

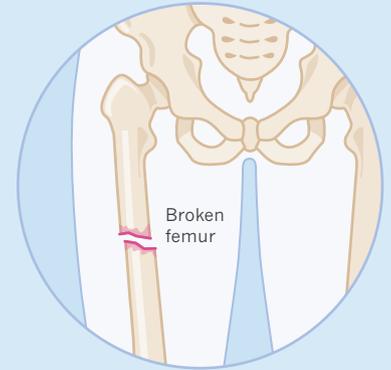
CLOSING THE GAP



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A bone fracture that fails to heal after initial treatment can lead to prolonged disability. Regenerative therapies might help to restart the bone-healing process, getting the people affected back in action.

By David Holmes; illustration by Lucy Reading-Ikkanda



STATE OF THE UNION

Although most fractures will heal fully, a small but notable proportion do not. These severe cases — known as non-union bone fractures — can cause long-term disability and pain, and often require surgery to rectify. To determine why non-union bone fracture occurs, it is important to understand how bone healing typically progresses.

SNAP TO IT

0–2 WEEKS

Immediately after fracture, blood from ruptured vessels inside the bone starts to coagulate into a swollen mass called a haematoma. At this early stage, it is crucial that the fragments of bone are guided back into place to ensure that they are correctly aligned and to help stem the loss of blood.

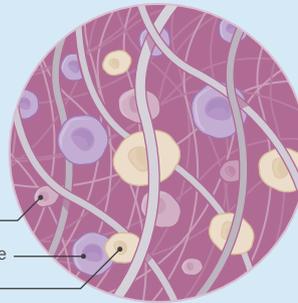
SOFTLY DOES IT

2–6 WEEKS

A soft callus starts to form, made up of new connective tissue, microscopic blood vessels, cartilage and soft spongy bone.

