COVID-19: What the Autopsies Reveal

W. Wayt Gibbs,Steve Mirsky

Steve Mirsky: This is another in our series of coronavirus episodes of Scientific American's Science Talk, posted on April 23, 2020. I'm Steve Mirsky.

In this episode, we hear again from our contributing editor W. Wayt Gibbs in Washington state, a region that now seems to have passed the peak of this first wave of the pandemic. Gibbs reports on how pathologists are starting to get a much closer look at the damage that COVID-19 does to the body by carefully examining the lungs, hearts, kidneys, and other organs of people who have died while infected with the novel coronavirus.

Wayt spoke with experts at the Cleveland Clinic and the University of Washington who have performed these high-risk autopsies, very few of which have been done so far in the United States.]

WWG: COVID-19 is a new disease, and doctors have been struggling to figure out how best to treat it. Putting people on ventilators is always a last resort: for other diseases, typically about half of the patients who go onto a ventilator do not survive. But COVID-19 patients seem to do even worse on mechanical ventilation. A study in the U.K. found that only about a third of coronavirus patients survived that experience. And in a report published on April 22 in the *Journal of the American Medical Association*, researchers found even more alarming outcomes recently in New York City. Analyzing data from 12 large New York hospitals during March, they found that out of 320 patients put onto ventilators, 282 died. So only about one in nine survived mechanical ventilation.

We know this new coronavirus damages the lungs, but how exactly? Does it differ in important ways from influenza and other viral lung infections? Some experts have suggested that the virus can infect and damage the heart as well, and maybe the kidneys, or even the brain. When people are seriously ill with COVID-19, they seem to be at higher risk of blood clots.

But it's really hard to determine from lab tests and fuzzy medical images whether it's the virus damaging these other organs—or whether the body's own immune system is fouling up the works, as it generates a massive inflammatory response to combat the coronavirus.

Desiree Marshall: "Any kind of lung injury can result in acute respiratory distress syndrome."

"This is a disease process that we've known about for a long time. It's a stereotypical pattern of injury that we see in the lungs when they're injured for many, many different kinds of reasons."

WWG: That's Desiree Marshall, a pathologist at the University of Washington. She says that it's often the cascading organ failure triggered by acute respiratory distress syndrome—or ARDS—that causes elderly people to die from influenza, and firefighters to die from smoke inhalation, and cancer patients to die from reactions to chemotherapy.

The pressing question we need to answer for COVID-19 is whether it's just ARDS that makes

the disease deadly, or whether this new disease is different and even more complicated to treat than what doctors have seen before.

Well, if you watch TV, you know what medical examiners do when they want to figure out what killed somebody. There's just no substitute for a thorough and detailed autopsy. Earlier this month, researchers published the first English-language autopsy results on people who died after becoming infected with the novel coronavirus. The paper appeared in the *American Journal of Clinical Pathology* on April 10. It describes two interesting cases, both from Oklahoma.

Case 1 was a 77-year-old man who had cycled between fever and chills for six days before finally calling for an ambulance on March 20. He had high blood pressure and some other health issues, but no cough. On the trip to the hospital, he was gasping for air, and his heart stopped. By the time they arrived at the emergency room, it was too late.

The gentleman had not seen a doctor for his fever. He had not been tested for COVID-19. So it wasn't clear what had caused the heart attack and taken his life.

The medical examiner's team in Oklahoma City decided that it was important to find out. They swabbed the man's nasal passages and also his lungs. Both swabs tested positive for the SARS-CoV-2 virus. And chest x-rays showed what they described as "complete whiteout" in what would normally be dark, empty lung cavities.

Doing an autopsy on a COVID-positive body is risky, but they had the special protective equipment and high-containment room they needed to do it. And maybe they could learn something that would help save some of the hundreds of thousands of people around the world who will fight COVID-19 for their lives in the months to come.

So they laid his body on the dissecting table, and they opened him up.

The team contacted a well-known lung pathologist at the Cleveland Clinic to help them interpret what they saw, especially as they examined tissue samples from various organs under the microscope.

Sanjay Mukhopadhyay: "My name is Sanjay Mukhopadhyay. I'm director of pulmonary pathology at the Cleveland Clinic."

Mukhopadhyay: "Autopsies give you another deeper look into tissue that is actually several layers of resolution higher than what you can get from a history of physical examination, routine lab tests, even the highest-resolution CT scans. None of them even approach the resolution that you can get from an autopsy."

