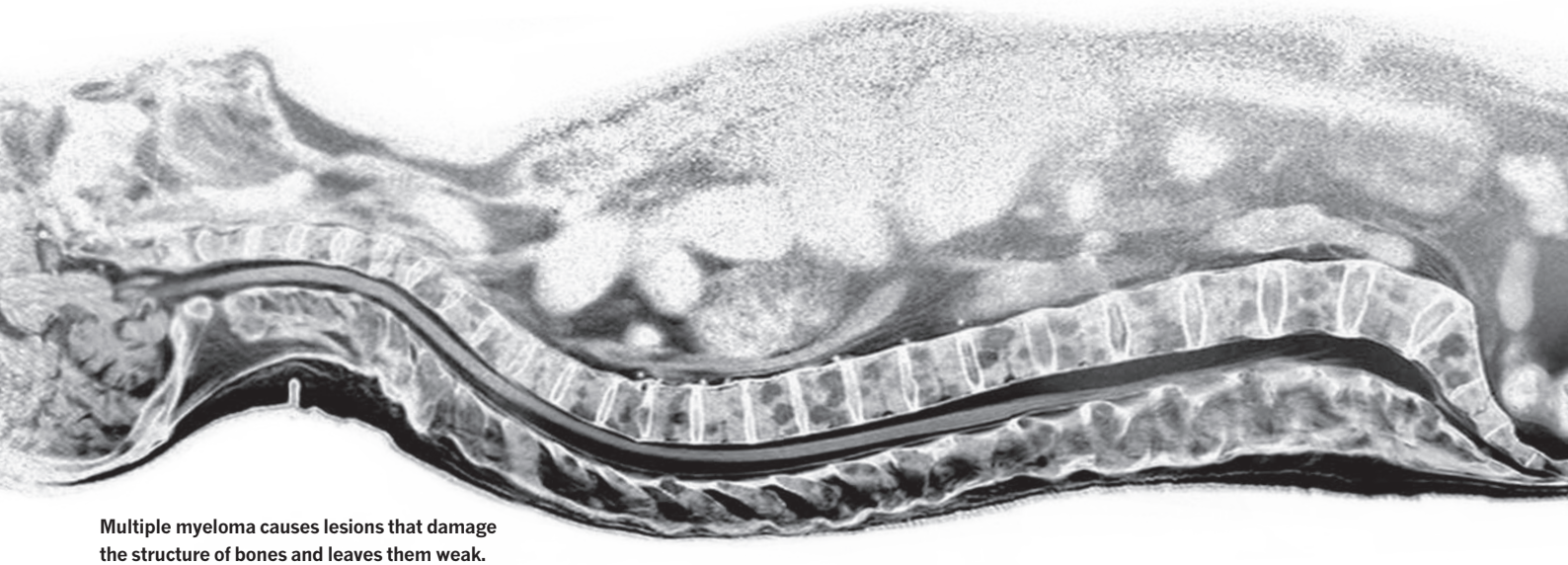

Multiple myeloma causes lesions that damage the structure of bones and leaves them weak.

ORTHOPAEDICS

Structural support

Finding a treatment for the bone destruction caused by myeloma helped researchers understand the biology of bone.

BY JENNIFER BERGLUND

In the 1960s, a remarkable substance called etidronate came into use as an effective treatment for bone problems. Etidronate is a bisphosphonate, a class of material known since the late 1800s to inhibit metal crystallization and corrosion, a feature that led to its wide usage in the oil and gas industry. More than 60 years later, researchers at Proctor & Gamble found that bisphosphonates are just as effective at preventing the destruction of bones in the human body as they are at stopping metal degradation. Proctor & Gamble began marketing etidronate as Didronel, and it soon became a standard treatment for muscle calcification, Paget's disease of bone, heterotropic ossification (in which bone is formed outside the skeleton), menopausal osteoporosis and, finally, bone degradation in multiple myeloma[1].

It was the use of bisphosphonates for multiple myeloma that led to further revelations. "The fact that these drugs were effective in myeloma led a lot of people to be interested in bone disease and what the pathophysiology was," says oncologist James Berenson, medical and scientific director for the Institute for Myeloma and Bone Cancer Research in West Hollywood, California.

So myeloma emerged as a model for studying bone disease. "A large part of our understanding of cancer and bone disease has come from myeloma-related work," says Nikhil Munshi, an oncologist at the Dana-Farber Cancer Institute in Boston, Massachusetts. Indeed, says Munshi, "myeloma is at the forefront" of research into bone pathology. Treatments developed primarily for multiple myeloma — including not only bisphosphonates but also proteasome inhibitors and surgical techniques — have revolutionized the way doctors treat bone diseases.

