work, and die. Finally, it is highly unlikely that the apoptotic nuclei in the giant osteoclasts that we described could divide.

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Molecular Basis of Metastasis

TO THE EDITOR: In their review article, Chiang and Massagué (Dec. 25 issue)[1] give limited attention to the intravascular phase of the metastatic process. With the exception of cells in hematopoietic cancers, tumor cells do not typically circulate as independent entities (as depicted in Fig. 2 and 3 of the article). Rather, they are usually found in clumps, surrounded by a "cloak" of platelets and leukocytes.[2,3] This fact is of more than just academic interest. First, this is the phase in which the vast majority of potentially metastatic malignant cells perish, with the few surviving cells ultimately leading to the death of the patient. Second, such tumor emboli can persist in the vasculature for some time,[2,3] when intravasation is assisted by normal blood elements.[4] Third, much is known about adhesion molecules, coagulation pathways, and other molecular contributors to this phase of metastasis.[4,5] Last but not least, this is the step of metastasis in which therapeutic intervention has a chance of being successful.[5] Indeed, there is good evidence that the well-known antimetastatic effects of heparin involve interdiction of some of these intravascular interactions.[3-5]

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TO THE EDITOR: We suggest that the "cancer cell–centric" perspective of metastasis overlooks the local microenvironment at distant sites. It appears that a premetastatic niche develops from recruited hematopoietic cells[1] during tumor onset and progression. This niche is probably due to necrosis and inflammation.[2,3] The importance of site-specific inflammation in metastasis has been shown in a study[4] in which pulmonary inflammation due to extended provocation of an allergic respiratory reaction enhanced metastasis to the lung in a mouse tumor model. More importantly, among patients with breast cancer, the incidence of lung metastases was approximately twice as high among patients with asthma as among patients without asthma.

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TO THE EDITOR: In their review article, Chiang and Massagué discuss the environment of the primary tumor, and they stress the importance of reduced cell–cell adhesion through down-regulation of E-cadherin expression in metastasis. We would like to add the concept of cell–cell dysadhesion through expression of dysadherin, a cancer-associated cell-membrane glycoprotein. Dysadherin expression is associated with in vitro and in vivo cancer metastasis.[1] In many tumors (e.g., thyroid, tongue, and other head and neck carcinomas) it acts through post-transcriptional down-regulation of E-cadherin. In others (e.g., melanoma and breast, pancreatic, colorectal, gastric, and non–small-cell lung carcinomas), dysadherin's prometastatic effects appear to be independent of E-cadherin and possibly related to up-regulation of chemokines. Thus, dysadherin concomitantly modulates the neoplastic cells and their stromal environment, facilitating metastasis. Another issue is the establishment of the neoplastic cells in their metastatic site and their growth to a tumor mass. For this process, it has been shown that the reestablishment of neoplastic cell–cell adhesion is necessary through restoration of the expression of E-cadherin and the loss of expression of dysadherin.[2]

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THE AUTHORS REPLY: Several letters to the editor highlight aspects of metastasis that certainly deserve attention and involve active areas of research, but these topics could not be covered in our review article. Additional aspects of metastasis warrant commentary. Varki et al. point to intravascular "premetastatic" events — in particular, the role of platelets and leukocytes in forming and protecting tumor emboli, mediating cancer-cell adhesion, and producing metabolites and factors that spur growth and invasion. The ongoing dialogue of tumor cells with the immediate microenvironment occurs during transit and at the premetastatic niche in a distant site.

The intriguing link between inflammation and cancer progression may occur through site-specific inflammatory infiltrates, which allow tumor initiation and colonization in the primary site.[1] As Lee and Lotze mention, these infiltrates also occur in the premetastatic niche in the lung. We refer to how selective pressures of the local tumor environment can modify tumor cells, and recent evidence

from animal models provides further support for the idea that paracrine interactions may also attract nontumor (e.g., bone marrow–derived) and tumor cells to establish a premetastatic niche.[2,3] The active dysadhesion of local tissues to allow tumor-cell invasion (e.g., via E-cadherin, dysadherin, or both) is also probably triggered by paracrine signaling, as Batistatou et al. point out. Finally, the complex roles played by the host-site microenvironment and by the immune system in metastatic dormancy are not yet fully understood, although recent intriguing results point to tumor-specific T-cell suppression of multistage carcinogenesis through cytokine signaling.[4]

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Stones in Primary Hyperoxaluria — A Clarification

TO THE EDITOR: We wish to clarify information published in our letter on primary hyperoxaluria, which recently appeared in the *Journal* (July 3, 2008, issue).[1] We had previously published an article concerning oxalate stones in the *Journal of Nephrology*.[2] Thirteen of the cases from our earlier report were included in the 74 cases described in our letter to the *Journal*, whereas 61 of the 74 cases (82%) were new. Our letter focused on the very peculiar stone morphologic characteristics at the micrometer level, as demonstrated by scanning electron microscopical examination. No images are duplicates of previously published material. In the recent letter, we did not reference our earlier report and apologize for that omission.

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Revertant Mosaicism — Patchwork in the Skin

TO THE EDITOR: Revertant mosaicism occurs when an inherited disease-causing mutation is corrected by a spontaneous genetic event within a somatic cell, followed by expansion of this reverted cell.[1] This phenomenon has been recognized as the cause of milder-than-expected clinical phenotypes in patients with primary immunodeficiency syndromes or muscular dystrophy.[2] In the skin of patients with the hereditary blistering disease epidermolysis bullosa, revertant mosaicism is manifested as small patches of homogeneously pigmented skin surrounded by skin that blisters easily (Fig. 1).

For years, the phenomenon of genetic reversion was thought to occur as a single rare event in patients with a genetic disease. More recently, however, it has been shown that revertant mosaicism

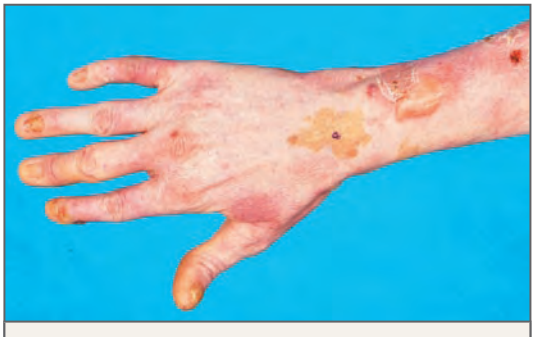

Figure 1. Revertant Mosaicism in a Patient with Non-Herlitz Junctional Epidermolysis Bullosa.
A hyperpigmented revertant patch is visible on the wrist, surrounded by pink, blistered skin. The site of the biopsy of the patch is circled in black ink. The patient is Patient 13.