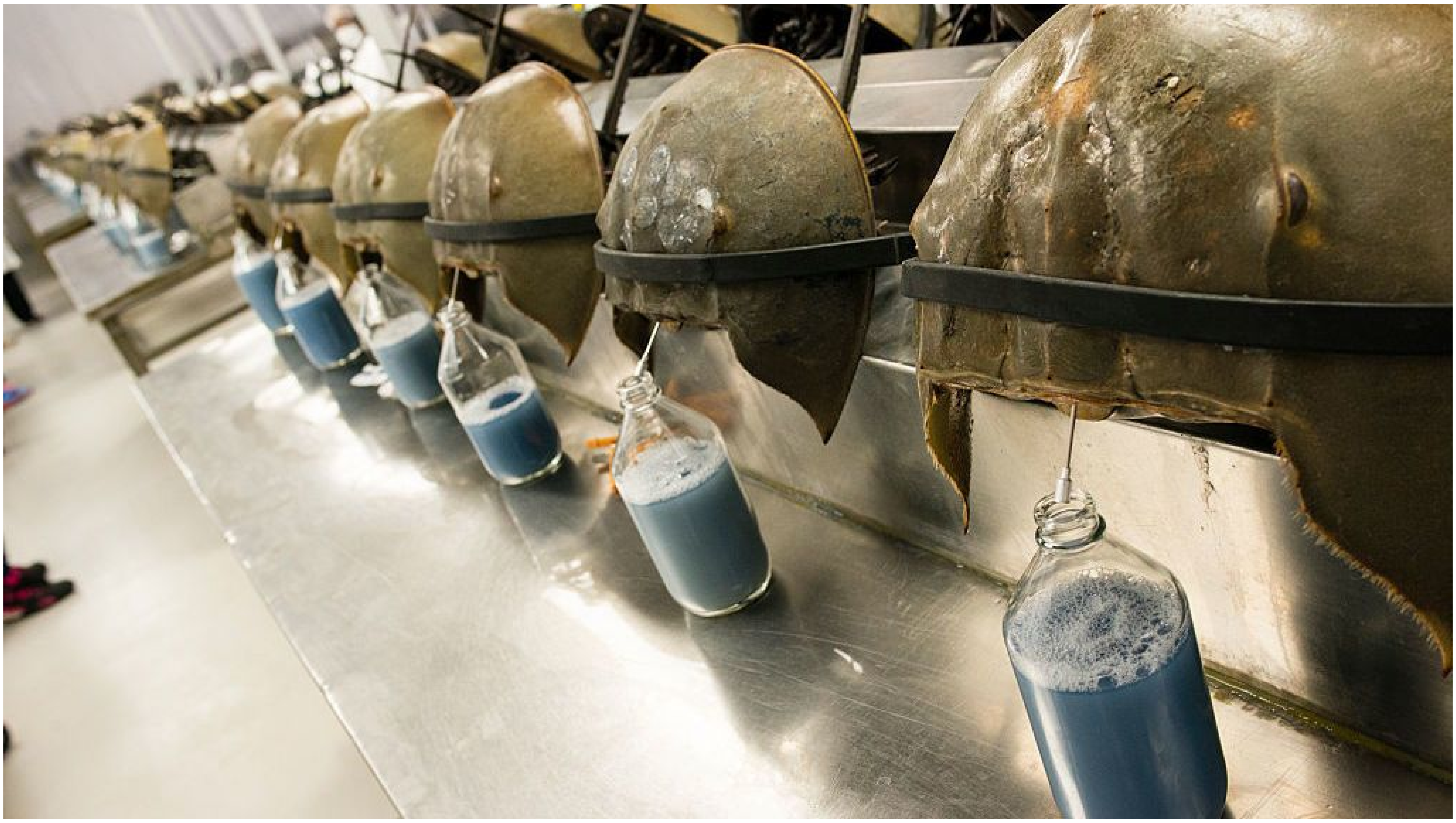

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The Blood of the Crab

By Caren Chesler Apr 13, 2017

HORSESHOE CRAB BLOOD IS AN IRREPLACEABLE MEDICAL MARVEL—AND SO BIOMEDICAL COMPANIES ARE BLEEDING 500,000 EVERY YEAR. CAN THIS CREATURE THAT'S BEEN AROUND SINCE THE DINOSAURS BE SAVED?