Cells build scaffold between bone fragments

Fibroblast
Chondrocyte
Osteoblast

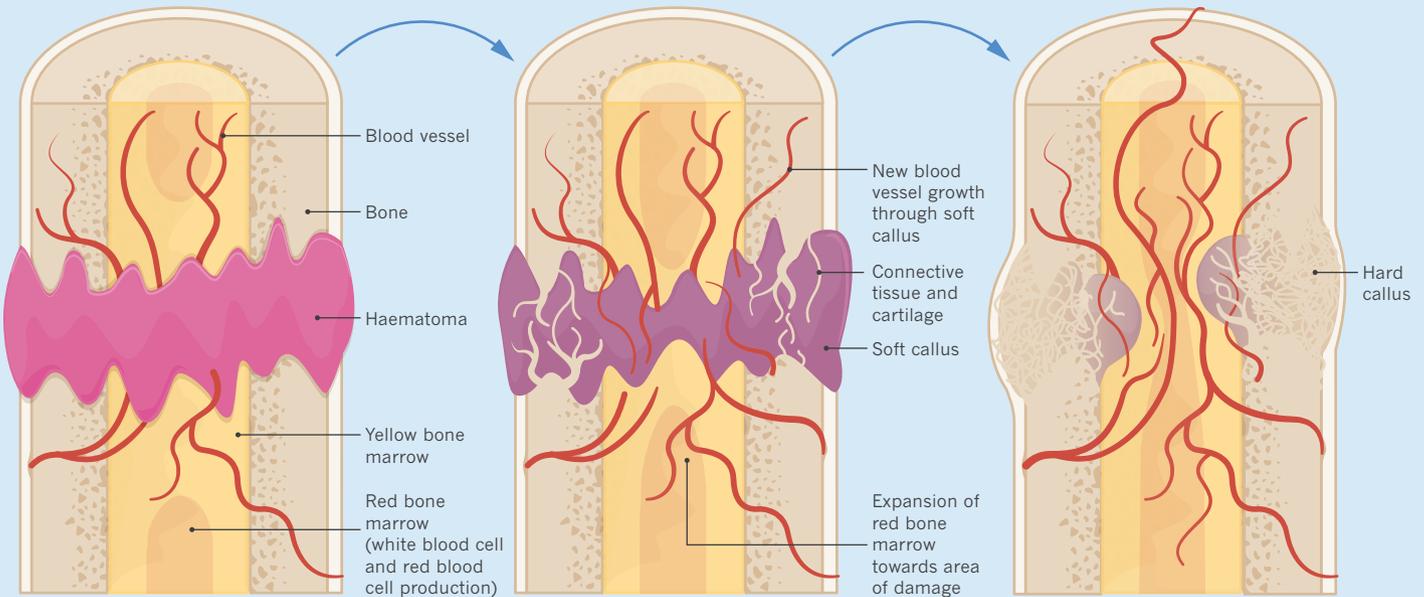


TOUGHENING UP

6–12 WEEKS

By 12 weeks after fracture, osteoblasts have transformed the soft callus into a hard callus. The length of the healing period depends on the fracture site — bones in the lower limbs can take longer because they are larger.

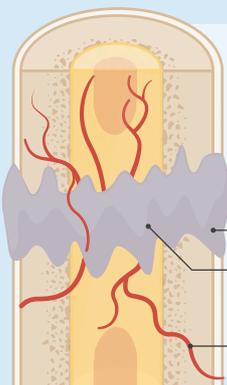
The healed bone will continue to be remodelled over the coming months and years, in response to stresses imposed by physical activity.



UNHAPPY MARRIAGE

6–9 MONTHS

Non-union bone fracture is diagnosed if there is no evidence that the broken bone will heal fully without further medical intervention.



Limited swelling
Soft connective tissue fails to mature into bone
Limited blood supply



Severe or complex fracture



Diabetes



Anti-inflammatory, opioid and anticoagulant drugs



Arthritis

RISK FACTORS

BREAKING POINT

Around 5–10% of bone fractures fail to heal¹. As the populations of developed countries age, the incidence of fractures, including non-union bone fractures, will increase.



In the United Kingdom, the incidence of fractures² is highest in men aged 15–24 and in women older than 85.

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The age beyond which women's risk of fracture increases steadily² — probably owing to a loss of bone density.

Almost **8 MILLION** fractures are reported each year in the United States³.



