

The Disease that turns You to Stone

Plus new discoveries about calcification and ossification of tendons

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by [Natasha Agabalyan](#) and [Clare Wilson](#) Magazine issue [2843](#)

A rare condition turns muscles and tendons to bone. Unlocking its secrets could help to combat the bone spurs so common with ageing and injury

STANDING next to the imposing skeleton of the "Irish Giant" Charles Byrne, who reached 2.31 metres in height, the skeleton known as Mr Jeffs in the Hunterian Museum in London must often be overlooked. But to my eyes, Mr Jeffs is by far the more interesting of the two. His bones are so distorted it's a wonder he could stand up. His vertebrae have fused together in a curve, leaving him hunched over. Plates and knots of bone exist in areas where bone is simply not meant to be.

Mr Jeffs, who lived in England and is thought to have died in the 1770s, suffered from a rare genetic disease in which bone replaces other tissue such as muscle, tendons and ligaments. As the person ages, more of their body is immobilised. At a certain point they may be offered a ghastly choice about which posture to adopt: seated or lying down. This is how they will spend the rest of their lives.

Fascinating though Mr Jeffs and the other museum exhibits are, I'm not here for a day's sightseeing. I am researching how, on a lesser scale, unwanted bone can form in all of us. The tissues of our bones and joints have a habit of growing small bony lumps, or "spurs", at points where there is too much pressure or wear and tear, or after injury. Sometimes these bone spurs go unnoticed, but they can put yet more pressure on nearby flesh, causing discomfort, stiffness and serious pain.

But there is a bright spot on the horizon. Research into Mr Jeffs's disease is shedding light on the causes of unwanted bone growth that affect all of us, and it may lead to new treatments. "Looking at things that change abnormally gives us a wider picture of the mechanisms that go on in normal physiology," says James Triffitt, emeritus professor of bone metabolism at the University of Oxford.

Bone spurs do not have to be outgrowths of existing bone; they also form when other kinds of tissue transform into bone, as with Mr Jeffs. Such ossification can happen in muscle and ligaments, but the tissue most often affected is tendons: the strong cords anchoring muscles to bones are indeed our Achilles' heel.

Tendon ossification is the subject of my PhD at Brighton and Sussex Medical School in the UK, and that is what sparked my interest in Mr Jeffs. As I have been discovering, tendons are a remarkable tissue that undergo immense mechanical stress. It has been calculated that the Achilles tendon can withstand an estimated 4000 newtons of force, equivalent to holding up a 400-kilogram weight.

Tendons are not just inert tethers; they are stretchy cords, storing kinetic and potential energy during movement and then releasing it, which reduces stress on muscles and helps power movement. They are made up of fibres of collagen, a strong and stringy protein. Collagen is found in many different forms in the body but collagen bundles in



tendons have a distinct zigzag appearance under the microscope, like crimped hair (see diagram below). Under force, the crimps compress or stretch, giving the tendon its elasticity.

Unfortunately, tendons have a major flaw: they do not repair very well. This could be because there are few cells within the collagen matrix, or because they have a poor blood supply compared with other tissues. As we get older, our tendons contain even fewer cells and the characteristic crimps seen under the microscope start straightening out.

But there's another kind of tendon degeneration that is even more problematic, and that is its tendency to become more bone-like. Sometimes calcium, the main mineral component of bone, gets deposited within the tendon. This calcification often affects the Achilles tendon, the knee or the rotator-cuff tendons in the shoulder area.

Ossification is a more severe condition, when not just calcium but bone and cartilage cells appear. This process makes the tendon stiff, brittle, and more prone to damage. About a quarter of people over 60 have bony spurs in their tendons, although not all of these cause symptoms. A third of us get rotator-cuff pain due to tendon problems. Some people can blame their tendon damage on a specific injury that failed to heal, but for many of us it is simply part of ageing.

Considering that tendon problems are so common, it is an area that is neglected when it comes to research, according to Karen Walker-Bone, a rheumatologist at Brighton and Sussex Medical School. "The tendon has been a very poor relation," she says.

There is little that can be done to help tendon problems, other than strengthening exercises, or wearing joint supports, and these strategies do not always work. Some people have surgery to remove bony spurs, but most of us tend to put up with the aches and pains they cause.

