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Scientists Say a Daily Pill to Treat COVID Could Be Just Months Away

At least three promising antivirals are being tested in clinical trials, with results expected as soon as late fall.

By JoNel Aleccia, Kaiser Health News

Within a day of testing positive for covid-19 in June, Miranda Kelly was sick enough to be scared. At 44, with diabetes and high blood pressure, Kelly, a certified nursing assistant, was having trouble breathing, symptoms serious enough to send her to the emergency room. When her husband, Joe, 46, fell ill with the virus, too, she really got worried, especially about their five teenagers at home: "I thought, 'I hope to God we don't wind up on ventilators. We have children. Who's going to raise these kids?"

But the Kellys, who live in Seattle, had agreed just after their diagnoses to join a clinical trial at the nearby Fred Hutch cancer research center that's part of an international effort to test an antiviral treatment that could halt covid early in its course.

By the next day, the couple were taking four pills, twice a day. Though they weren't told whether they had received an active medication or placebo, within a week, they said, their symptoms were better. Within two weeks, they had recovered.

"I don't know if we got the treatment, but I kind of feel like we did," Miranda Kelly said. "To have all these underlying conditions, I felt like the recovery was very quick."

The Kellys have a role in developing what could be the world's next chance to thwart covid: a short-term regimen of daily pills that can fight the virus early after diagnosis and conceivably prevent symptoms from developing after exposure.

"Oral antivirals have the potential to not only curtail the duration of one's covid-19 syndrome, but also have the potential to limit transmission to people in your household if you are sick," said Timothy Sheahan, a virologist at the University of North Carolina-Chapel Hill who has helped pioneer these therapies.

Antivirals are already essential treatments for other viral infections, including hepatitis C and HIV. One of the best known is Tamiflu, the widely prescribed pill that can shorten the duration of influenza and reduce the risk of hospitalization if given quickly.

The medications, developed to treat and prevent viral infections in people and animals, work differently depending on the type. But they can be engineered to boost the immune system to fight infection, block receptors so viruses can't enter healthy cells, or lower the amount of active virus in the body.

At least three promising antivirals for covid are being tested in clinical trials, with results expected as soon as late fall or winter, said Carl Dieffenbach, director of the Division of AIDS at the National Institute of Allergy and Infectious Diseases, who is overseeing antiviral development.

"I think that we will have answers as to what these pills are capable of within the next several months," Dieffenbach said.

The top contender is a medication from Merck & Co. and Ridgeback Biotherapeutics called molnupiravir, Dieffenbach said. This is the product being tested in the Kellys' Seattle trial. Two others include a candidate from Pfizer, known as PF-07321332, and AT-527, an antiviral produced by Roche and Atea Pharmaceuticals.

They work by interfering with the virus's ability to replicate in human cells. In the case of molnupiravir, the enzyme that copies the viral genetic material is forced to make so many mistakes that the virus can't reproduce. That, in turn, reduces the patient's viral load, shortening infection time and preventing the kind of dangerous immune response that can cause serious illness or death.

So far, only one antiviral drug, remdesivir, has been approved to treat covid. But it is given intravenously to patients ill enough to be hospitalized, and is not intended for early, widespread use. By

contrast, the top contenders under study can be packaged as pills.

Sheahan, who also performed preclinical work on remdesivir, led an early study in mice that showed that molnupiravir could prevent early disease caused by SARS-CoV-2, the virus that causes covid. The formula was discovered at Emory University and later acquired by Ridgeback and Merck.

Clinical trials have followed, including an early trial of 202 participants last spring that showed that molnupiravir rapidly reduced the levels of infectious virus. Merck chief executive Robert Davis said this month that the company expects data from its larger phase 3 trials in the coming weeks, with the potential to seek emergency use authorization from the Food and Drug Administration "before year-end."

Pfizer launched a combined phase 2 and 3 trial of its product Sept. 1, and Atea officials said they expect results from phase 2 and phase 3 trials later this year.

If the results are positive and emergency use is granted for any product, Dieffenbach said, "distribution could begin quickly."

That would mean millions of Americans soon could have access to a daily orally administered medication, ideally a single pill, that could be taken for five to 10 days at the first confirmation of covid infection. "When we get there, that's the idea," said Dr. Daniel Griffin, an infectious diseases and immunology expert at Columbia University. "To have this all around the country, so that people get it the same day they get diagnosed."

Once sidelined for lack of interest, oral antivirals to treat coronavirus infections are now a subject of fierce competition and funding. In June, the Biden administration announced it had agreed to obtain about 1.7 million treatment courses of Merck's molnupiravir, at a cost of $1.2 billion, if the product receives emergency authorization or full approval. The same month, the administration said it would invest $3.2 billion in the Antiviral Program for Pandemics, which aims to develop antivirals for the covid crisis and beyond, Dieffenbach said.

The pandemic kick-started a long-neglected effort to develop potent antiviral treatments for coronaviruses, said Sheahan. Though the original SARS virus in 2003 gave scientists a scare — followed by Middle East respiratory syndrome, or MERS, in 2012 — research efforts slowed when those outbreaks did not persist.

"The commercial drive to develop any products just went down the tubes," said Sheahan.

Widely available antiviral drugs would join the monoclonal antibody therapies already used to treat and prevent serious illness and hospitalizations caused by covid. The lab-produced monoclonal antibodies, which mimic the body's natural response to infection, were easier to develop but must be given primarily through intravenous infusions. The federal government is covering the cost of most monoclonal products at $2,000 a dose. It's still too early to know how the price of antivirals might compare.

Like the monoclonal antibodies, antiviral pills would be no substitute for vaccination, said Griffin. They would be another tool to fight covid. "It's nice to have another option," he said.

One challenge in developing antiviral drugs quickly has been recruiting enough participants for the clinical trials, each of which needs to enroll many hundreds of people, said Dr. Elizabeth Duke, a Fred Hutch research associate overseeing its molnupiravir trial.

Participants must be unvaccinated and enrolled in the trial within five days of a positive covid test. Any given day, interns make 100 calls to newly covid-positive people in the Seattle area — and most say no. "Just generally speaking, there's a lot of mistrust about the scientific process," Duke said. "And some of the people are saying kind of nasty things to the interns."

If the antiviral pills prove effective, the next challenge will be ramping up a distribution system that can rush them to people as

soon as they test positive. Griffin said it will take something akin to the program set up last year by UnitedHealthcare, which sped Tamiflu kits to 200,000 at-risk patients enrolled in the insurer's Medicare Advantage plans.

Merck officials predicted the company could produce more than 10 million courses of therapy by the end of the year. Atea and Pfizer have not released similar estimates.

Even more promising? Studies evaluating whether antivirals can prevent infection after exposure. "Think about that," said Duke, who is also overseeing a prophylactic trial. "You could give it to everyone in a household, or everyone in a school. Then we're talking about a return to, maybe, normal life."

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Cancer Without Chemotherapy: 'A Totally Different World'

A growing number of cancer patients, especially those with breast and lung cancers, are being spared the dreaded treatment in favor of other options.

By Gina Kolata

Dr. Seema Doshi, a dermatologist near Boston, thought it was a foregone conclusion that she would have to undergo chemotherapy when a cancerous lump was found in her breast in 2019.

Dr. Seema Doshi was shocked and terrified when she found a lump in her breast that was eventually confirmed to be cancerous.

"That rocked my world," said Dr. Doshi, a dermatologist in private practice in the Boston suburb of Franklin who was 46 at the time of her diagnosis. "I thought, 'That's it. I will have to do chemotherapy.'" She was wrong.

Dr. Doshi was the beneficiary of a quiet revolution in breast cancer treatment, a slow chipping away at the number of people for whom chemotherapy is recommended. Chemotherapy for decades was considered "the rule, the dogma," for treating breast cancer and other cancers, said Dr. Gabriel Hortobagyi, a breast cancer specialist at MD Anderson Cancer Center in Houston. But data from a variety of sources offers some confirmation of what many oncologists say anecdotally — the method is on the wane for many cancer patients.

Genetic tests can now reveal whether chemotherapy would be beneficial. For many there are better options with an ever-expanding array of drugs, including estrogen blockers and drugs that destroy cancers by attacking specific proteins on the surface of tumors. And there is a growing willingness among oncologists to scale back unhelpful treatments.

The result spares thousands each year from the dreaded chemotherapy treatment, with its accompanying hair loss, nausea, fatigue, and potential to cause permanent damage to the heart and to nerves in the hands and feet.

The diminution of chemotherapy treatment is happening for some other cancers, too, including lung cancer, the most common cause of cancer deaths among men and women in the United States, killing about 132,000 Americans each year. Breast cancer is the second leading cause of cancer deaths among women, killing 43,000.