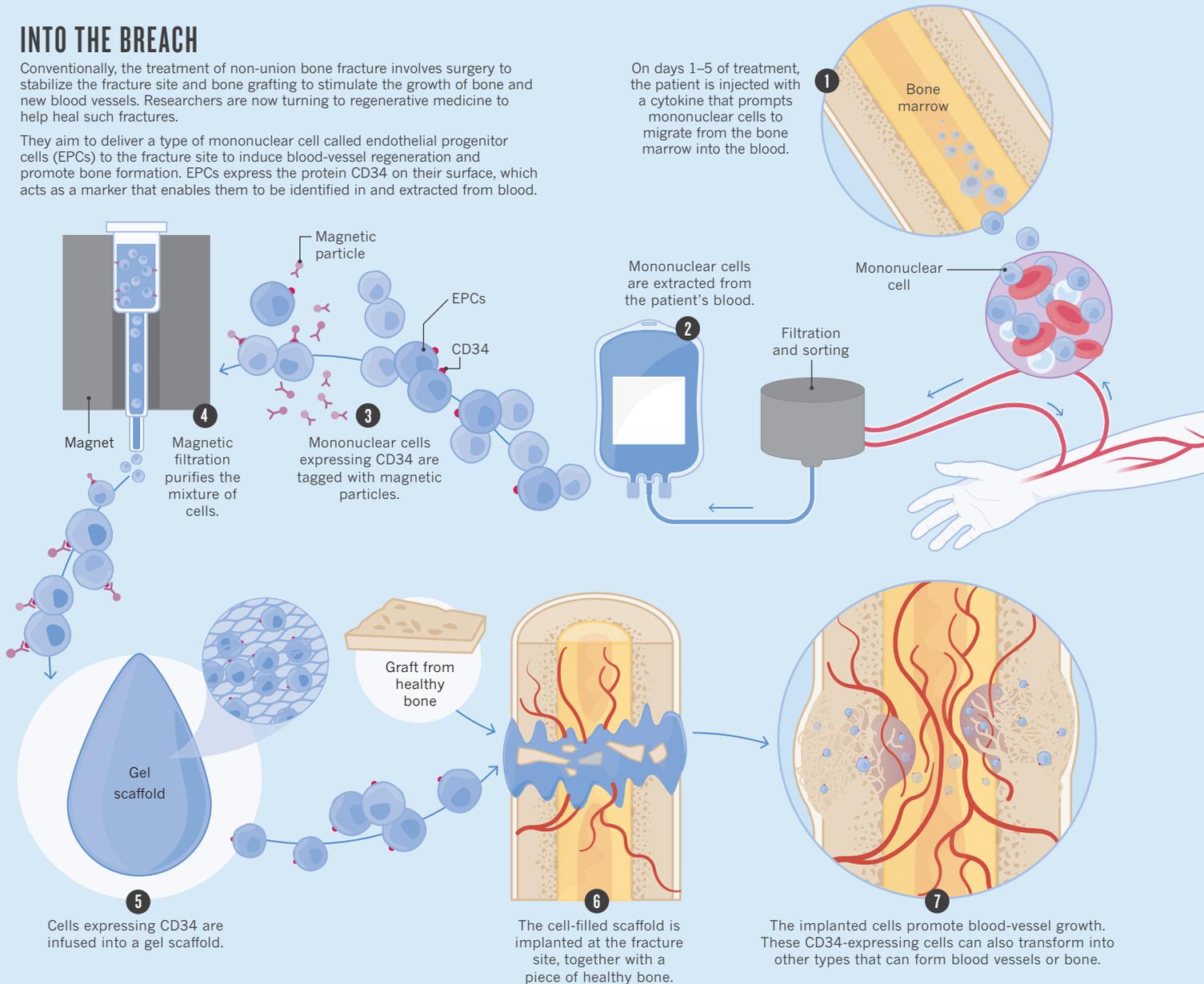
At least **400,000** of these fractures will fail to heal.

INTO THE BREACH

Conventionally, the treatment of non-union bone fracture involves surgery to stabilize the fracture site and bone grafting to stimulate the growth of bone and new blood vessels. Researchers are now turning to regenerative medicine to help heal such fractures.

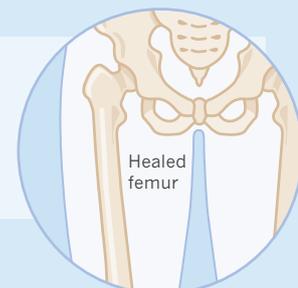
They aim to deliver a type of mononuclear cell called endothelial progenitor cells (EPCs) to the fracture site to induce blood-vessel regeneration and promote bone formation. EPCs express the protein CD34 on their surface, which acts as a marker that enables them to be identified in and extracted from blood.

On days 1–5 of treatment, the patient is injected with a cytokine that prompts mononuclear cells to migrate from the bone marrow into the blood.



NEXT STEPS

A 2014 study⁴ by researchers in Japan showed that treatment with CD34-expressing cells seems to be safe, and bone fractures healed in all people who received the therapy. But the study was too small to determine any clinical benefit. A larger, three-year trial at several institutions to study the effects of CD34-based therapy started in 2015. The results should reveal whether regenerative medicine can help to heal broken bones.



Sources: 1. Mills, L. A. & Simpson, A. H. R. W. *BMJ Open* **3**, e002276 (2013). 2. Donaldson, L. J., Reckless, I. P., Scholes, S., Mindell, J. S. & Shelton, N. J. *J. Epidemiol. Community Health* **62**, 174–180 (2008). 3. Buza, J. A. III & Einhorn, T. *Clin. Cases Miner. Bone Metab.* **13**, 101–105 (2016). 4. Kuroda, R. *et al. Stem Cells Transl. Med.* **3**, 128–134 (2014).