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How Maggots Made It Back into Mainstream Medicine

By ACSH Staff — May 14, 2016

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By Carrie Arnold

A writhing mass of maggots in a wound might seem like a good reason to seek medical help. But, reports Carrie Arnold, sometimes it's the doctors who have put them there, adopting an ancient treatment to help heal painful infected injuries.

By the time Michelle Marineau saw her patient, James*, there was little she could do to help him. His big toe had been removed, a complication from years of uncontrolled type 2 diabetes, but the amputation site had stubbornly refused to heal. An infection had eaten away flesh and left tendon and bone exposed, streaks of off-white against the angry, red, weeping wound. Several of his other toes had developed gangrene, turning black and slowly dropping off.

If unchecked, diabetes leads to damaged nerve endings, meaning small injuries can go unnoticed and turn into ulcers prone to life-threatening bacterial infections. The bacteria build a nearly impenetrable shield called a biofilm that protects them from antibiotics, so instead surgeons use scalpels to clear away dead tissue and infected flesh, a procedure known as sharp debridement. Unfortunately, this often misses spots, letting the infection come roaring back with an even larger area to colonise.

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Marineau, a nurse practitioner and wound care specialist on Oahu, Hawaii, had seen many patients like James before and decided that he, like over 70,000 other people with diabetes in the US each year, needed to have his foot amputated in order to save his life.

Seeing his father's distress at the looming procedure, James's son proposed a different solution: maggots.

The larvae of the greenbottle blowfly (*Lucilia sericata*) feast on the bacteria and dead tissue in chronic wounds, cleaning out the wound and giving it more of a chance to heal. This is an ancient therapy, used since Biblical times, but fell out of favour with the invention of antibiotics. However, the rise of drug-resistant bacteria, combined with skyrocketing rates of chronic wounds from diabetes, has led to a resurgence of interest in using creepy-crawlies as treatment, usually referred to these days as maggot debridement therapy or larval therapy.

Although larval therapy had been studied in the lab, few clinical trials had tested it head-to-head against more modern surgical techniques. So although Marineau agreed to try the maggots, she had no idea whether they would actually work for James.

She also had no idea how to use maggots, and had to be talked through the procedure over the phone. But it worked perfectly: "We had amazing success with him," she says. "We were just astounded." Lots of medical products hype the wonders they can work for patients, but Marineau says maggots are one of the only things that "really blow your mind at what a big difference they can make".

Marineau received the maggots via overnight mail from Monarch Labs in Long Beach, California. As she placed them one by one on James's foot in early 2009, she became the latest in a long series of healers. Cultures around the world, including the Maya of Central America, Aboriginal tribes in Australia and the Myanmar Hill People, have used maggots to treat wounds.

Much of the historical writing on the role of maggots in helping wounds heal revolves around battlefield injuries. Although such wounds can and do kill outright, the majority of deaths from war injuries have been caused by infection. Festering wounds often attract blowflies looking for a spot to lay their eggs, which then hatch into larvae. Napoleon's battlefield surgeon, Dominique Larrey, noted in an 1832 book [2] that they were "greedy only after putrefying substances, and never touch the parts which are endowed with life". And they were not just harmless but helpful, by "cutting short the process of nature" to heal wounds more quickly. Despite Larrey's advice, though, his wounded soldiers were annoyed and terrified by the larvae: "nothing short of experience" would convince them to trust the insects.

While Larrey noticed their benefits, he hadn't deliberately placed blowfly larvae on the wounds. The first documented intentional use of maggots in modern times came during the American Civil War. Confederate physician John Forney Zacharias reported: "During my service in the hospital at Danville, Virginia, I first used maggots to remove the decayed tissue in hospital gangrene and with eminent satisfaction. In a single day, they would clean a wound much better than any agents we had at our command. I used them afterwards at various places. I am sure I saved many lives by their use, escaped septicaemia, and had rapid recoveries."

19th-century knowledge of the intricate series of events by which a wound heals was primitive by today's standards, but these doctors did know two things: infected wounds were likely to kill the patient, and healing would stop if the healthy tissue of a wound died. What maggots did was remove infection and dead tissue while sparing healthy flesh. It was a remarkably effective and

efficient way to help wounds heal, deployed even in 20th-century conflicts.

Faced with battlefield wounds on an unprecedented scale in the trenches of France during World War I, Johns Hopkins University physician William Baer began seeing injuries that had become infested with maggots. His first instinct was to clean out the larvae but then, like other doctors before him, he noticed something strange: the wounds with maggots didn't become infected, they healed faster, and the soldiers were much less likely to die of their injuries.

After the war, Baer returned to Johns Hopkins and brought his insights into maggot therapy with him. In particular, he wanted to try it on chronic bone infections known as osteomyelitis. He bred and raised *Lucilia sericata* maggots on the windowsill of his Baltimore laboratory, and used the larvae on 21 patients for whom all previous treatments had failed. Two months later, Baer noted, all of their wounds had healed. However, he discovered that several of the wounds had become infected with tetanus and gangrene. He realised that he needed to sterilise the larvae before using them on patients. After several years of experiments, he finally found that a solution of mercuric chloride, alcohol and hydrochloric acid did the trick without killing the eggs.