Still, the opportunity to avoid chemotherapy is not evenly distributed, and is often dependent on where the person is treated and by whom. But for some patients who are lucky enough to visit certain cancer treatment centers, the course of therapy has changed. Now, even when chemotherapy is indicated, doctors often give fewer drugs for less time.

"It's a totally different world," said Dr. Lisa Carey, a breast cancer specialist at the University of North Carolina.

Dr. Robert Vonderheide, a lung cancer specialist who heads the University of Pennsylvania's Abramson Cancer Center, remembers his early days on the job, about 20 years ago.

"The big discussion was, Do you give patients two different types of chemotherapy or three?" he said. There was even a clinical trial to see whether four types of chemotherapy would be better.

"Now we are walking in to see even patients with advanced lung cancer and telling them, 'No chemo,'" Dr. Vonderheide said.

Breaking down the dogma.

The breast cancer treatment guidelines issued by the National Cancer Institute 30 years ago were harsh: chemotherapy for about 95 percent of patients with breast cancer.

The change began 15 years ago, when the first targeted drug for breast cancer, Herceptin, was approved as an initial treatment for about 30 percent of patients who have a particular protein on their tumor surface. It was given with chemotherapy and reduced the chance of a recurrence by half and the risk of dying from breast cancer by a third, "almost regardless of how much and what type of chemotherapy was used," Dr. Hortobagyi said.

In a few studies, Herceptin and another targeted drug were even given without chemotherapy, and provided substantial benefit, he added. That, Dr. Hortobagyi said, "started to break the dogma" that chemotherapy was essential.

But changing cancer therapies was not easy. "It is very scary," to give fewer drugs, Dr. Hortobagyi said. "It is so much easier to pile on treatment on top of treatment," he continued, "with the promise that 'if we add this it might improve your outcome.'"

But as years went by, more and more oncologists came around, encouraged by new research and new drugs.

The change in chemotherapy use is reflected in a variety of data collected over the years. A study of nearly 3,000 women treated from 2013 to 2015 found that in those years, chemotherapy use in early-stage breast cancer declined to 14 percent, from 26 percent. For those with evidence of cancer in their lymph nodes, chemotherapy was used in 64 percent of patients, down from 81 percent.

More recent data, compiled by Dr. Jeanne Mandelblatt, a professor of medicine and oncology at Georgetown, and her colleagues, but not yet published, included 572 women who were 60 or older and enrolled in a federal study at 13 medical centers. Overall, 35 percent of older women received chemotherapy in 2012. That number fell to 19 percent by the end of 2019.

Cheaper and faster genetic sequencing has played an important role in this change. The technology made it easier for doctors to test tumors to see if they would respond to targeted drugs. Genetic tests that looked at arrays of proteins on cancer cells accurately predicted who would benefit from chemotherapy and who would not.

There are now at least 14 new targeted breast cancer drugs on the market — three were approved just last year — with dozens more in clinical trials and hundreds in initial development.

Some patients have reaped benefits beyond avoiding chemotherapy. The median survival for women with metastatic breast cancer who are eligible for Herceptin went from 20 months in the early 1990s, to about 57 months now, with further improvements expected as new drugs become available. For women with tumors that are fed by estrogen, the median survival increased from about 24 months in the 1970s to almost 64 months today.

Now some are in remission 10 or even 15 years after their initial treatment, Dr. Hortobagyi said. "At breast cancer meetings, a light bulb went off. 'Hey, maybe we are curing these patients,'" Dr. Hortobagyi said.

'Some cases keep me up at night.'

Dr. Doshi's oncologist, Dr. Eric Winer of the Dana-Farber Cancer Institute, gave her good news: A genetic test of her tumor indicated she would not get any significant benefit from chemotherapy. Hormonal therapy to deprive her cancer of the estrogen that fed it would suffice.

But as much as Dr. Doshi dreaded chemotherapy, she worried about forgoing it. What if her cancer recurred? Would chemotherapy, awful as it is, improve her outcome?

She got a second opinion. The doctor she consulted advised a "very aggressive" treatment, Dr. Doshi said — a full lymph node dissection followed by chemotherapy.

She had multiple conversations with Dr. Winer, who ended up discussing her case with four other specialists, all of whom recommended against chemotherapy.

Finally, Dr. Doshi said, "my husband said I should just pick a horse and run with it." She trusted Dr. Winer.

Her struggles mirror what oncologists themselves go through. It can take courage to back off from chemotherapy.

One of the most difficult situations, Dr. Winer said, is when a patient has far more advanced disease than Dr. Doshi did — hers had spread to three lymph nodes but no further — and is not a candidate for one of the targeted treatments. If such a patient has already had several types of chemotherapy, more is unlikely to help. That means there is no treatment.

It falls to Dr. Winer to tell the patient the devastating news.

Dr. Susan Domchek, a breast cancer specialist at the University of Pennsylvania, can relate to those struggles.

"It is the nature of being an oncologist to be perpetually worried that you are either overtreating or undertreating a patient," she said.

"Some cases keep me up at night," she said, "specifically the cases where the risks and benefits of chemotherapy are close, yet the stakes still feel so high."

Survival rates are tripling for lung patients.

When Dr. Roy Herbst of Yale started in oncology about 25 years ago, nearly every lung cancer patient with advanced disease got chemotherapy.

With chemotherapy, he said, "patients would be sure to have one thing: side effects." Yet despite treatment, most tumors continued to grow and spread. Less than half his patients would be alive a year later. The five-year survival rate was just 5 to 10 percent.

Those dismal statistics barely budged until 2010, when targeted therapies began to emerge. There are now nine such drugs for lung cancer patients, three of which were approved since May of this year. About a quarter of lung cancer patients can be treated with these drugs alone, and more than half who began treatment with a targeted drug five years ago are still alive. The five-year survival rate for patients with advanced lung cancer is now approaching 30 percent.

But the drugs eventually stop working for most, said Dr. Bruce Johnson, a lung cancer specialist at Dana-Farber. At that point many start on chemotherapy, the only option left.

Another type of lung cancer treatment was developed about five years ago — immunotherapy, which uses drugs to help the immune system attack cancer. Two-thirds of patients from an unpublished study at Dana-Farber were not eligible for targeted therapies but half of them were eligible for immunotherapy alone, and others get it along with chemotherapy.

Immunotherapy is given for two years. With it, life expectancy has almost doubled, said Dr. Charu Aggarwal, a lung cancer specialist at the University of Pennsylvania.

Now, said Dr. David Jackman of Dana-Farber, chemotherapy as the sole initial treatment for lung cancer, is shrinking, at least at that cancer treatment center, which is at the forefront of research. When he examined data from his medical center he found that, since 2019, only about 12 percent of patients at Dana-Farber got chemotherapy alone, Dr. Jackman said. Another 21 percent had a targeted therapy as their initial treatment, and among the remaining patients, 85 percent received immunotherapy alone or with chemotherapy.

In contrast, in 2015, only 39 out of 239 patients received a targeted

therapy as their initial treatment. The rest got chemotherapy.

Dr. Aggarwal said she was starting to witness something surprising — some who had received immunotherapy are still alive, doing well, and have no sign of cancer five years or more after their initial treatment. She said: "I started out saying to patients, 'I will treat you with palliative intent. This is not curative.'"

Now some of those same patients are sitting in her clinic wondering if their disease is gone for good.

'It's almost surreal.'

Chong H. Hammond's symptoms were ambiguous — a loss of appetite and her weight had dropped to 92 pounds.

"I did not want to look at myself in the mirror," she said.

It took from October 2020 until this March before doctors figured it out. She had metastatic lung cancer.

Then Dr. Timothy Burns, a lung cancer specialist at the University of Pittsburgh, discovered that Mrs. Hammond, who is 71 and lives in Gibsonia, Pa., had a tumor with two unusual mutations.

Although a drug for patients with Mrs. Hammond's mutations has not been tested, Dr. Burns is an investigator in a clinical trial involving patients like her. He offered her the drug osimertinib, which is given as a pill. This allowed her to avoid chemotherapy.

Ten days later she began feeling better and started eating again. She had energy to take walks. She was no longer out of breath.

Dr. Burns said her lung tumors are mostly gone and tumors elsewhere have shrunk. If Mrs. Hammond had gotten chemotherapy, her life expectancy would be a year or a little more, Dr. Burns said. Now, with the drug, it is 38.6 months.