Meghan Owings plucks a horseshoe crab out of a tank and bends its helmet-shaped shell in half to reveal a soft white membrane. Owings inserts a needle and draws a bit of blood. "See how blue it is," she says, holding the syringe up to the light. It really is. The liquid shines cerulean in the tube.

When she's done with the show and tell, Owings squirts the contents of the syringe back into the tank. I gasp. "That's thousands of dollars!" I exclaim, and can't help but think of the scene in *Annie Hall* when Woody Allen is trying cocaine for the first time and accidentally sneezes, blowing the coke everywhere.

I'm not crazy for my concern. The cost of crab blood has been quoted as high as $14,000 per quart.

Their distinctive blue blood is used to detect dangerous Gram-negative bacteria such as *E. coli* in injectable drugs such as insulin, implantable medical devices such as knee replacements, and hospital instruments such as scalpels and IVs. Components of this crab blood have a unique and invaluable talent for finding infection, and that has driven up an insatiable demand. Every year the medical testing industry catches a half-million horseshoe crabs to sample their blood.

"EVERY MAN, WOMAN, AND CHILD AND DOMESTIC ANIMAL ON THIS PLANET THAT USES MEDICAL SERVICES IS CONNECTED TO THE HORSESHOE CRAB."

But that demand cannot climb forever. There's a growing concern among scientists that the biomedical industry's bleeding of these crabs may be endangering a creature that's been around since dinosaur days. There are currently no quotas on how many crabs one can bleed because biomedical laboratories drain only a third of the crab's blood, then put them back into the water, alive. But no one really knows what happens to the crabs once they're slipped back into the sea. Do they survive? Are they ever the same?

Scientists like Owings and Win Watson, who teaches animal neurobiology and physiology at the University of New Hampshire, are trying to get to the bottom of it.

They're worried about the toll on the creatures, from the amount of time crabs spend out of the water while in transit to the extreme temperatures they experience sitting on a hot boat deck or in a container in the back of a truck.

To that end, these two scientists are putting this strange catch to the test. The pair took 28 horseshoe crabs from the Great Bay Estuary behind their lab, left them out in the heat, then drove them around in a car for four hours and then left them in containers overnight to simulate what might happen in a bleeding facility. Then they bled half the crabs (so they'd have a control group that wasn't bled). All of the crabs remained in containers a second night, as would likely happen at a bleeding lab. The following day, Owings and Watson put $350 transmitters on their backs, attached them snugly with little zip ties, and put the crabs back into the bay to see if they could make their way. What they find might have a lot to say about the future of this odd routine.

The Potential

Horseshoe crab blood is an *E. coli* detective.

Scientists use the precious substance—specifically, the crab blood's clotting agent—to make a concoction called Limulus Amoebocyte Lysate (LAL). LAL is used to detect Gram-negative bacteria like *Escherichia coli* ("*E. coli*"), which can wreak havoc on humans.

The horseshoe crab plays a vital, if little-known, role in the life of anyone who has received an injectable medication.

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Basically, you can divide the bacteria of the world into two groups based on a test developed by Christian Gram, a Danish physician of the late 1800s. The two classes differ physiologically, especially in the composition of their cell walls. Gram-negative bacteria like *E. coli* contain a type of sugar called an endotoxin in their cell walls, while Gram-positive types like *Staphylococcus* (of the Staph infection) do not. (The "positive" and "negative" refer to how the microorganisms reacts to a staining test Gram invented.)

Those endotoxins are harmful to human beings and can survive the high heat and harsh conditions under which drugs and medical devices are sterilized and tested. They persist like zombies. Endotoxins wreak havoc on the immune system and make humans susceptible to life-threatening conditions like sepsis. LAL detects these endotoxins by turning from a liquid to a clotted gel when they come in contact with those toxins.

While industry experts say the $14,000-a-quart estimate is high—the figure is more likely the price tag for the coveted amoebocytes that are extracted from the blood—it is testament to how precious LAL has become.

