

Stuck on you

Recent studies are pointing the way for new uses of an ancient treatment — leeches. Helen Pilcher wades in to find out how these creatures could help the arthritic.

They've got three jaws, with some 300 teeth, and they like to feast on human blood. "I've only been bitten around 20 times," says Carl Peters as he plunges his hand into a tank of swirling, hungry leeches. "There's about 5,000 in here," he adds casually.

Peters is assistant manager at Biopharm, a company in Wales that breeds and supplies the carnivorous worms (*Hirudo medicinalis*) for medical use worldwide. Most of the 70,000 leeches produced here annually end up draining blood from the swollen faces, limbs and digits of patients undergoing reconstructive surgery. But researchers now think that the slippery hermaphrodites may have other uses.

Recent studies suggest that leeches can lessen the pain of osteoarthritis and restore lost mobility¹. Current osteoarthritis treatments are palliative at best, so the hunt is on for any new, effective treatments — even if they involve attaching live, hungry creatures to your knees. How the beasts produce their effect is still uncertain, but scientists are keen to seek out the therapeutic proteins found in leeches, hoping then to make them synthetically and use them in the clinic.

Leeches may seem a rather outdated form of therapy, but these days they're big business. Alongside those produced in Britain, Leeches USA, based in New York, turns out thousands more and says that 10,000 are used in the United States each year. You can order your

leeches from Leeches USA for just \$7.70 each (the minimum order is seven), and have them delivered to your door, complete with a 'mobile home' for the creatures at just over \$100 a shot. And the market may be growing: in June this year, the French company Ricarimpex SAS was granted a licence to market the creatures as 'medical devices' in the United States. It was the first firm to get such a licence since regulation started in the 1970s.

Humans and leeches have a long history together. Images of leeches have been found on the walls of an ancient Egyptian tomb, and it is thought that the doctor of the Roman Emperor Marcus Aurelius used them for blood-letting some 1,500 years later². In the nineteenth century, medics thought the worms drained the body of impure blood that causes disease, and they were used to treat just about anything, from headaches to haemorrhoids.

Parasite's progress

As modern medicine developed, the tiny blood-suckers fell from favour until the 1960s, when physicians realized their potential to aid vascular surgery. During an operation, it can be hard to rejoin ruptured veins. Without functional vessels to drain blood away, tissue can be deprived of oxygen, causing cells to die. Leeches suck this excess fluid away, buying the body time to re-establish its own network of blood vessels. An astounding 80% of Britain's 62



Blood vessels: leeches attach themselves by suckers (above) and can drink ten times their own body weight in blood.

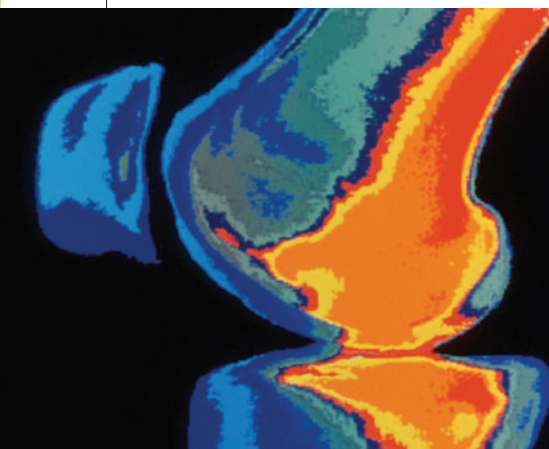
plastic-surgery units have used leeches post-operatively in the past five years².

Other uses are now being explored. Researchers Andreas Michalsen and Gustav Dobos, from the University of Duisburg-Essen in Germany, have set up clinical trials to assess the effects of leeches on knee osteoarthritis — an idea that occurred to them after speaking to local lay healers about their leech use. The degenerative condition affects up to 20% of people aged over 65, and occurs as protective tissue, called cartilage, in the knee joint breaks down, causing pain and inflammation.

In several preliminary experiments, including a trial of 24 people, the investigators slapped up to six worms on to painful joints and left them there for about an hour. The creatures drank up to ten times their own body weight in blood before they fell off. Control patients used an anti-inflammatory gel up to twice a day for a month.



Stiff drink: joints can become painful and inflamed in old age as the cartilage breaks down, but leeches ease the symptoms of osteoarthritis.



One week after treatment started, patients using leeches reported a 64% reduction in pain, as measured by self-reported questionnaire. Functional benefits lasted for up to three months. "After treatment, I could run down the stairs," says Elfriede Klein, who endured the leech therapy. "I couldn't do that before." By contrast, controls reported a 17% lessening of pain, and had no such urge to leap down staircases¹.