Throughout the 1930s and 40s, the popularity of maggot therapy blossomed – at least, until the discovery of penicillin. Within a few decades, maggot therapy was relegated to a "historical backwater, of interest more for its bizarre nature than its effect on the course of medical science," said the microbiologist Milton Wainwright. It was "a therapy the demise of which no one is likely to mourn".

A tsunami of hard-to-heal wounds, however, brought this backwater back to the forefront of medicine.

Wounds go through a series of stages to close and heal. After bleeding stops, white blood cells flock to the scene to break down dead tissue and clear out any bacteria. When this process is finished, the body begins to lay down collagen, a protein that provides structural support as well as helping skin cells divide and mature. Skin cells at the edges of the wound begin to divide and slowly migrate to the centre. Once the surface of the wound is covered with a new, thin layer of cells, blood vessels form to service the new tissue, and slowly, a layer of scar tissue forms over the top.

Healing, however, doesn't always go according to plan. Many people with diabetes develop foot ulcers as an indirect result of chronic high blood sugar levels destroying nerve endings and small blood vessels. While the destroyed nerves mean small injuries can be missed, the reduced blood flow means that injury-fighting cells and chemicals can't get to the injury, so it just gets worse.

There are other conditions that interfere with healing. If the veins in your legs don't return blood to your heart as well as they should, fluid can pool in your feet and ankles. This swelling means that a simple scratch can turn into a venous leg ulcer. A similar thing can happen if your arteries don't deliver enough blood to your hands or feet. For people with conditions that mean they spend most or all of their time in bed or a wheelchair, pressure ulcers are common. For others, the problem is poor nutrition, old age, or any of a number of variables that suppress the immune system.

The result in all these cases is wounds that won't heal. The process gets stuck permanently in the

very first stage. White blood cells hang around the wound longer and in higher numbers, secreting chemicals that interfere with the growth of new cells. They also trigger production of a group of enzymes that break down the base layer of collagen upon which wound healing is built, which in turn impedes the formation of new blood vessels. As a result, some of the cells around the wound begin to die, making the wound even larger and harder to repair.

With the wound open and unhealed, bacteria move in. Even when this doesn't result in an overt infection, a thin layer of bacteria can create a biofilm that covers the sore. Large groups of biofilm bacteria coat themselves in sugars and other barriers that keep antibiotics from killing them off. Biofilms, along with dead tissue, mean that even the most advanced wound treatments won't work.

As conditions like type 2 diabetes began to grow more common in the 1980s, physicians like Ron Sherman in California saw increasing numbers of patients with wounds that refused to heal. He remembered learning about chronic wounds and the archaic-sounding maggot therapy when he was fresh out of medical school. Far from being a historical backwater, maggot therapy sounded exactly like what his chronic wound patients needed.

"The maggots were able to dissolve the dead and infected tissue, thereby cleaning the wound faster than any of the other non-surgical treatments available," he says. "I was able to treat patients who were scheduled for amputation because they had failed all other therapies."

But there was a problem: US labs were no longer producing medical-grade maggots commercially. If he wanted to do more maggot therapy, he was going to have to breed his own.

Finding maggots is easy but, as Sherman discovered, finding the right maggots is hard. He needed a species of fly that could be reared in lab colonies over many generations and that wouldn't be harmful to humans or animals. He settled on Baer's favourite, the greenbottle blowfly *Lucilia sericata*. Sherman baited small traps with rotting beef liver and placed them at various locations around his hometown of Long Beach. Eventually, in the spring of 1990, he managed to capture a female fly that had yet to lay her eggs – she was exactly what he needed to start a lab colony. At first, he raised his flies in his apartment, constructing cages out of window screens, duct tape and cardboard. As the numbers grew, he transferred the boxes to a spare closet near his lab at the University of California, Irvine.

In 2004, the US Food and Drug Administration (FDA) approved medical-grade maggots as a "medical device" to debride chronic or non-healing wounds. It gave Sherman's maggots a level of legitimacy he needed to treat patients on a wider scale. It also meant that he needed to raise his maggots in a dedicated lab to create a better-quality product and stay within FDA guidelines. So in 2007, he founded Monarch Labs, the first modern American company devoted solely to the production of sterile therapeutic maggots.

In Europe, a competing company, BioMonde, was also gaining momentum. They used the same blowfly species, but they hoped that their 2005 invention of the BioBag would set them apart. Instead of selling their maggots loose, like Monarch Labs and others, BioMonde sold theirs in a white silk mesh bag that, to an outsider, looks like a large teabag containing miniature grains of rice.

“You don’t have to see the maggots, you don’t have to touch the maggots. Everything is contained in the bag. And when you’re done, you just pitch it and place a new bag on,” says Katy Nicell, a product manager at BioMonde’s new office in Gainesville, Florida.

Sherman maintains that loose larvae do a better job than the bagged ones, since their movement across the wound surface helps to remove dead cells. “The maggots are a little lumpy-bumpy on the outside, and as they crawl across the wound, they’re acting like a file, similar to how a toothbrush cleans teeth. The physical action is important – you don’t just use mouthwash on your teeth,” he says.