Dr. Burns is amazed by how lung cancer treatment has changed. "It's been remarkable," he said. "We still quote the one-year survival but now we are talking about survival for two, three, four or even five years. I even have patients on the first targeted drugs that are on them for six or even seven years."

Mark Catlin, who is being treated at Dana-Farber, is one of those patients. On March 8, 2014, Mr. Catlin, who has never smoked, noticed a baseball-size lump under his arm. "The doctors told me to hope for anything but lung," he said. But lung it was. It had already spread under his arm and elsewhere. Oncologists in Appleton, Wis., where he lives, wanted to start chemotherapy.

"I was not a fan," Mr. Catlin said. His son, who lives in the Boston area, suggested he go to Dana-Farber.

There, he was told he could take a targeted therapy but that it would most likely stop working after a couple of years. He is 70 now, and still taking the therapy seven years later — two pills a day, with no side effects.

He rides a bike 15 to 25 miles every day or runs four to five miles.

His drug, crizotinib, made by Pfizer, has a list price of $20,000 a month. Mr. Catlin's co-payment is $1,000 a month.

But, he says, "it's keeping me alive."

"It's almost surreal," Mr. Catlin said.

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You May Need More Vitamin C – New Analysis of Landmark Scurvy Study Leads To Update on Vitamin C Needs

Establishing healthy levels of vitamin C in humans - needs more than an "eyeball method" of data assessment

It was wartime and food was scarce. Leaders of England's effort to wage war and help the public survive during World War II needed to know: Were the rations in lifeboats adequate for survival at sea? And, among several experiments important for public as well as military heath, how much vitamin C did a person need to avoid the deadly disease scurvy?

In one experiment at the Sorby Research Institute in Sheffield, called the "shipwreck" experiment, volunteers were fed only what

the navy carried in lifeboats. The grueling experiment resulted in more water and less food being carried in lifeboats.

One of the more robust experiments run on human subjects during this time in England, which has had long-lasting public health consequences, was a vitamin C depletion study started in 1944, also at Sorby. This medical experiment involved 20 subjects, most of whom were conscientious objectors living in the building where many experiments, including the shipwreck experiment, were conducted. They were overseen by a future Nobel Prize winner, and detailed data was kept on each participant in the study.

"The vitamin C experiment is a shocking study," said Philippe Hujoel, lead author of a new analysis of the Sorby vitamin C experiment, a practicing dentist and professor of oral health sciences in the UW School of Dentistry. "They depleted people's vitamin C levels long-term and created life-threatening emergencies. It would never fly now."

Even though two trial participants developed life-threatening heart problems because of the vitamin C depletion, Hujoel added, none of the subjects were permanently harmed, and in later interviews several participants said they would volunteer again given the importance of the research.

Because of the war and food shortages, there was not enough vitamin C available, and they wanted to be conservative with the supplies, explained Hujoel, who is also an adjunct professor of epidemiology. The goal of the Sorby investigators was not to determine the required vitamin C intake for optimal health; it was to find out the minimum vitamin C requirements for preventing scurvy.

Vitamin C is an important element in your body's ability to heal wounds because the creation of scar tissue depends on the collagen protein, and the production of collagen depends on vitamin C. In addition to knitting skin back together, collagen also maintains the integrity of blood vessel walls, thus protecting against stroke and heart disease.

In the Sorby trial, researchers assigned participants to zero, 10, or 70 milligrams a day for an average of nine months. The depleted subjects were then repleted and saturated with vitamin C. Experimental wounds were made during this depletion and repletion. The investigators used the scar strength of experimental wounds as a measure of adequate vitamin C levels since poor wound healing, in addition to such conditions as bleeding gums, are an indication of scurvy.

In the end, the Sorby researchers said 10 milligrams a day was enough to ward off signs of scurvy. Partly based on these findings, the WHO recommends 45 milligrams a day. Hujoel said that the findings of the re-analyses of the Sorby data suggest that the WHO's recommendation is too low to prevent weak scar strength.

In a bit of scientific detective work, Hujoel said he tracked down and reviewed the study's data, and with the aid of Margaux Hujoel, a scientist with Brigham and Women's Hospital/Harvard Medical School, put the data through modern statistical techniques designed to handle small sample sizes, techniques not available to the original scientists. The results of their work were published on August 16, 2021, in the *American Journal of Clinical Nutrition*.

The Hujoels discovered that the data from this unique study — which has been a cornerstone used by WHO and other agencies for establishing healthy levels of vitamin C in humans — needed more than an "eyeball method" of data assessment.

"It is concluded that the failure to reevaluate the data of a landmark trial with novel statistical methods as they became available may have led to a misleading narrative on the vitamin C needs for the prevention and treatment of collagen-related pathologies," the researchers wrote.

"Robust parametric analyses of the (Sorby) trial data reveal that an

average daily vitamin C intake of 95 mg is required to prevent weak scar strength for 97.5% of the population. Such a vitamin C intake is more than double the daily 45 mg vitamin C intake recommended by the WHO but is consistent with the writing panels for the National Academy of Medicine and (other) countries," they add.

The Hujoels' study also found that recovery from a vitamin C deficiency takes a long time and requires higher levels of vitamin C. Even an average daily dose of 90 milligrams a day of vitamin C for six months failed to restore normal scar strength for the depleted study participants.

Reference: "Vitamin C and scar strength: analysis of a historical trial and implications for collagen-related pathologies" by Philippe P Hujoel and Margaux L A Hujoel, 16 August 2021, American Journal of Clinical Nutrition. DOI: 10.1093/ajcn/nqab262

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Late Pleistocene Humans May Have Hatched and Raised "World's Most Dangerous Bird" 18,000 Years Ago

Humans in New Guinea may have collected cassowary eggs near maturity and then raised the birds to adulthood

As early as 18,000 years ago, humans in New Guinea may have collected cassowary eggs near maturity and then raised the birds to adulthood, according to an international team of scientists, who used eggshells to determine the developmental stage of the ancient embryos/chicks when the eggs cracked.

Cassowaries are wary of humans, but if provoked, they are capable of inflicting serious, even fatal, injuries to both dogs and people. The cassowary has often been labeled "the world's most dangerous bird."

"This behavior that we are seeing is coming thousands of years before domestication of the chicken," said Kristina Douglass, assistant professor of anthropology and African studies, Penn State. "And this is not some small fowl, it is a huge, ornery, flightless bird that can eviscerate you. Most likely the dwarf variety that weighs 20 kilos (44 pounds)."

The researchers reported on September 27, 2021, in the *Proceedings of the National Academy of Sciences* that "the data presented here may represent the earliest indication of human management of the breeding of an avian taxon anywhere in the world, preceding the early domestication of chicken and geese by several millennia."

A modern day cassowary chick. **Credit: Andy Mack**

Cassowaries are not chickens; in fact, they bear more resemblance to velociraptors than most domesticated birds. "However, cassowary chicks imprint readily to humans and are easy to maintain and raise up to adult size," the researchers report. Imprinting occurs when a newly hatched bird decides that the first thing it sees is its mother. If that first glance happens to catch sight of a human, the bird will follow the human anywhere.

According to the researchers, cassowary chicks are still traded as a commodity in New Guinea.

Importance of eggshells

Eggshells are part of the assemblage of many archeological sites, but according to Douglass, archaeologists do not often study them. The researchers developed a new method to determine how old a chick embryo was when an egg was harvested. They reported this work in a recent issue of the Journal of Archaeological Science.

"I've worked on eggshells from archaeological sites for many years," said Douglass. "I discovered research on turkey eggshells

that showed changes in the eggshells over the course of development that were an indication of age. I decided this would be a useful approach."

The age assignment of the embryos/chicks depends on the 3-dimensional features of the inside of the shell. To develop the method needed to determine the eggs' developmental age when the shells broke, the researchers used ostrich eggs from a study done to improve ostrich reproduction. Researchers at the Oudtshoorn Research Farm, part of the Western Cape Government of South Africa, harvested three eggs every day of incubation for 42 days for their study and supplied Douglass and her team with samples from 126 ostrich eggs.

They took four samples from each of these eggs for a total of 504 shell samples, each having a specific age. They created high-resolution, 3D images of the shell samples. By inspecting the inside of these eggs, the researcher created a statistical assessment of what the eggs looked like during stages of incubation. The researchers then tested their model with modern ostrich and emu eggs of known age.

The insides of the eggshells change through development because the developing chicks get calcium from the eggshell. Pits begin to appear in the middle of development.

"It is time dependent, but a little more complicated," said Douglass. "We used a combination of 3D imaging, modeling and morphological descriptions."

The researchers then turned to legacy shell collections from two sites in New Guinea — Yuku and Kiowa. They applied their approach to more than 1,000 fragments of these 18,000- to 6,000-year-old eggs.