WWG: The medical examiners had noticed that this man's lungs were two to three times heavier than usual—a common consequence of ARDS. Pathologists actually refer to that syndrome by a different name, one that describes the end result of the disease in lung cells. They call it diffuse alveolar damage.

Mukhopadhyay: "In that gentleman, we found…diffuse alveolar damage under the microscope…when you take a breath and it goes down your windpipe, the windpipe actually branches into two, and one goes into the left lung, and one goes into the right. And then those branches of the windpipe branch like the branches of a tree: you know, they get smaller and

smaller and smaller as you go further and further away. And the endpoint of the branch is what we call an alveolus. Or colloquially you can call it an air sac.

"And what that is just a very tiny balloon. You need a microscope to see it. There are just thousands and thousands of those little balloons in the lung. That's what makes up the lung.

WWG: So each time you inhale, you inflate thousands of microscopic alveoli.

Mukhopadhyay: "As the air enters into that little balloon with oxygen in it, the point of the balloon is to take that oxygen into the bloodstream. So the wall of the balloon has little blood vessels in it. In the normal lung, when you take a breath, the oxygen goes from the middle of the balloon into the wall of the balloon, and that's where the arteries are, and then the oxygen goes into your blood cells—red blood cells we call them—and then that takes it back to the heart and the heart sends the oxygen to the rest of the body.

WWG: For this exchange of oxygen and carbon dioxide to work properly, the thin lining of the air sac has to be very close to the walls of the blood vessels.

Mukhopadhyay: "Now what happens in COVID—and in actually in any severe viral infection—is that the virus starts causing damage where it attaches first, which is the back of the throat, and then all the way down the windpipe, down the branches, to the smallest branches and then into the air sacs. And when it gets into the air sacs, we call that a viral pneumonia. The virus is damaging the walls of the air sacs."

WWG: Those little webs of capillaries that surround the walls of the air sacs start to leak. Proteins, fluids, white blood cells, and debris from destroyed lung tissue seep into the air sacs. The debris clogs the balloons, but maybe even more important, it also thickens the walls of the air sacs.

Mukhopadhyay: "Literally, it's making a barrier for the oxygen to go from the middle of the alveolus to the bloodstream. This is the reason that oxygen levels are so low in these patients who are very sick from COVID."

WWG: The researchers concluded that Case 1, the 77-year-old man, had died from COVID-19, even though he had never been diagnosed with it.

Mukhopadhyay says he was struck by how similar the pattern of organ damage was to what he is used to seeing from autopsies on people who died from other viral infections.

Mukhopadhyay: "It's actually very similar to what happens in influenza…and just to mention a few other examples: SARS, you know, the SARS from 2000 to 2003— identical. MERS, the Middle Eastern Respiratory Syndrome: identical findings. I did autopsies and reported them on H1N1, when that happened, the swine flu: identical findings.

Mukhopadhyay: "And I'll give you one more example. You know, the when the vaping thing happened just recently, and many people were getting sick from that, the most sick patients were actually developing diffuse alveolar damage."

WWG: Case 2 was different. This man had gone to the hospital a day earlier, on March 19. He was only 42, but he had myotonic muscular dystrophy, a hereditary disease that causes the muscles to weaken or atrophy, sometimes so much that food can back up from the stomach

and go down the wrong tube, into the lungs, where it causes bacterial pneumonia.

He felt sharp abdominal pains and went to the hospital, where a CT scan showed fluid in his lungs. Just hours later, his heart gave out, and he passed away.

Mukhopadhyay: "Although he was labeled as community-acquired pneumonia and died and was found to be COVID-positive, the microscopic examination of this patient does not support the idea that he died of COVID. So there was no diffuse alveolar damage."

WWG: Instead, they found food particles and bacterial infection in the airway, clear signs of aspiration pneumonia. So Case 2 died *with* COVID-19, but he did not die *of* COVID-19.

Mukhopadhyay: "Which now makes it very interesting because it brings up the issue of how often is this happening? How often are people who are positive for COVID on a nasal swab dying of things other than COVID?"

WWG: I put that question to Desiree Marshall, whom we heard from earlier.