To make enough of it for LAL testing, the biomedical industry now bleeds about 500,000 crabs a year. Global pharmaceutical markets are expected to grow as much as 8 percent over the next year. The medical devices market in the Americas is expected to grow about 25 percent by 2020. The demand for crabs will only grow.

The Problem

When a species is impacted on land, it's easy to see the effects. When the adverse effects occur under water, we don't really know about it—or don't really care. It's why we used to dump garbage and toxic chemicals into the water. What happens under water stays under water.

As such, scientists don't know exactly what biomedical testing does to horseshoe crabs. But they know enough to be worried.

The International Union for Conservation of Nature, which sets global standards for species extinction, created a horseshoe crab subcommittee in 2012 to monitor the issue. The group decided last year that the American horseshoe crab is "vulnerable" to extinction—a higher level of danger compared to the last Red List assessment in 1996. "Vulnerable" is just one notch below "endangered," after all. Furthermore, the report said crab populations could fall 30 percent over the next 40 years. (This risk varies by region. While populations are increasing in the Southeast and stable in the Delaware Bay, spawning in the Gulf of Maine is no longer happening at some historic locations and the population continues to decline in New England, largely because of overharvesting.)

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The same story plays out across the Pacific Ocean. The horseshoe crab native to Asia, called Tachypleus, produces a different but equally useful version of LAL called Tachypleus Amoebocyte Lysate, or TAL. But horseshoe crabs are already disappearing from beaches in China, Japan, Singapore, Taiwan, and Hong Kong, places where they once thrived. Some fear that if the pharmaceutical industry continues to grow and horseshoe crabs disappear in Asia, companies producing bacteria identifiers there will set their sights on crabs here, further depleting the U.S. population.

If the species were to dwindle, it wouldn't just be an issue for conservationists but for everyone, as LAL is currently the only substance able to detect gamma-negative bacteria in the health field. As one conservationist put it, "Every man, woman, and child and domestic animal on this planet that uses medical services is connected to the horseshoe crab."

"THEY'RE VERY HEARTY. BUT I THINK THEY PAY A PRICE FOR THAT."

The Pings

Owing's crab transmitters give off a series of acoustic pings every 45 seconds. When the crabs get within 300 to 400 meters of an underwater receiver, that gadget picks up and records the ping. Each ping is different—it indicates which crab was there, how deep it was, and how active it had been in the prior 45 seconds. Every week or two, Owings and Watson sail out in a boat to download the data, and move the receivers if they need to follow the crabs. I rode along on one of these voyages last fall.

Owing and Watson wrestle with a detector.
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The Great Bay Estuary is about 60 feet deep in the middle, though the crabs tend to hang out around the edges, foraging for food. As we drive around the waterway, the researchers gaze across the water looking for the moorings that hold the receivers. They nearly lost a receiver once when a boat ran over the rope that held it to the mooring. Nobody said science would be easy. Thankfully, a secondary rope had been attached that kept the device from dropping to the bottom of the bay.

About three minutes from the dock, we find the first one. Watson pulls a seaweed-covered rope out of the water with a hook and reels it in until he reaches the missile-shaped receiver. Owings takes it from him and inserts a key, enabling the Bluetooth device on her laptop to download the receiver data, a log of every time it detected a crab's ping.

"It's frozen," Owings says.

"The computer? Can you reboot?" Watson says.

"Trying," she says.

Nobody said technology would be easy, either.

The reboot works. As the data finishes downloading, Owings shouts, "19,000!", referring to the number of pings the receiver has picked up. She removes the key and drops the device back into the water to continue its task. The world needs that data.

The Catch

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The Atlantic States Marine Fisheries Commission (ASMFC), which manages the fishery resources along the Atlantic coast, has harvest quotas in place on bait fishermen who use horseshoe crabs to catch eels and conch. But not for biomedical laboratories. They can take as many crabs as they like, and that harvest continues to grow. The number of crabs harvested by the U.S. biomedical industry jumped from an estimated 200,000 to 250,000 in the 1990s to more than 610,000 crabs in 2012, according to the ASMFC's latest stock assessment report.

"We were successful in exempting ourselves from quotas," said Thomas Novitsky, a scientist and former CEO of Associates of Cape Cod, an LAL company in East Falmouth, Mass. "We lobbied the ASMFC, telling them we're not hurting the crabs. We're putting them back. We have a very important medical application here, so give us a break and don't put the regulations on us."