"What we found was that a large majority of the eggshells were harvested during late stages," said Douglass. "The eggshells look very late; the pattern is not random. They were either into eating baluts or they are hatching chicks."

A balut is a nearly developed embryo chick usually boiled and eaten as street food in parts of Asia.

The original archaeologists found no indication of penning for the cassowaries. The few cassowary bones found at sites are only those of the meaty portions — leg and thigh — suggesting these were hunted birds, processed in the wild and only the meatiest parts got hauled home.

"We also looked at burning on the eggshells," said Douglass. "There are enough samples of late stage eggshells that do not show burning that we can say they were hatching and not eating them."

To successfully hatch and raise cassowary chicks, the people would need to know where the nests were, know when the eggs were laid and remove them from the nest just before hatching. Back in the late Pleistocene, according to Douglass, humans were purposefully collecting these eggs and this study suggests people were not just harvesting eggs to eat the contents.

Reference: "Late Pleistocene/Early Holocene sites in the montane forests of New Guinea yield early record of cassowary hunting and egg harvesting" by Kristina Douglass, Dylan Gaffney, Teresa J. Feo, Priyangi Bulathsinhala, Andrew L. Mack, Megan Spitzer and Glenn R. Summerhayes, 27 September 2021, Proceedings of the National Academy of Sciences. DOI: 10.1073/pnas.2100117118

Also working on this project from Penn State were Priyangi Bulathsinhala, assistant teaching professor of statistics; Tim Tighe, assistant research professor, Materials Research Institute; and Andrew L. Mack, grants and contract coordinator, Penn State Altoona.

Others working on the project include Dylan Gaffney, graduate student, University of Cambridge, U.K.; Theresa J. Feo, senior science officer, California Council of Science and Technology; and Megan Spitzer, research assistant; Scott Whittaker, manager, scientific imaging; Helen James, research zoologist and curator of birds; and Torben Rick, curator of North American Archaeology, all at the Natural Museum of Natural History, Smithsonian Institution. Glenn R. Summerhayes, professor of archaeology, University of Otago, New Zealand; and Zanell Brand, production scientist, Oudtshoorn Research Farm, Elsenburg, Department of Agriculture, Western Cape Government, South Africa, also worked on the project.

The Smithsonian National Museum of Natural History, the National Science Foundation and Penn State's College of the Liberal Arts supported this work.

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This May Be the First Planet Found Orbiting 3 Stars at Once

It's called a circumtriple planet, and evidence that one exists suggests that planet formation is less unusual than once believed.

By Jonathan O'Callaghan

GW Ori is a star system 1,300 light years from Earth in the constellation of Orion. It is surrounded by a huge disk of dust and gas, a common feature of young star systems that are forming planets. But fascinatingly, it is a system with not one star, but three.

As if that were not intriguing enough, GW Ori's disk is split in two, almost like Saturn's rings if they had a massive gap in between. And to make it even more bizarre, the outer ring is tilted at about 38 degrees.

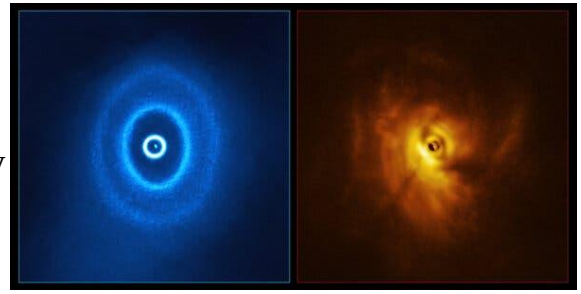
Scientists have been trying to explain what is going on there. Some hypothesized that the gap in the disk could be the result of one or more planets forming in the system. If so, this would be the first known planet that orbits three stars at once, also known as a circumtriple planet.

Now the GW Ori system has been modeled in greater detail, and researchers say a planet — a gassy world as massive as Jupiter — is the best explanation for the gap in the dust cloud. Although the planet itself cannot be seen, astronomers may be witnessing it carve out its orbit in its first million years of its existence.

A paper on the finding was published in September in the Monthly Notices of the Royal Astronomical Society. The scientists say it disproves an alternative explanation — that the gravitational torque of the stars cleared the space in the disk. Their paper suggests there is not enough turbulence in the disk, known as its viscosity, for this explanation to suffice.

The finding also highlights how much more there is to learn about the unexpected ways in which planets can form.

Anyone who has watched George Lucas' original "Star Wars" is familiar with planets that can have two stars rising and falling in its skies. Luke Skywalker's dusty home of Tatooine was in such a binary star system. But a planet orbiting three stars would be more unusual.



An image made by the ALMA telescope, left, shows the GW Ori disc's ringed structure, with the innermost ring separated from the rest of the disc. The SPHERE observations, right, show the shadow of this innermost ring on the rest of the disc. **Credit...ESO/L. Calçada, Exeter/Kraus et al.**

If a familiar life form could dwell on a gas giant like the one that would be orbiting GW Ori, it would not actually be able to see the three stars in its skies. Rather, they would see only a pair as the two innermost stars orbit so close as to appear like a single point of light. Yet as the planet rotated, its stars would rise and fall in fascinating sunrises and sunsets unlike any other known world.

"'Star Wars' missed a trick," said Rebecca Nealon from the University of Warwick in England, a co-author on the paper.

Scientists have been on the lookout for a planet orbiting three stars, and found potential evidence in another system, GG Tau A, located about 450 light years from Earth. But the researchers say the gap in GW Ori's gas and dust ring makes it a more convincing example.

"It may be the first evidence of a circumtriple planet carving a gap in real time," said Jeremy Smallwood from the University of Nevada, Las Vegas, lead author of the new paper.

William Welsh, an astronomer at San Diego State University, said the researchers "make a good case. If this turns out to be a planet, it would be fascinating."

Alison Young from the University of Leicester in England who has

argued that GW Ori's stars caused the gap in the system's disk, rather than a planet, notes that observations from the ALMA telescope and Very Large Telescope in Chile in the coming months could end the debate.

"We'll be able to look for direct evidence of a planet in the disk," Dr. Young said.

If the planet hypothesis is confirmed, the system would reinforce the idea that planet formation is common. Several worlds, known as circumbinary planets, are already known to orbit two stars at once. But circumtriple planets have been harder to come by — despite estimates that at least a tenth of all stars cluster in systems of three or more. Yet their possible existence suggests that planets spring up in all sorts of places, even here in this most bizarre of systems.

"Three stars is not enough to kill planet formation," Dr. Nealon said. That suggests that exoplanets are likely to arise in more and more unusual locations. "What we've learned is any time planets can form, they do," said Sean Raymond, an astronomer from the University of Bordeaux in France who was not involved in the paper.

Perhaps even a world orbiting four, or five, or six stars at once?

"I don't see why not," he said.

https://wb.md/3m91E2s

The Seven Symptoms That Best Predict COVID

With respiratory virus season around the corner, identifying COVID-specific symptoms is more important than ever

F. Perry Wilson, MD, MSCE

This transcript has been edited for clarity.

Welcome to *Impact Factor*, your weekly dose of commentary on a new medical study. I'm Dr. F. Perry Wilson of the Yale School of Medicine.

This week, we're going to talk about COVID symptoms. I know — we're almost 2 years into this pandemic; why do we need to talk about symptoms now? The short answer is because testing isn't ubiquitous enough. We need to know what symptoms are sensitive and specific for COVID in order to know who should be tested or potentially isolated. And with respiratory virus season around the corner, identifying COVID-specific symptoms is more important than ever.

One problem with figuring out what symptoms are seen in COVID is that most studies look at people who test positive for COVID, and most people get tested when they have symptoms.

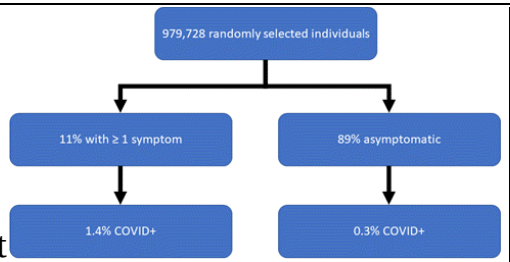
This means certain symptoms might become an almost self-fulfilling prophecy. The only way around this is to do random, population-based screening for COVID, and that is exactly what this paper, appearing in *PLOS Medicine*, does.

Throughout the pandemic, the National Health Service in England has been doing random COVID prevalence surveys throughout the country, testing a subset of their population regardless of symptom status, to figure out where the disease is and where it is going. I know — it must be nice, right? This particular paper looks at successive samples during the first "wild-type" surge of cases in England and then the subsequent alpha variant outbreak.