DM*: "I'm the director of autopsy and after death services at the University of Washington Medical Center."*

WWG: Since early March, Marshall has performed more than a dozen autopsies of people who died after testing positive for coronavirus infection. She says the results of those autopsies have been submitted to a medical journal for publication but are still undergoing peer review.

Marshall says that the risk of infection that this virus poses has changed how they perform all autopsies, regardless of whether the person was suspected to have COVID-19 or not.

DM: "We've actually started to swab all of our decedents and get those results before we'll perform an autopsy in our facility that isn't the negative-pressure suite."

WWG: So has Marshall also found that—like Case 2 in Oklahoma—some patients are dying of something else but turning out to have coronavirus infection as well?

DM: "We have not. We have not had any unexpected positive results yet. It's still a limited number, but of the probably 15 that we've done, we have not had a positive come back where we weren't expecting it."

WWG: And what about the finding from Case 1 in Oklahoma? Here in Washington, are most of the COVID-19 patients dying from more-or-less standard ARDS, or are the autopsies revealing evidence of the virus infecting and damaging other organs as well?

DM: "Hearing concerns of the clinicians and folks on the frontlines, … questions like is the virus infecting the heart? Or is it just kind of secondary effects related to the critical illness? Is there excess clotting related to this disease, different things like that…

"It looks like it's helping us to see that COVID is actually causing typical acute respiratory distress syndrome. Initially, there were thoughts that it was behaving a bit differently, but I think as we get more numbers of people, and there's less of the individual variability, the vast majority of these cases are showing the typical pathologic features of acute respiratory distress syndrome, which we call diffuse alveolar damage in pathology. It does look like it is that

phenomenon. And there's not something sticking out pathologically that's different. And in a way that will inform them that, you know, they should probably continue to use the evidence-based, tried-and-true therapies for ARDS.

WWG: In particular, Marshall says, they aren't seeing an unusual number of small blockages in blood vessels that would require treatment beyond the usual blood thinners such as heparin. Nor has her group or others she has heard from around the country found the coronavirus causing serious heart infections in the autopsies they have completed so far.

That's an important finding because ICU physicians in the Netherlands, New York and other places have been reporting that 20 to 40 percent of COVID-19 patients in intensive care have blood that clots abnormally. These doctors worry that tiny clots may be interfering with blood circulation in those sickest with coronavirus. That could be one reason the mortality rate among these patients is so high.

Mukhopadhyay and Marshall acknowledge that possibility. But they say that ARDS often damages blood vessels in ways that can cause tiny clots to form, and it is not yet clear whether this coronavirus infection is generating more clotting than happens in ARDS caused by other viruses or injuries. We need more evidence from more autopsies to know for certain, they say.

The jury is still also out, Marshall says, on whether the virus can cause encephalitis or other brain disease. Investigators in Washington have so far examined four brains from COVID-19 patients.

DM: "One of those showed some small hemorrhages on the brain surface and then rare small hemorrhages in the brainstem. But no obvious, frank cases where there was definite inflammation or infection by the virus. So that needs to be continued to be looked at.

WWG: Kidney disease is thought to be a risk factor for serious COVID-19 illness, but doctors have also reported a high rate of kidney damage among patients hospitalized for the virus. Acute kidney injury was seen in nearly one in five COVID-19 patients in those 12 New York City hospitals.

DM: "Any time people are severely ill or may have severe infection or shock, you can have kidney injury. So I think the question was, is it related to just the general critical illness? Or is the virus impacting and infecting the kidney tissue as well? And so far we didn't see anything that looked like obvious inflammation in the kidneys."

WWG: Nor did they see clots blocking the blood vessels in the kidneys, she says. So that's all good news.

But it's bad news that COVID-19 appears to kill mainly by causing acute respiratory distress syndrome, because biotech and drug companies have tried for decades to find effective treatments for ARDS. And so far they have largely failed.

In the near term, our best hope for a treatment is an antiviral drug that works directly to thwart SARS-CoV-2, rather than a drug that somehow shuts down the runaway immune response it causes in the worst cases.

Dozens of drug trials are now underway, and Marshall points out that autopsies may play a crucial role in these studies, as well.

DM: “One of the other places where we think autopsy can be really helpful is patients that are getting these trial therapies. And so if unfortunately patients do die while they are receiving those, just to be able to understand if there's differences in their immune response versus others. So that's another area that we'll want to be focusing on.”

WWG: For *Scientific American*’s Science Talk, I’m Wayt Gibbs.