The LAL labs argued that after the crabs are bled, they go back into the water and recover. That assumption is now being questioned. The ASMFC's decision not to restrict the biomedical industry assumed that some crabs, about 15 percent, would die. Now, that threshold has been broken in the last nine years. And evidence is accumulating that the death rate of bled horseshoe crabs is much higher (more like 29 percent versus 15 percent), that females may have an impaired ability to spawn, and that bled crabs become disoriented and debilitated for various lengths of time, Novitsky said. In Pleasant Bay on Cape Cod, where horseshoe crabs are known to be bled for biomedical use, he says fewer females are spawning than in other regions.

"There's been a dramatic effect," Novitsky said. "The industry will unite and say these studies were done in a lab, and you can't compare that with what's done in nature, but that argument doesn't hold water."

Restricting the biomedical harvest is no easy task, and it starts with the red tape. According to Michael Schmidtke, the Fishery Management Plan Coordinator for ASMFC, the stock assessments (a measure of how many crabs are out there in the first place) have not taken the biomedical crab harvest into account. That's about to change. The commission voted to allow biomedical data to be used in its assessment due in 2018.

But getting a more accurate count is only part of the equation. Even if there were a quota, there's no guarantee that the organization could enforce it. First there's the question of authority. "ASMFC has no jurisdiction over the biomedical industry. It's not a fishery. It's like ASMFC trying to monitor the tobacco industry," said Jeff Brust, a research scientist with the New Jersey Department of Environmental Protection.

And then there's the pure damn necessity. While several companies have come up with synthetic alternatives for detecting the presence of endotoxins in vaccines, medicine, and medical instruments, LAL is still the only test that has received FDA approval.

The Stress

It's hard enough on a creature to lose a large quantity of blood and then survive in the wild. But that's only part of the problem for the crab. According to scientists like Owings and Watson, there's a growing body of evidence that factors related to the capture and transportation are hurting the crabs, too.

"I imagine when you put them back in the water, if you were to measure their breathing rate, it would be intense," Watson said, noting that their time spent out of the water has probably made them anaerobic for a while. "If I was put through a period where I couldn't breathe, and you put me back where you found me, I'd just sit there and breathe for a day."

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Watson says the companies catch so many crabs at one time that they can't keep them in tanks. There's just too many. And so the catchers just pile crabs out on the deck of the boat.

"Name me another marine creature who breathes under water who can survive on land the way they can," Watson says. "You can't do that with a fish, or a lobster. They're very hearty. But I think they pay a price for that."

The firms involved in this fishing will say they use best management practices in their harvesting, but it's totally voluntary, open-ended, and vague, Novitsky says, which isn't surprising. The rules were put forward by representatives of the LAL labs, which sit on ASMFC's committees. ASMFC has best practices spelled out, but they have neither enforcement nor surveillance capabilities.

"IT ALSO MADE US REALIZE WE DON'T KNOW WHAT THESE GUYS DO MOST OF THE YEAR."

"I was getting directives from the ownership that we weren't profitable enough, and you know how that goes," said Novitsky, who was actually pushed out of Cape Cod Associates after it was acquired by a Japanese firm.

Owings and Watson say they don't want to stop biomedical companies from bleeding crabs. They just want them to do it in a less damaging way. For instance: Companies may not know that when the crabs are bled—or even just held in the laboratory for a long period of time—they have a hard time replenishing their blood supply because their hemocyanin levels remain low, Watson says. Hemocyanin is a protein similar to hemoglobin that transports oxygen through the body. It's as if the crabs become anemic, and it happens by just taking them out of the water, whether you bleed them or not, though the recovery is worse if they've been bled. Their studies have shown that just being in captivity had a negative effect, Owings said.

"Imagine if you had a cow, and every time you milked it, it took a month before it had more milk. That's the problem here," Watson said, noting that if you take a quart of blood from a human, they recover within days. "In terms of the things we've found? That, to me, is a red flag. It's something that is a clear target that we can start to address."