Participants completed a survey reporting symptoms over the past 4 weeks and the list was broad, as you can see.

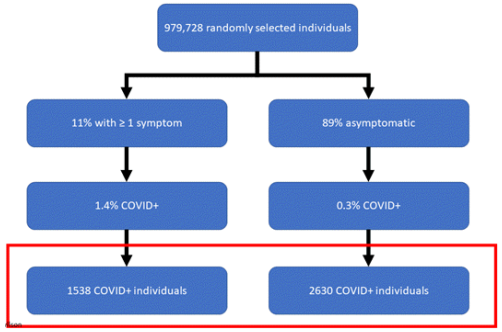
Then, a PCR test was performed. Now, since this was a general population sample, you won't be surprised to see that the positivity rate was pretty low; just around 4000 individuals out of 1 million tested positive. And the presence of any of these symptoms was strongly associated with COVID-19.

But the math here is quirky. Since symptoms are rare in the general population, the majority of the COVID cases were actually in asymptomatic people.



The take-home here is that asymptomatic (or at least presymptomatic) COVID is real and common. But also that symptoms still make it more likely that you actually have COVID.

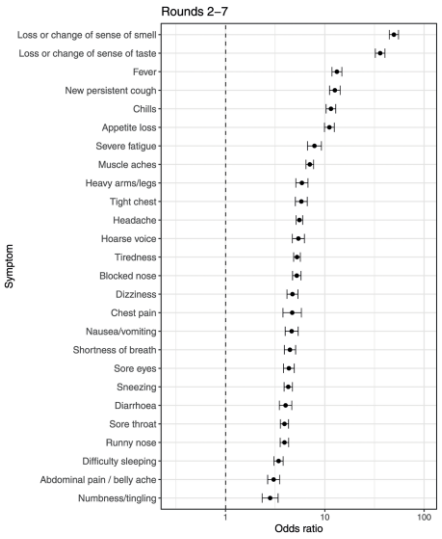
But this is *any* symptom. The paper breaks down the whole panoply of potential symptoms to see which are more strongly associated with COVID than others. All of the symptoms on the list made COVID more likely, but this figure shows which were most strongly associated.



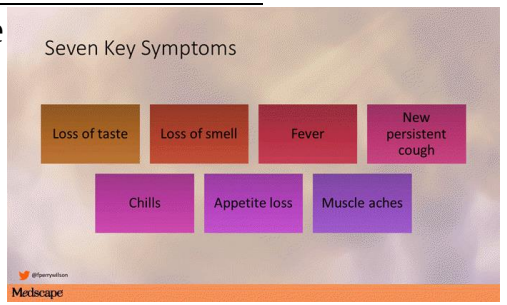
Loss of taste and smell were dramatic, strong predictors of disease, outstripping fever, chills, muscle aches, and even persistent cough.

No big surprises in the rest of the list, though "heavy arms and legs" is not one I've heard of before.

The authors used a statistical technique known as LASSO regression to create a multivariable model of symptoms that would help to predict disease. They tuned the model to be parsimonious — to select only the most important symptoms — and they found seven that, together, might be used to better target scarce testing resources.

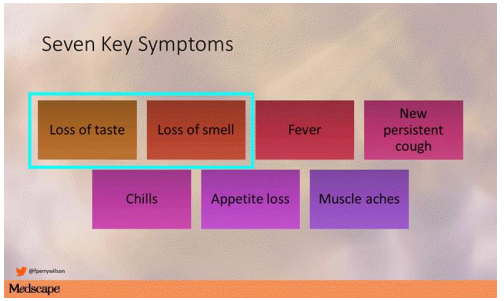


Here are those seven, and there are some interesting things to learn here.



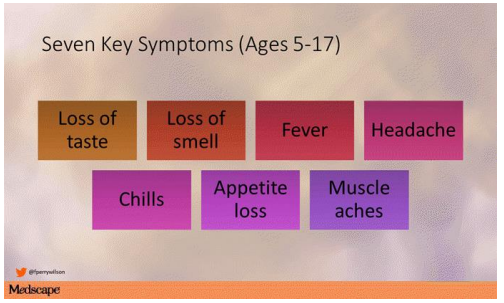
First, you'll note that the two most powerful predictors of PCR positivity were loss of smell and loss of taste.

That *both* of these symptoms were selected by the model is a bit surprising, as one of the advantages of LASSO is that it tends not to select highly correlated variables. Since loss of taste is usually due, in reality, to loss of smell, these variables should be quite correlated. But self-report is a mysterious thing, and it is conceivable that some patients simply don't register the loss of smell in the same way they notice the loss of taste or vice versa. Still, if there were one symptom to rule them all, it would be one of these.



Cough and fever and chills are no surprise, but the appearance of loss of appetite this high up on the predictive power hierarchy is worth consideration. I have definitely seen this with multiple COVID patients, though we often don't keep it in our list of major symptoms. Maybe we should.

Kids with COVID had a slightly different symptom profile than adults, with headache replacing persistent cough among the top seven symptoms — which has important implications for deciding when to screen schoolchildren. It's also worth noting that, in kids, the presence of a



runny nose slightly reduced the risk of a positive COVID test.

The authors also provide evidence that different variants have different constellations of symptoms, with Alpha having more sore throat, cough, fever, nausea, and vomiting than the wild-type variant. No data in this study on Delta, though.

But here's the main issue with using symptoms in this way to guide testing. Symptoms are a product of the constellation of things that cause those symptoms that exists at any given point of time. As we mask and distance less, and other respiratory viruses creep back into the populace, the specificity for a cough or a fever being COVID and not flu or something else will decrease. This is why the only real answer to "Who should we test for COVID?" is "anyone." Testing needs to be ubiquitous because even a statistical model based on a constellation of symptoms may only be an effective screening tool in the context in which it was derived. Aside from loss of smell and taste, which do seem to be particularly COVID-ish, the symptoms of COVID are just like those of every other respiratory virus, only more so.

Credits:
Image 1: F. Perry Wilson, MD, MSCE *Image 2: F. Perry Wilson, MD, MSCE*
Image 3: F. Perry Wilson, MD, MSCE *Image 4: F. Perry Wilson, MD, MSCE*
Image 5: Elliott J, et al. PLoS Med. 2021;18(9):e1003777. https://doi.org/10.1371/journal.pmed.1003777
Image 6: F. Perry Wilson, MD, MSCE *Image 7: F. Perry Wilson, MD, MSCE*
Image 8: F. Perry Wilson, MD, MSCE

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Gene Variant Points to Starvation's Evolutionary Legacy

Ancient and modern genomes reveal that a variant of the human growth hormone receptor likely helped our ancestors survive when food was scarce.

Sophie Fessl

A globally rare variant of the growth hormone receptor also seen in Denisovans and Neanderthals may have helped our ancestors survive periods without food, a new study published on September 24 in *Science Advances* claims.

Reconstructing the evolutionary history of a particular variant of the growth hormone receptor gene (*GHR*) variant—the so-called *GHRd3* variant, which is defined by a deletion of the gene's third exon—researchers have found that its frequency declined sharply around 40,000 years ago. Follow-up experiments in mice pointed to a potential explanation for why: the deletion appeared to limit male animals' size when fed a calorie-restricted diet. This sort of growth limitation could help males survive lean times but limit their reproductive success in times of plenty.

"This paper is exciting because it illustrates the power of combining evolutionary analyses of modern and ancient genomes with in-depth molecular characterization of the effects of genetic variants," writes Tony Capra, a specialist in evolutionary and computational genomics at the University of California, San Francisco, in an email to *The Scientist*. "I believe that the context-dependent complexity revealed here for the effects of the *GHRd3* variant (in terms of sex and environment) are likely common. We just haven't been able to explore the molecular effects of other variants with evidence of recent selection in such detail."

In previous work, Omer Gokcumen, an evolutionary biologist at the University at Buffalo, and his colleagues scanned Neanderthal, Denisovan, and ancient and modern *Homo sapiens* genomes for shared structural gene variants (such as deletions), with the aim of finding ones that have "been lurking around since we were *Homo erectus,"* says Gokcumen. One such variant that they identified was *GHRd3*, so for the new study, they dug deeper into its evolutionary history and potential function, to get at why it might have persisted for so long.