The jury is still out on what might cause ossification. One idea is that injury or overuse, say from playing a favourite sport, causes inflammation and increased blood supply, which could be the source of the bone cells.

Another line of inquiry is to study what happens in extreme ossification. Which brings me back to Mr Jeffs. The condition he had is now known as fibrodysplasia ossificans progressiva (FOP). There have been only about 700 cases recorded worldwide.

The remains of three of those people reside in the Hunterian Museum. As well as Mr Jeffs, another two skeletons were donated in the past decade. These are not displayed in the main museum, as one is still in preparation (pictured, opposite), and the other specimen came from a 77-year-old woman who wanted her remains to be used for education but did not want her skeleton to be on public display.

Astounding damage

Luckily for me, the museum's head of conservation, Martyn Cooke, is happy to give me a private viewing of the two recent specimens, and I am ushered behind the scenes at the museum.

Now there is no glass case acting as a barrier and I can get up close to pore over the bones. It is the skeleton from the elderly woman that really brings home the severity of this disease. Large plates of bone cover her back, fuse her ribs shut and fix her pelvis in position. The extent of the damage is astounding (see photo on next page).

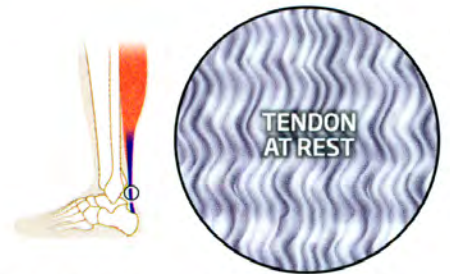
What appears a small and irrelevant area of ossification, barely noticeable to the non-anatomist, fuses her jaws together. Cooke explains that the woman had teeth removed so that she could take liquid food.

People with classical FOP tend to be born with no obvious sign except shortened big toes. Once excess bone starts forming, doctors may initially have a hard time figuring out what is wrong. Often people are misdiagnosed and are given anti-cancer treatments. "There have been instances where people have been irradiated or had large portions of their body amputated," says Triffitt, who has dealt with people with FOP for 40 years.

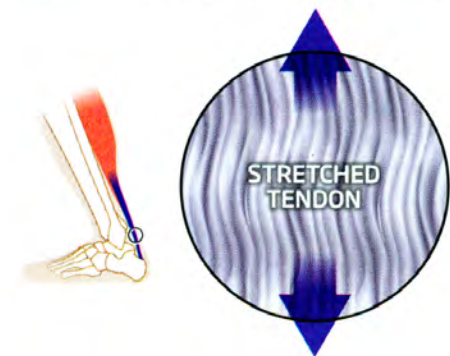
Even once the diagnosis is made, though, there is nothing that doctors can do to stop the bone from growing. Surgery to remove it triggers inflammation, which stimulates further bone formation. Giving injections has the same effect.

Stretch... and relax

Tendons are the tissue that anchors muscles to bones, such as the Achilles tendon, below



Under the microscope, tendon fibres have a characteristic crimped appearance, allowing them to stretch under tension, storing energy during movement and reducing stress on muscles



Once someone is diagnosed with FOP, the rule is to avoid all such medical interventions unless they are a matter of life or death. Such problems make tissue samples from these patients hard to come by.

All Triffitt can do is tell people with FOP what to expect and how to avoid making things worse. Because the condition is so rare there are fewer than 40 patients in the UK. "It's a very lonely disease," he says.

Contrary to appearances, bone is a dynamic tissue that is constantly being broken down and remade. A key insight came in 1965, when US orthopaedic surgeon Marshall Urist found that small scraps of dead, demineralised bone placed in the muscles of live rabbits prompted new bone growth. He speculated this was triggered by chemicals in the bone that he called bone morphogenetic proteins.

It turns out that BMPs are a large family of signalling molecules that tell the developing embryo where different tissues should form. After we are born they play other signalling roles and the different members of the family have been implicated in diverse diseases.

Urist had a hunch that BMPs could be implicated in FOP, says Triffitt, who worked as Urist's postdoc in the 1980s at the University of California, Los Angeles. But it was only in 2006 that genetic studies proved Urist right.