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BONING UP

Myeloma cells are able to survive, differentiate and proliferate because they receive structural support from stromal cells in the bone marrow, along with soluble materials and extracellular protein. The cancer cells then release agents that suppress bone development and accelerate bone degradation. Up to 80% of multiple myeloma patients have either osteoporosis, lytic lesions or bone damage, which "tells us something important about bone biology", according to Munshi. This knowledge is applicable to most forms of cancer, because bone is one of the most common places for cancer to metastasize. For example, up to 75% of advanced prostate cancers end up in the bones, as do 30% of lung and renal cancers, says David Roodman, who leads research into multiple myeloma at the University of Pittsburgh Cancer Institute in Pennsylvania.

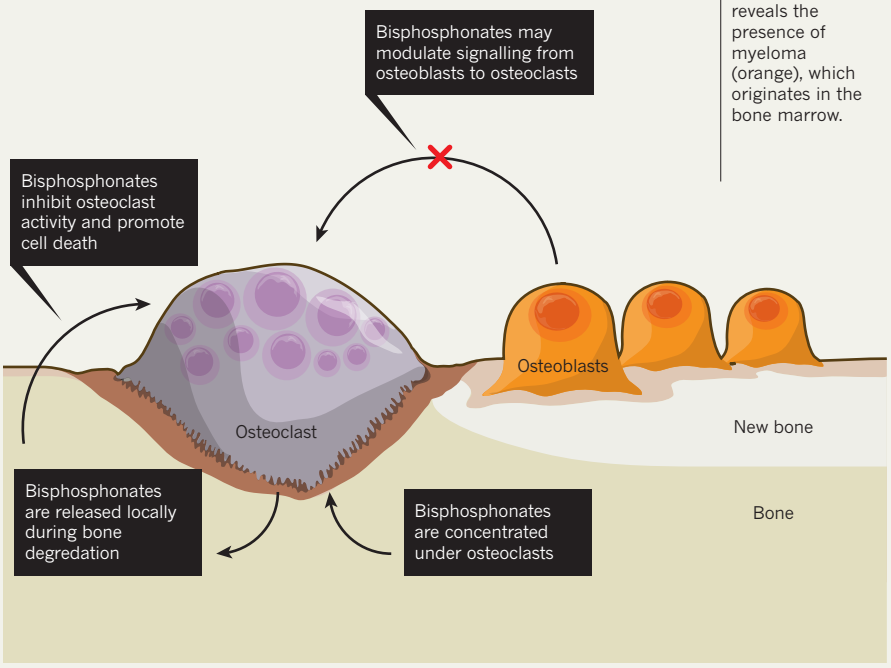
Cancerous cells in bone tissue trigger a destructive cascade of events that often reduces the patient's quality of life. As advances in the treatment of multiple myeloma have prolonged the lives of patients, the focus has turned to preventing the progression of bone disease and repairing damaged bone. "Myeloma has provided a good model for normal bone pathogenesis, that is, new bone formation versus bone resorption," says Kenneth Anderson, who leads multiple myeloma research at the Dana-Farber Cancer Institute. "It has also allowed us to evaluate new cancer targets as well as new target therapies to enhance bone formation and block resorption — not only in cancer, but in non-malignant diseases as well."

In healthy bone, there is a balance between the activity of cells that build up new bone tissue, called osteoblasts, and those that break it down, called osteoclasts. Myeloma cells upset this balance by promoting the activity of the destructive osteoclasts and inhibiting the work of osteoblasts, resulting in increased bone resorption. Moreover, in a vicious cycle, bone destruction releases several cell signalling molecules, or cytokines, that promote the further growth of myeloma cells. Bisphosphonates restore the balance by suppressing osteoclast activity, thereby discouraging bone resorption and suppressing tumour growth.

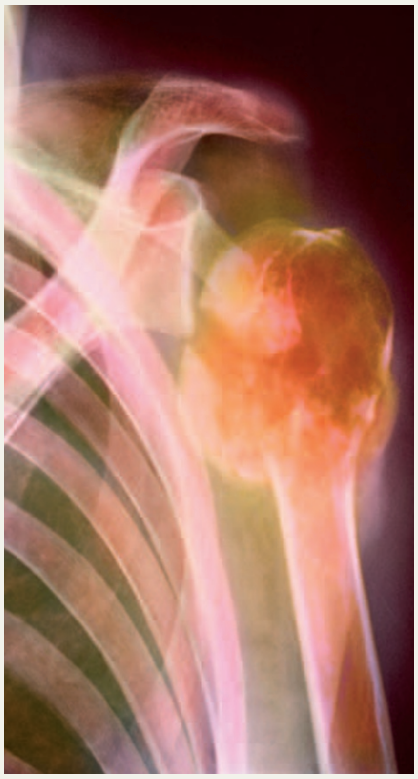
Bisphosphonates have "totally transformed the way we treat multiple myeloma", says Anderson, "I can't overstate how different it was when we were able to decrease the bone complications." And etidronate was only the beginning. Monthly injections of newer bisphosphonates, such as pamidronate and zoledronic acid, have become a central element of treatment for multiple myeloma. Their effectiveness in inhibiting bone resorption makes bisphosphonates effective in treating other forms of bone disease too, such as brittle bone disease (osteogenesis imperfecta), Paget's disease, postmenopausal osteoporosis and