Since then, Michalsen and Dobos have performed a larger, as yet unpublished, study of 400 patients with osteoarthritis of the knee. A promising 80% reported a significant reduction in pain a week after treatment. After six months, about 40% said they could still feel the benefit. In the future, we may chose to reapply fresh leeches twice a year, suggests Michalsen.

Most patients had no problem getting intimate with the blood-suckers. Less than 10% of the female patients expressed disgust at their treatment, and the men said they were not repelled at all. "When they're put on you feel a gentle pinch, then a sucking feeling," says Klein. "It takes three to four minutes for them

to latch on properly, then you feel nothing at all." Around three-quarters of patients said the bite felt a little itchy, but this soon faded.

This is great when compared with the side-effects that conventional treatments can bring, points out Dobos. Non-steroidal anti-inflammatory drugs, such as ibuprofen, can ease pain sometimes, but prolonged use can lead to stomach and renal problems. Knee replacement, the other main option, involves major surgery.

But getting leeches accepted as a mainstream treatment will be hard. Large drug companies are unlikely to latch on to live creatures as a product, and may be unwilling to put derivatives from the beasts into trials until there is firmer evidence of their worth. Although the experiments show impressive results, many attribute the leech success to the placebo effect. After all, no 'proper' control could eliminate the patients' knowledge of which treatment they were using — there's no such thing as a non-blood-sucking leech. Michalsen says they have compared the patients' expectations of therapy against the actual results, and found no relationship. "The placebo effect may add to the leech effect, but it's probably not responsible for it," says Michalsen.

The secrets of saliva

There are other possible explanations for the effect: leech bites might numb a brain's response to pain, for example. Acupuncture is thought to work this way, but repetitive treatments are needed to maintain an analgesic effect. As a single leech treatment can have long-term benefits, Michalsen and Dobos think that another explanation is more likely.

Leeches don't just take, they also give, explains Dobos. As the worm bites, it injects a complex cocktail of proteins into the host through its saliva. These may be responsible for the therapeutic effects.

Certainly the saliva contains at least one anti-inflammatory molecule, called leech-derived tryptase inhibitor². Researchers suspect that the sloppy bite of a leech may contain many more such molecules.

But this may be just part of the story. Although inflammation can occur in people with osteoarthritis, researchers dispute its extent and importance. Giving patients anti-inflammatory drugs doesn't always yield improvements, and some think that any positive effects are due to the drugs' analgesic effects, rather than their ability to calm inflammation. So something else may be going on.

Osteoarthritis may be more than a disease of joint wear and tear: it may also be a vascular disorder⁴. Patients with osteoarthritis often have high cholesterol and blood that clots easily, says rheumatologist Paul Dieppe at the University of Bristol. Small clots that occur in

the blood vessels supplying bone could starve joints of oxygen and trigger the condition's symptoms, he says. Chemicals that thin the blood and break clots apart could in theory ease a patient's misery. However, Dieppe says no trials have been done with traditional anticoagulating medications for osteoarthritis: "It would be a very expensive undertaking and is somewhat speculative, so the risk-benefit issue would be a big one."

Leech saliva is full of such molecules. The best known, hirudin, was discovered more than 100 years ago⁵. The protein binds to and blocks the blood protein thrombin, a key enzyme in the clotting process. This in turn slows the production of fibrin, a tough, sticky, fibrous protein that is a key component of blood clots. A synthetic form of hirudin (lepirudin) has already made its way to the drug market as Refludan, but there could be more to follow. Another molecule, called destabilase, helps break apart any interlinked fibrin fibres; other molecules tackle the second major ingredient of blood clots: platelets⁶.

The leeches' arsenal of anti-inflammatory and anticoagulant molecules helps it go unnoticed by its host while it slurps down its liquid lunch. The beasts may also maintain a low profile by secreting a homemade analgesic. When one researcher put this to the test, she found that rats allowed to inhale a solution of powdered leech extract showed less sensitivity to pain⁷. But these results have proven hard to reproduce, and no one has been able to demonstrate a similar effect with leech saliva.

Dobos and others are now working hard to isolate and characterize the pharmacologically effective substances in leech saliva. They hope to reproduce the active ingredients chemically and to reduce the slimy treatment to a pill.

In the meantime, thousands of leeches will continue nobly to lose their lives each year in the name of medicine: once their work is done, the leeches from Biopharm and Leeches USA are gently and humanely pickled in alcohol. Life is brighter for some lucky European leeches. Those bred at the ZAUG farm in Biebertal, Germany, can expect to live out their 20 years to the full in retirement ponds. "These are hard-working animals," says Dobos. "It's only fair that they should have somewhere to grow old." ■

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