Initially, the researchers hypothesized that the variant may have been maintained by a phenomenon called the heterozygous advantage, where individuals that carry both versions of a gene (are

heterozygous) have an advantage over people who carry duplicates of one version (are homozygous). A well-known example for this is the sickle cell allele, which protects heterozygous carriers from some forms of malaria. But this did not fit with *GHRd3*'s reconstructed evolutionary history. Instead of being maintained at stable levels throughout human history, *GHRd3* emerged as the dominant growth hormone receptor allele in ancient humans roughly 1 million to 2 million years ago, and it stayed that way for a very long time, until 30,000 to 40,000 years ago, when it rapidly declined in frequency in much of the world, a sign of change in selection pressure. "This was very interesting because you rarely see selection on human variation," Gokcumen explains.

That begged the question: Why did the deletion suddenly become largely disadvantageous in the Upper Paleolithic, after appearing to be advantageous prior to that? In the literature, *GHRd3* is associated with smaller birth size, early onset of puberty, and increased longevity—traits that Gokcumen observed are also associated with a starvation-related phenomenon known as "catch-up growth," where growth later in life compensates for smaller birth weight and size due to malnutrition.

The team decided to look closer at *GHRd3*'s potential role in starvation resilience by examining the frequency of the deletion among children in Malawi who had survived malnutrition. The deletion was less common in children who exhibited a more severe response to malnutrition called Kwashiorkor, which includes edema, loss of muscle mass, and an extended belly, than in children with a less-severe response. "In other words, the deletion seems to be protective against that particular metabolic syndrome," says Gokcumen.

To further interrogate the link between malnutrition's effects and *GHRd3*, the team used CRISPR-Cas9 to knock out the third exon from the mouse version of the gene, generating a murine model of the gene variant. That revealed a sex-specific difference: when male mice carrying the deletion were fed a calorie-restricted diet, they ended up weighing the same as their female counterparts, while in wildtype mice, male mice were always larger than females (the deletion had no effect on female mouse weight). "This deletion may be helpful, for males especially, to survive under resource-restricted conditions," Gokcumen says.

A sex-specific effect of the deletion might not be so surprising, as there are sex-dependent differences in *GHR* gene expression in the liver, a place where the growth hormone receptor is highly expressed. While male mice typically show a cyclical daily expression pattern of *GHR*, the expression is stable in female mice. In the study, female mice exhibited this stable *GHR* expression throughout the day regardless of which allele they carried. However, the cyclical daily expression pattern of *GHR* normally seen in male mice was dampened in those with the deletion. And downstream of the altered *GHR* expression, the researchers found several genes that were differentially expressed in males with and without the exon deletion.

"It seems that the calorie-restricted male mice with the deletion end up expressing a female-like transcriptome in their liver, which in turn, we think, leads to a lack of sexual dimorphism in size," Gokcumen writes in an email to *The Scientist*.

Linking these results back to the evolutionary history of *GHRd3*, Gokcumen says males may benefit from being smaller in resource-limited environments, but when resources are abundant, being larger may help secure mates. In that way, the deletion "may be detrimental for fitness if starvation is not a big deal," Gokcumen writes. Gokcumen and his team hypothesize that ancient humans and Neanderthals may have faced starvation more frequently, and that with the invention of tools that would have increased the

flexibility of their diet, resource limitations became less important between 70,000 and 30,000 years ago, coinciding with the decline of *GHRd3*.

While that idea creates a coherent story, it leaves some things about *GHRd3* unexplained, says University of Haifa and Albert Einstein College of Medicine geneticist Gil Atzmon, who has researched *GHRd3*. Namely, the current geographic differences in frequency: nearly 50% of the population carries the allele in some African populations, while it is much rarer in populations in East Asia. “Invention of tools . . . should have [affected] the world evenly more or less and not as we see [in the paper] more in China and less in Africa,” writes Atzmon in an email. Capra agrees, writing that “the dynamics and potential drivers of the decrease in frequency over time and geography need further investigation.”

https://bit.ly/2ZRVqfW

Byzantine warrior with gold-threaded jaw unearthed in Greece

His jaw had been shattered in two.

By Laura Geggel

A rugged Byzantine warrior, who was decapitated following the Ottoman's capture of his fort during the 14th century, had a jaw threaded with gold, a new study finds.

An illustration of the decapitated Byzantine warrior's head. **(Image credit: Anagnostis P. Agelarakis)**

An analysis of the warrior's lower jaw revealed that it had been badly fractured in a previous incident, but that a talented physician had used a wire — likely gold crafted — to tie his jaw back together until it healed.

"The jaw was shattered into two pieces," said study author Anagnostis Agelarakis, an anthropology professor in the Department of History at Adelphi University in New York. The discovery of the nearly 650-year-old healed jaw is an amazing find because it shows the accuracy with which "the medical professional was able to put the two major fragments of the jaw together."

What's more, the medical professional appears to have followed advice laid out by the fifth-century B.C. Greek physician Hippocrates, who wrote a treatise covering jaw injuries about 1,800 years before the warrior was wounded.

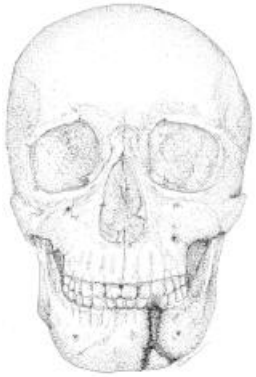
Agelarakis and colleagues discovered the warrior's skull and lower jaw at Polystylon fort, an archaeological site in Western Thrace, Greece, in 1991. When the warrior was alive in the 14th century, the Byzantine Empire, also known as the Eastern Roman Empire, was facing attacks from the Ottomans. Given that the warrior was beheaded, it's likely that he fought until the Ottomans overcame Polystylon fort. In other words, it appears that "the fort did not surrender, but that it must have been taken by force," Agelarakis wrote in the study.

As the fort fell, the Ottomans likely captured and then decapitated the warrior; then, an unknown individual likely took the warrior's head and stealthily buried it, probably without the "permission of the subjugators, given that the rest of the body was not recovered," Agelarakis wrote in the study. But the warrior wasn't given his own grave; his head was interred in the pre-existing grave of a 5-year-old child, who was buried in the center of a 20-plot cemetery at Polystylon fort. A broken ceramic vessel, which may have been used to dig the hole for the warrior's head, was uncovered at the burial, Agelarakis added.

It's unknown if there was any familial or other tie between the warrior and the child. Given that the man's skull and jaw were found together, his head likely had soft tissues on it when it was buried in the mid-1380s, Agelarakis noted. The skull showed evidence of a "horrendous frontal impact," which was inflicted

around the time of the man's death, he said.

Agelarakis detailed the unique burial in a study published in 2017 in the journal Byzantina Symmeikta. However, the study only briefly addressed the warrior's healed jaw, so Agelarakis investigated that in detail, penning a second, new paper.

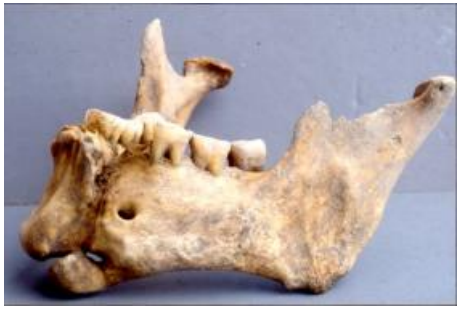


Jawbreaker

The cause of the jaw fracture isn't clear, but possibilities include a forceful fall while horseback riding; a battle trauma from a thrust spearhead or another sharp, hand-held weapon; or a ballistic projectile fueled by black powder, Agelarakis wrote in the new study, published online in the September issue of the journal Mediterranean Archaeology and Archaeometry.

An illustration of the Byzantine warrior's skull and fractured jaw. **(Image credit: Anagnostis P. Agelarakis)**

What's known is this: The warrior died between the ages of 35 and 40 years old, and about 10 years before that, likely in 1373, he experienced the devastating jaw fracture. An analysis of the teeth on the warrior's lower jaw revealed a line of dental calculus that built up where a thin wire was threaded, zigzagging around the base of the man's teeth to hold his jaw together as it healed, Agelarakis said.



Notice the healed fracture at the front of the the warrior's lower jaw. **(Image credit: Anagnostis P. Agelarakis)**

The wire is long gone, but Agelarakis suspects it was gold. There was no evidence of a silver alloy, which would have left grayish discoloration, nor were there traces of a patina or greenish cupric acid stains that would have been left by copper or bronze wires, he found.

"It must have been some kind of gold thread, a gold wire or something like that, as is recommended in the Hippocratic corpus that was compiled in the fifth century B.C.," Agelarakis said. Gold is soft and pliable but strong and nontoxic, he added, making it a good choice for this type of medical treatment.

"In one of the dentitions, I saw that the tooth was filed a little bit so that the knot that was tied in the wire would not scratch the cheek," Agelarakis said. "It's very sophisticated — it's flabbergasting."