But the BioBag was perfect for Linda Cowan, a nurse investigator at the Malcom Randall Veterans Affairs Hospital in Gainesville. She wanted to start a trial of maggot therapy and the bagged larvae were just more convenient for patients and their caregivers. With loose larvae, you have to count them as you place them on the wound, and count them again as they’re removed, as part of a technique Cowan wryly refers to as “no maggot left behind”.

“The problem with that is when you put in 100 maggots, that’s a big, time-consuming thing,” she says. “And then if you bring out 90 maggots, there’s a huge concern, you can see on the face of the patient, where did the other 10 go? Did they climb in my ears at night? Did they escape? Where did they go?”

A bag avoids any such concerns. It’s also a bonus for patients in hospitals, where many physicians are reluctant to allow loose maggots into their facilities.

Whether you take your maggots loose or in a bag, they work on unhealed wound tissue in the same way. Although maggots do have a mouth, they don’t munch directly on a wound. Instead, enzymes in their saliva start to break down the bacteria and dead cells, a process called extracorporeal digestion. Laboratory studies have shown that these enzymes help to kill bacteria and also increase the production of immune-system chemicals that help the body fight infection and heal wounds. Once the cells have dissolved into a nutritious smoothie, the maggots slurp it up.

“The bacteria are mixed up in everything, and the maggots just suck it all right up and break it down internally,” says Cowan’s colleague, entomologist Micah Flores.

The larvae are left on the wound for two to four days, or until they stop eating and start to become adult flies. By this point, they have grown to the size of plump jellybeans.

“The maggots go in there as God’s miniature little surgeons,” says Cowan. “They can see what we can’t see, and they can eat the bacteria and the dead tissue, and our theory is that we think that they might even do a better job than sharp debridement, but we don’t know.”

To find out if maggots were indeed better than a human with a scalpel, Cowan and Flores set up a clinical trial. People with chronic wounds, many of whom were middle-aged men with foot, venous or arterial ulcers, would receive either two applications of maggots in the BioBag or two treatments of sharp debridement. After eight days, the researchers would compare the amounts of biofilm left in the wounds to measure how effective each technique was. Cowan and Flores would also follow the patients for up to two years to see if there was a difference in how quickly their wounds healed.

They had planned their trial well. What they didn't know was whether they could get enough people to sign up.

The nature of objections to the trial surprised Cowan. Instead of finding maggot therapy off-putting, as she had expected, nearly all of the people who signed up really wanted to have it. Several dropped out after being assigned to the sharp debridement group. The maggots were so overwhelmingly popular that BioMonde agreed to provide the sharp debridement group with two free rounds of maggot therapy after the trial was over. To be fair, Cowan offered two free sessions of sharp debridement therapy for those in the maggot group as well.

Far harder than convincing patients was convincing physicians: "Some care providers see it as ancient. 'That's old fashioned and ancient and we're doing evidence-based practice', which in their minds means new. But they're not looking at the evidence behind larval debridement therapy, which there's a lot of," Cowan says.

While many patients don't care what a treatment looks like as long as it might help them, doctors will often have to overcome their inherent aversion to creepy-crawlies as well. "Many physicians just don't like the idea. They just don't like maggots. When they see the therapy, they buck," says Gwendolyn Cazander, a vascular surgeon in the Netherlands. "It's not alternative medicine, it's scientific medicine. They just don't know the details."

Dermatologist Ed Maeyens has spent more than two decades helping patients with all types of skin injuries, and it was only out of a sense of desperation that he initially turned to maggots to treat patients for whom nothing else had worked. "Doctors tend to believe they know more than maggots and can do a better job. But when I tried them, the maggots cleaned the wound beautifully," he says. "It was love at first bite."

Results from other clinical trials show that medical reluctance to embrace the maggot could be depriving patients of effective therapies, at least in the short term. In a study of 267 people in the UK with venous leg ulcers, the VenUS II trial compared loose and bagged maggots with hydrogel, an ointment that helps to promote the body's own enzymes to remove dead tissue. In results published in 2009 [3], scientists found that it took the same amount of time for the wound to heal in all three patient groups, although the maggots were better at actually debriding the wound. And in a 2011 French trial [4], researchers found that maggots did a significantly better job than conventional treatment at removing dead tissue in chronic wounds during the first week of treatment, although both treatments were equally effective by week two.

Given that it was debridement that maggots were approved for, these findings make sense to Cowan. We should see larval therapy as getting the wound ready for the next stage of healing, rather than the last step of the process, she says. "If we can clean up that wound bed and prepare it for an advanced therapy, I think that might be one of the key gaps to clinical treatment that larvae could fix."

Sherman agrees. A chronic wound is uncomfortable and painful, caring for it is time-consuming and expensive, and it can have a huge impact on everyday life. Some people have been dealing with their wounds for five years.

“Compared to a large, weeping, infected wound, a bunch of baby flies aren’t that bad,” he says.

**The patient’s name has been changed.*

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