Watson also worries that the needle itself impairs something that acts like a pacemaker in the crab's heart. In the biomedical lab, the needle is inserted in a soft membrane that runs along a hinge in the crab's shell. But that membrane runs across the crab's heart. If the needle hits the crab's pacemaker, it could disrupt its heartbeat permanently. Companies may not even know about that—Watson only does because of his thesis on horseshoe crab neurobiology.

One other thing: Horseshoe crabs have a strong tidal rhythm. They know when high tide is coming, and they move to the edge of the water. Watson tested this several years ago with a colleague, by building a version of a hamster wheel out of two five-gallon buckets with the openings facing each other but leaving just enough space in between for the crab's tail. They then placed it inside the buckets and found it would run every 12.4 hours, about the same cycle as the tides.

"It made us realize that the tides were more important to these guys than we thought. I thought it was just during mating season," he said. It was an important discovery because it meant they would lose that rhythm pretty quickly if you take them out of water and bring them into a lab. "It also made us realize we don't know what these guys do most of the year. No one observes these guys except when they're mating."

He'd like to eventually take some of his discoveries to the medical labs with the hope that they can improve their bleeding practices. If we know the bleeding process reduces the crab's hemocyanin, which compromises their immune system, feeding them a diet of copper before they are returned to the water might help bring their hemocyanin levels back up. He'd like to sell the idea to the bleeding labs. But to date, his attempts to reach them, he says—even to simply confirm that their bleeding simulations are accurate —have gone unanswered.

"I'm not trying to shut the companies down. I just want to see if there's a better way to do it," he said.

Finding Their Way

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There are about a dozen receivers in the water, and when the crabs move far out of range—and they can move several miles in a day—the researchers have to relocate them to make sure the pings continue to be read.

"We've used this method for tracking lobsters in the ocean. But sometimes, you'd have to drive around for hours looking for them. At least in here, you can drive down the middle of the bay and find them," Watson said.

We're sitting in the boat and Owings is holding one of the receivers. She's trying to get me to hear one of the pings coming from a nearby crab.

"There's one!" Owings says.

"I didn't hear it," I said.

"There!" she said, hearing another ping.

It reminded me of when our smoke alarm battery was dying, and it kept beeping, but my husband and I couldn't find the detector. For two weeks, the beep would sound but never long enough for us to locate the device. Our dog eventually found it for us.

Watson puts the boat in gear and gets ready to drive off.

"We have to put the (receiver) back!" Owings says.

"Good point, Meghan," Watson says.

As we drive off, Watson remarks on how the crabs have a mysterious understanding of where they are in the estuary and where they need to be at different times of year. Horseshoe crabs like the shallow mudflats in the spring, summer, and fall, because they can forage for snails and worms there during high tide. In the cold winter months, they don't eat much if at all, so it's hard to know where they go once they descend into deeper darker waters.

"They disperse. I don't know how they find their way," Watson said.

And yet they do. There are four hot spots for crabs in the estuary, he says, and you'll see the same crabs there at certain times of year. He knows this because researchers have tagged them. There are certain spots where the females lay their eggs, the males fertilize them, and the eggs hatch 30 days later, he says, pointing to one of those spots along the shore. And yet the larvae must be carried off by the current to a different location because the juvenile crabs aren't usually found in the spawning site but rather somewhere else in the estuary, he says. It leads him to believe there's a complex pattern to their life cycle that we don't fully understand yet.

"There's a whole connectivity going on, where you reproduce, where the eggs hatch, where the larvae get carried," even where the birds come to eat the eggs, he said. "When the biomedical labs take the crabs out to bleed them and put them back in a different spot, it could disrupt that connectivity thing."

When we get back to shore, Watson says he is going scuba diving with two other students. They need to log a certain amount of time in the water to maintain their diving credentials. As he puts on his wet suit, he tells me about a camera system he and a colleague once mounted on a lobster trap to see what happened when they were caught. What they found was that all but about a tenth of the lobsters were able to escape.

"We were dumbfounded by the results," he says.

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He puts on his weight belt, tank, fins, and goggles and walks to the end of the dock and steps into the water. He walks for a while in the shallow water, and for a time, I can still see the top of his head. But as he swims off, his head begins to disappear under the surface of the water, and he gets one more glimpse of what goes on in the darkness below.