If the warrior was still on active duty, it must have been difficult for him to lay low and drink liquid foods while his bandaged jaw healed, Agelarakis noted. It's unclear if the warrior's tongue was also wounded in the incident, and whether his speech or pronunciation were affected following treatment, he added. However, if the warrior had a beard or mustache, he could have hidden any disfigurements that persisted after the treatment.

This exceptional medical treatment suggests the warrior was a very important person.

"He was the military leader, most probably of the fort," Agelarakis said. "Therefore, he was decapitated ... by the Ottomans when they took over the fort."

https://bit.ly/3orbr6B

Beware of Dog Parks: Canine Parasite Has Evolved Resistance to All Treatments

Hookworms have evolved to evade all FDA approved medications veterinarians use to kill them.

Hookworms are one of the most common parasites plaguing the companion animal world. They use their hooklike mouths to latch onto an animal’s intestines, where they feast on tissue fluids and blood. Infected animals can experience dramatic weight loss, bloody stool, anemia and lethargy, among other issues.

Now they’ve become multiple-drug resistant, according to new

research from the University of Georgia.

Right now, U.S. veterinarians rely on three types of drugs to kill the hookworms, but the parasites appear to becoming resistant to all of them. Researchers from the UGA College of Veterinary Medicine first reported this concerning development in 2019, and new research, published recently in the *International Journal for Parasitology: Drugs and Drug Resistance*, provides deeper insight into where the problem started and how bad it's since become.

For the present study, the researchers focused on current and former racing greyhounds. Dog racetracks are particularly conducive to spreading the parasite due to the sandy ground of the facilities, an ideal breeding ground for hookworms. Because of the conditions, all the dogs are dewormed about every three to four weeks.

After analyzing fecal samples from greyhound adoption kennels, three veterinary practices that work with adoption groups and an active racing kennel, the researchers found the parasites were highly prevalent in the breed. Four out of every five greyhounds tested came up positive for hookworms. And the ones that tested negative are probably also infected, said Ray Kaplan, the study's corresponding author and a former professor of veterinary parasitology at UGA.

Hookworms can sometimes "hide" in tissues, where they won't reproduce and shed eggs until the infection worsens and leaks into the dog's intestines. But perhaps more alarming, the team saw that the dogs still had high levels of infection with hookworms even after they were treated for them.

The study marks the first demonstration of widespread multiple-drug resistance in a dog parasite reported in the world.

Parasite mutations

In situations where there are a lot of dogs infected with a lot of parasites, such as on racing dog breeding farms and kennels, there are many more opportunities for parasites to develop rare mutations allowing them to survive the dewormer treatments. If dewormers are applied frequently, the newly emerging resistant worms will survive and pass on the mutation that helped them sneak past the drug to their offspring. With repeated treatments over time, most of the drug-susceptible worms at the farm or kennel will be killed, and the resistant worms will then predominate.

Compounding the problem, veterinarians don't typically test animals after treatment to ensure the worms are gone, so the drug-resistant worms go unnoticed until the dog has a heavy infection and starts showing signs of hookworm disease.

"Personally, I would not take my dog to a dog park. If your dog picks up these resistant hookworms, it's not as easy as just treating them with medication anymore."

— *Ray Kaplan, professor of veterinary parasitology*

The researchers found that almost all the fecal samples tested positive for the mutation that enables hookworms to survive treatment with benzimidazoles, a broad-spectrum class of dewormers used in both animals and humans. Although a molecular test does not yet exist to test for the resistance to the other two types of drugs, other types of testing by the team showed that the hookworms were resistant to those drugs as well.

"There's a very committed greyhound adoption industry because they are lovely dogs," said Kaplan. "I used to own one. But as those dogs are adopted, the drug-resistant hookworms are going to show up in other pet dogs."

One possible breeding ground for a potential drug-resistant hookworm outbreak is also the place many dog owners use to exercise their animals: dog parks. "Personally, I would not take my dog to a dog park," Kaplan said. "If your dog picks up these resistant hookworms, it's not as easy as just treating them with medication anymore. Until new types of drugs are available, taking your dog to a dog park has to be considered a risky activity."

The consequences

Dogs don't have to ingest the worms to become infected. Hookworm larvae live in the soil and can also burrow through the dog's skin and paws. And female dogs can pass the parasite on to their puppies through their milk.

If that's not scary enough, dog hookworms can also infect humans.

The infection doesn't manifest in the same way in people, but after the worms penetrate the skin, they cause a red, very itchy rash as they travel under the skin. As the number of drug-resistant worms grows, they'll also pose a risk to humans.

Previously, doctors would treat patients with an ointment that contains a dewormer along with a corticosteroid. "Unfortunately, that's not going to work against these drug-resistant hookworms," Kaplan said.

But hope isn't entirely lost.

Kaplan and Pablo Jimenez Castro, lead author of the study and a recent doctoral graduate from Kaplan's lab, found in another recent study that these multiple-drug resistant dog hookworms do appear to be susceptible to emodepside, a dewormer currently only approved for use in cats in the U.S. But use of this cat drug on dogs should only be performed by a veterinarian, as it requires veterinary expertise and supervision.

Based in part on Castro's work, the American Association of Veterinary Parasitologists recently formed a national task force to address the issue of drug resistance in canine hookworms.

Reference: "Multiple drug resistance in hookworms infecting greyhound dogs in the USA" by Pablo D. Jimenez Castro, Abhinaya Venkatesan, Elizabeth Redman, Rebecca Chen, Abigail Malatesta, Hannah Huff, Daniel A. Zuluaga Salazar, Russell Avramenko, John S. Gilleard and Ray M.Kaplan, 2 September 2021, International Journal for Parasitology: Drugs and Drug Resistance. DOI: 10.1016/j.ijpddr.2021.08.005

Co-authors on this study include Abigail Malatesta, a veterinary student from Tuskegee University, Hannah Huff, currently a veterinary student at the University of Georgia, and researchers from the University of Calgary in Canada.

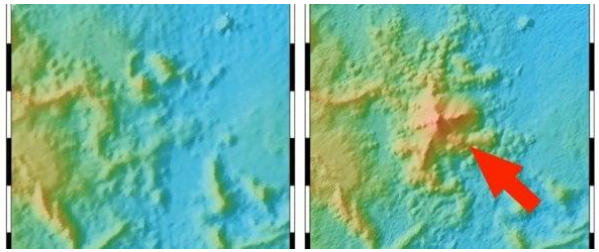
https://bit.ly/3uLwYbD

Largest Underwater Eruption Ever Recorded Gives Birth to Massive New Volcano

A huge seismic event that started in May of 2018 and was felt across the entire globe has officially given birth to a new underwater volcano.

Michelle Starr

Off the eastern coast of the island of Mayotte, a gigantic new feature rises 820 meters (2,690 feet) from the seafloor, a prominence that hadn't been there prior to an earthquake that rocked the island in May 2018.



Elevation maps in 2014 and 2019 reveal the new volcano. **(Feuillet et al., Nature Geoscience, 2021)**

"This is the largest active submarine eruption ever documented," the researchers wrote in their paper. The new feature, thought to be part of a tectonic structure between the East African and Madagascar rifts, is helping scientists understand deep Earth processes about which we know relatively little.

The seismic rumbles of the ongoing event started on 10 May 2018. Just a few days later, on 15 May, a magnitude 5.8 quake struck, rocking the nearby island. Initially, scientists were perplexed; but it didn't take long to figure out that a volcanic event had occurred, the likes of which had never been seen before.

The signals pointed to a location around 50 kilometers from the Eastern coast of Mayotte, a French territory and part of the volcanic Comoros archipelago sandwiched between the Eastern coast of Africa and the Northern tip of Madagascar.

So a number of French governmental institutions sent a research team to check it out; there, sure enough, was an undersea mountain

that hadn't been there before. Led by geophysicist Nathalie Feuillet of the University of Paris in France, the scientists have now described their findings in a new paper.

The team began monitoring the region in February of 2019. They used a multibeam sonar to map an 8,600-square-kilometer area of seafloor. They also placed a network of seismometers on the seafloor, up to 3.5 kilometers deep, and combined this with seismic data from Mayotte.

Between 25 February and 6 May 2019, this network detected 17,000 seismic events, from a depth of around 20 to 50 kilometers below the ocean floor – a highly unusual finding, since most earthquakes are much shallower. An additional 84 events were also highly unusual, detected at very low frequencies.