PROTECTING THE BONE

Bisphosphonates restore the balance of bone creation and destruction by suppressing the activity of osteoclasts.



Right: Coloured X-ray of the upper arm reveals the presence of myeloma (orange), which originates in the bone marrow.



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bone metastasis, which all are triggered by imbalanced osteoclast and osteoblast activity.

But the role of bisphosphonates in treating bone disease goes beyond slowing degradation that is already under way. A study published last year in *The Lancet* revealed that bisphosphonates may also prevent future degradation, although the mechanism is not yet fully understood. In terms of myeloma therapy, "that changes every stage of the disease", says Munshi.

Bisphosphonate therapy "may be especially useful for patients who have a propensity to develop metastases", says Roodman. "If we could identify a really high-risk group, those might be the people we should treat," he adds, because some myeloma patients go on for years without developing bone damage.

DIFFERENT DISEASES

The drugs that are the gold standard in treating myeloma, proteasome inhibitors (see 'More shots on target', page S40), are also potentially beneficial in fighting bone disease. Although not currently used to treat other forms of bone disease, they have provided some interesting insight.

Over the past few years, researchers have found that the most commonly used proteasome inhibitor — bortezomib — not only inhibits osteoclast formation but also promotes bone generation in three ways. First, it stimulates the activity of osteoblasts; second, it promotes the production of the bone-building protein BMP-2; and third, it inhibits *DKK1*, the gene that encodes the DKK1 protein, which is believed to block bone growth. "These kinds of insights will allow people to look for new targets," says Roodman.

A range of anti-DKK1 antibodies is being developed, including BHQ880 from Novartis, currently in phase I/II clinical trials. Although it is primarily intended for myeloma patients, the Novartis antibody might also be useful for treating osteolytic bone diseases, such as breast cancer, which often metastasizes into bone tissue. If the anti-DKK1 antibodies can promote bone formation, leading to fewer fractures and less bone pain, they could potentially be used for other diseases, such as osteoporosis.

The similarities between myeloma and other bone diseases extend beyond pharmaceuticals. A surgical technique called kyphoplasty is routinely used to treat myeloma-related bone degradation in the spine. In this minimally invasive technique, a balloon is blown up inside the collapsed vertebra and medical cement is pumped into it. A randomized trial conducted by Berenson and his colleagues showed that kyphoplasty is extremely effective at relieving pain and reducing painkiller use, improving function, and enhancing the quality of life for myeloma patients[2].

Research into multiple myeloma also has implications for rheumatoid arthritis. The inflammation in rheumatoid arthritis is related to the activity of the cell's cytokines, which are also involved in the progression of multiple myeloma. One such cytokine, interleukin-17, causes inflammation by increasing the activity of osteoblasts and myeloma cells and thus encouraging bone degradation and tumour growth. By studying the cytokine networks, researchers have learned a great deal about the driving forces behind these two diseases.

The learning curve is not just in one direction — drugs used to treat other bone conditions could be used to treat myeloma too. One example is denosumab, which targets the RANK ligand (RANKL), the protein that gives the primary signal promoting bone removal. Denosumab is currently used to treat hormone-induced osteoporosis in post-menopausal women[3]. In the summer of 2011, it entered clinical trials to treat multiple myeloma with bone metastases.

All these insights have their roots in the realization that a substance that stopped pipe corrosion could also help the human body build its own skeletal structure. Without bisphosphonates, multiple myeloma and other forms of bone disease may have remained a slow death sentence. But thanks to the innovations in treating bone disease for which bisphosphonates paved the way, this is no longer the case. Patients often survive for many years after being diagnosed with multiple myeloma, and the focus of research is widening from prolonging patients' lives to ensuring that those lives are more comfortable. ■

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1. Francis, M. D. & Valent, D. J. *J. Musculoskelet. Neuron. Interact.* **7,** 2–8 (2007).
2. Berenson, J. *et al. Lancet Oncol.* **12,** 225–235 (2011).
3. Cummings, S. R. *et al. N. Engl. J. Med.* **361,** 756–765 (2009).