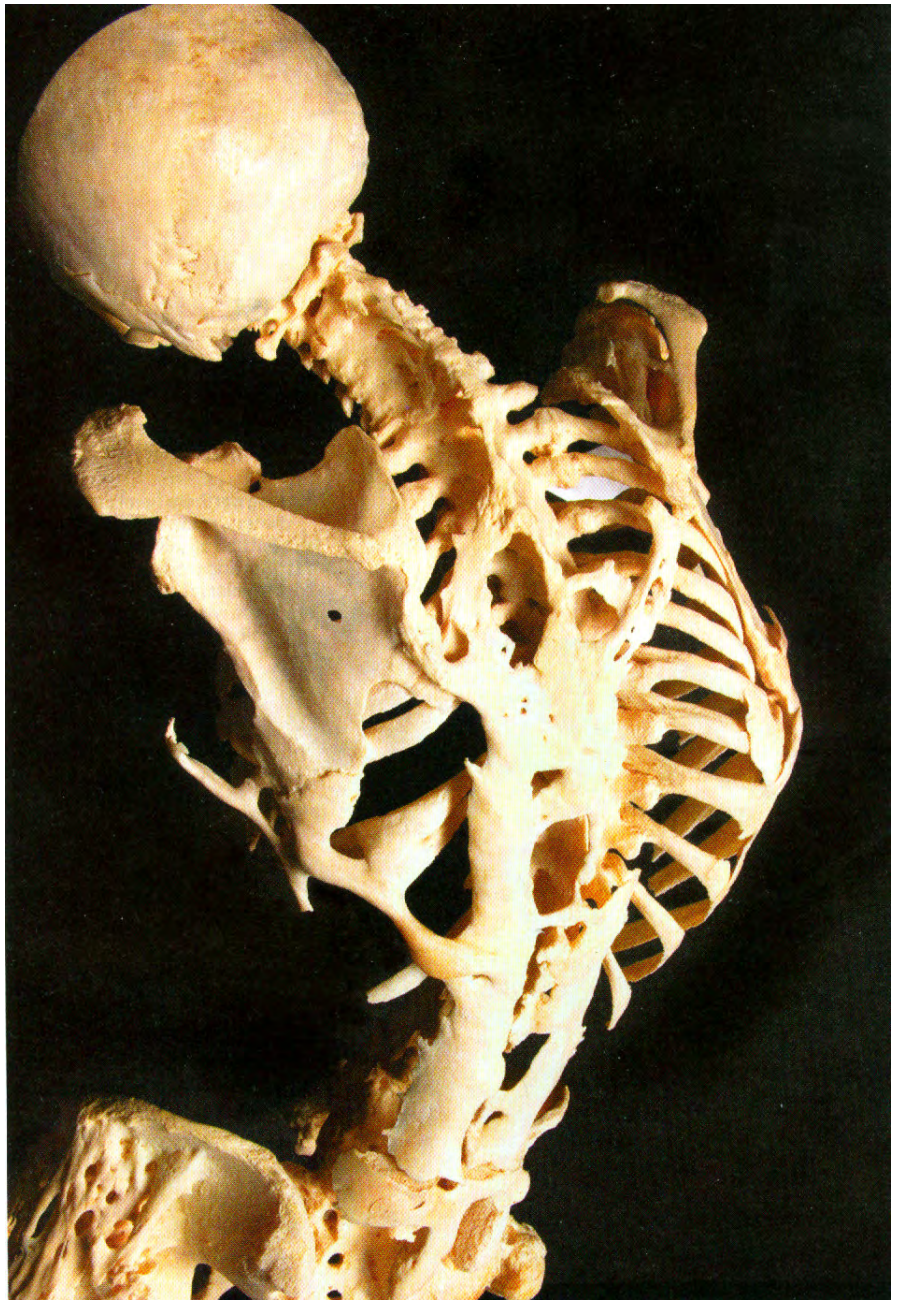
The mutation that causes FOP was identified by a large collaboration of researchers that included Triffitt. It affects one of the receptors for BMPs present on the surface of many cells including muscle and cartilage; it leaves the receptor, called ACVR1, permanently switched on ([Nature Genetics, vol 38, p 525](#)).

Several cell and animal studies suggest that BMP signalling pathways are also involved in more common forms of unwanted bone growth, including tendon ossification. For instance, a protein called "noggin" that blocks BMP reduces bone formation in the Achilles tendon of mice after it has been cut ([Journal of Bone and Joint Surgery, vol 86, p 80](#)).

Noggin is a large molecule, so it cannot be given as an oral medicine; it would not be absorbed by the gut. In the mouse study it was delivered to the Achilles tendon by gene therapy.

Surgeon Johnny Huard and the group that did the mouse study at the University of Pittsburgh, Pennsylvania, is now investigating whether this could work as a gene therapy for people with muscular dystrophy. They suspect the progressive muscle degeneration in that disorder could be caused by muscle cells becoming more bone-like.

But an oral drug to block bone formation may yet be forthcoming, thanks to a discovery by Paul Yu, a cardiologist at Harvard Medical School in Boston. Yu was trying to develop treatments for a rare form of high blood pressure that can kill people in early adulthood, which has been linked with a mutation in a different BMP receptor.



Yu's team screened a vast array of chemicals to find small molecules that affected BMP signalling. His team hit on one chemical, dorsomorphin, which reduced the activity of several BMP receptors, including ACVR1.

Yu's group tinkered with the chemical structure of dorsomorphin, trying to make similar molecules that were even more potent and specific. In 2008 they showed that one such compound, currently called LDN-193189, blocked ACVR1 so well that it reduced bone formation in mice genetically engineered to have FOP ([Nature Medicine, vol 14, p 1363](#)).

"We are now pursuing the development of these molecules as therapeutic candidates," says Yu. That might produce treatments not just for FOP but also for any kind of excess bone formation.

There are other approaches to tendon repair being explored too, including the use of stem cells - in common with diseases affecting just about every other part of the body. Arguably medicine's hottest topic at the moment, stem cells have so far been found in many tissues, including the heart, eye, pancreas and even the brain. Some groups have been trying to repair tendons with a jack-of-all-trades stem cell found in bone marrow, called mesenchymal stem cells, but so far with limited success.

In 2007, though, a type of cell was found in tendons that had all the hallmarks of stem cells: when grown in a dish they can multiply repeatedly, as well as developing into different cell types, including tendon cells ([Nature Medicine, vol 13, p 1219](#)). "At this point, no one had ever clearly shown that tendon had stem cells," says Marian Young from the National Institutes of Health in Bethesda, Maryland, who led the work.

Young and others are now investigating if these stem cells could be a better source for regenerating damaged tendons. But they need to be careful as it could be that these very cells are the source of ossification. Depending on the chemical milieu in their dish, the tendon stem cells can turn into tendon, cartilage, fat or bone.

Work by other groups supports Young's research. For instance, mice that have run too much on treadmills get inflamed tendons, with high levels of an inflammation signal called prostaglandin E2. Adding this compound to tendon stem cells in a dish makes them more likely to turn into bone cells ([Journal of Orthopaedic Research, vol 28, p 198](#)). "This may explain why overuse of tendons tends to lead to calcification," says James Wang at the University of Pittsburgh, who led the research.

And in work due to be published next month, Wang has shown that the signalling molecule that translates high prostaglandin E2 into bone formation is another member of the BMP family ([Journal of Orthopaedic Research, vol 30, p 1](#)).

This dark side of tendon stem cells might be unwelcome news for those who want to transplant them into damaged tissues, unless they can figure out ways of controlling their development. But it does shed further light on the hitherto mysterious process of ossification. If we understand how the stem cells are pushed down the wrong pathway, perhaps we can prevent or even reverse it.

Wang believes that in future, athletes' training and rehabilitation programmes will be designed around the needs of their tendon stem cells. "We know that too little mechanical loading is detrimental to tendons, but also that too much loading equally causes tendon problems," he says.

Investigating the causes of such problems is no longer a poor relation in medical research. And that's good news because a vast array of studies have demonstrated that exercise and maintaining an active lifestyle into old age has a wealth of health benefits, both physical and mental.

"It is paramount that research focuses on the safest way for us to exercise - and when injuries do occur, offers strategies for the individual to return to exercise," says Walker-Bone. Exercise is so important to our health and happiness that we cannot afford it to have any Achilles' heel.

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