Armed with this data, the researchers were able to reconstruct how the formation of the new volcano may have occurred. It started, according to their findings, with a magma reservoir deep in the asthenosphere, the molten mantle layer located directly below Earth's lithosphere.

Below the new volcano, tectonic processes may have caused damage to the lithosphere, resulting in dykes that drained magma from a reservoir up through the crust, producing swarms of earthquakes in the process. Eventually, this material made its way to the seafloor, where it erupted, producing 5 cubic kilometers of lava and building the new volcano.

The low-frequency events were likely generated by a shallower, fluid-filled cavity in the crust that could have been repeatedly excited by seismic strain on faults close to the cavity.

As of May 2019, the extruded volume of the new volcanic edifice is between 30 and 1,000 times larger than estimated for other deep-sea eruptions, making it the most significant undersea volcanic eruption ever recorded. "The volumes and flux of emitted lava during the Mayotte magmatic event are comparable to those observed during eruptions at Earth's largest hotspots," the researchers wrote.

"Future scenarios could include a new caldera collapse, submarine eruptions on the upper slope or onshore eruptions. Large lava flows and cones on the upper slope and onshore Mayotte indicate that this has occurred in the past.

"Since the discovery of the new volcanic edifice, an observatory has been established to monitor activity in real time, and return cruises continue to follow the evolution of the eruption and edifices." The research has been published in *Nature Geoscience*.

https://bit.ly/3A86rWF

Sunlight affects whether languages have a word for 'blue'

Culture and topography also play important roles

By Cathleen O'Grady

Color is a spectrum: Red fades from orange to yellow, whereas green merges to turquoise, then blue. Languages treat this spectrum in different ways: Some have separate words for "green" and "blue," others lump the two together. Some barely bother with color terms at all.

"The question is, why?" says Dan Dediu, an evolutionary linguist at Lumière University Lyon 2. Now, he and his colleagues have found evidence for an unexpected answer: People with more exposure to sunlight are more likely to speak languages that lump green and blue together, under a term that linguists dub "grue." That's because of the effects of a lifetime of light exposure, the team speculates: Lots of Sun causes a condition called "lens brunescence" that makes it harder to distinguish the two hues.

Lens brunescence is just one of many theories explaining why color vocabulary is so different across languages, says study co-author Asifa Majid, a psychologist at the University of York. Others originate primarily with the environment: One theory holds that people who live near large bodies of water—like seas or lakes—

could be more likely to have a word for blue. And if cultures begin to dye clothing with hard-to-produce blue pigments, that could also prompt the emergence of new color terms.

Everyone has their own pet theories, and "people normally test the theory that they like best," Majid says. So she and her colleagues decided to put all the main ones through the wringer.

The researchers gathered data from 142 populations on every continent except Antarctica, covering widely spoken languages such as Korean and Arabic to those spoken by just a few hundred people in Australia and the Amazon. The scientists noted what color terms the main language of each population used and then gathered data on factors that might influence those terms, including sunlight exposure and proximity to large bodies of water, like lakes. They couldn't find comprehensive data on historic dyeing technology, so they used the proxy of population size, instead: Larger populations tend to have more complex technologies, including dyeing.

Light exposure played a big role in whether languages separate blue from green, the researchers conclude this week in *Scientific Reports*. In brighter places (either those that were closer to the equator or had less annual cloud cover) such as Central America and East Africa, languages were significantly less likely to separate "green" from "blue." That suggests a lifetime of exposure to bright light pushes whole communities away from baking a blue-green distinction into their language.

But the team also found support for the other two theories: Living near a lake increased the chance of having a separate word for "blue." So did living in a larger society. That means visual perception, culture, and environment all play a role in shaping how a language carves up the color spectrum, Dediu says.

This isn't the first study to find such factors linked to color vocabulary, says University of Bristol linguist Sean Roberts, who was not involved with the work. "But this paper is special because it considers all these factors together."

Linguists have found evidence that small changes in how people communicate can snowball across generations of speakers, making big changes to languages over time. The researchers think that's what happened here: Over generations, individual biases—based on visual perception and the importance of certain color terms—influenced which languages developed a separate term for the color blue.

This kind of language variation is an old puzzle in linguistics. Why would one language develop in a certain direction, whereas another takes a different path? For a long time, Dediu says, the standard answer was circular: "Languages just change … because." Linguists thought all languages faced the exact same pressures—like people wanting to communicate as easily as possible, while still being understood. And so languages taking different paths could only be explained as the product of random chance.

But more recent research has been digging deeper for an answer, finding that languages can change rapidly because of environmental or cultural factors, says Simon Greenhill, a linguist at the Max Planck Institute for the Science of Human History, who was not involved with the research: "It's really exciting that we're seeing more studies looking at the big picture."

https://bit.ly/3Bir5VP

Bioengineers Develop New Class of Giant Magnetoelastic Effect Human-Powered Bioelectronics

Converts human body motions into electricity

A team of bioengineers at the UCLA Samueli School of Engineering has invented a novel soft and flexible self-powered bioelectronic device. The technology converts human body motions — from bending an elbow to subtle movements such as a pulse on one's wrist — into electricity that could be used to power wearable

and implantable diagnostic sensors.

The researchers discovered that the magnetoelastic effect, which is the change of how much a material is magnetized when tiny magnets are constantly pushed together and pulled apart by mechanical pressure, can exist in a soft and flexible system — not just one that is rigid.

UCLA-designed self-powered, stretchable, waterproof magnetoelastic generator for bioelectronics. **Credit: Jun Chen/UCLA**

To prove their concept, the team used microscopic magnets dispersed in a paper-thin silicone matrix to generate a magnetic field that changes in strength as the matrix undulated. As the magnetic field's strength shifts, electricity is generated.

Nature Materials published today (September 30, 2021) a research study detailing the discovery, the theoretical model behind the breakthrough, and the demonstration. The research is also highlighted by *Nature*.

"Our finding opens up a new avenue for practical energy, sensing and therapeutic technologies that are human-body-centric and can be connected to the Internet of Things," said study leader Jun Chen, an assistant professor of bioengineering at UCLA Samueli. "What makes this technology unique is that it allows people to stretch and move with comfort when the device is pressed against human skin, and because it relies on magnetism rather than electricity, humidity and our own sweat do not compromise its effectiveness."

Chen and his team built a small, flexible magnetoelastic generator (about the size of a U.S. quarter) made of a platinum-catalyzed silicone polymer matrix and neodymium-iron-boron nanomagnets. They then affixed it to a subject's elbow with a soft, stretchy silicone band.

The magnetoelastic effect they observed was four times greater than similarly sized setups with rigid metal alloys. As a result, the device generated electrical currents of 4.27 milliamperes per square centimeter, which is 10,000 times better than the next best comparable technology.

In fact, the flexible magnetoelastic generator is so sensitive that it could convert human pulse waves into electrical signals and act as a self-powered, waterproof heart-rate monitor. The electricity generated can also be used to sustainably power other wearable devices, such as a sweat sensor or a thermometer.

There have been ongoing efforts to make wearable generators that harvest energy from human body movements to power sensors and other devices, but the lack of practicality has hindered such progress. For example, rigid metal alloys with magnetoelastic effect do not bend sufficiently to compress against the skin and generate meaningful levels of power for viable applications.

Other devices that rely on static electricity tend not to generate enough energy. Their performance can also suffer in humid conditions, or when there is sweat on the skin.

Some have tried to encapsulate such devices in order to keep water out, but that cuts down their effectiveness. The UCLA team's novel wearable magnetoelastic generators, however, tested well even after being soaked in artificial perspiration for a week.

Reference: "Giant magnetoelastic effect in soft systems for bioelectronics" by Yihao Zhou, Xun Zhao, Jing Xu, Yunsheng Fang, Guorui Chen, Yang Song, Song Li and Jun Chen, 30 September 2021, Nature Materials.

DOI: 10.1038/s41563-021-01093-1

UCLA Samueli postdoctoral scholar Yihao Zhou and graduate student Xun Zhao are co-first authors of the study. They are both advised by Chen, who directs UCLA's Wearable Bioelectronics Group and is part of the UCLA Society of Hellman Fellows. Other authors are UCLA graduate students Jing Xu and Guorui Chen, postdoctoral scholars Yunsheng Fang and Yang Song, as well as Song Li — a professor and chair of the Bioengineering Department.

A patent on the technology has been filed by the UCLA Technology Development Group.

https://wb.md/2Y7nye4

Many Patients, Doctors Unaware of Advancements in Cancer Care

Many patients with cancer, as well as doctors in fields other than oncology, are unaware of just how much progress has been made in recent years in the treatment of cancer, particularly with immunotherapy.

Kristin Jenkins

This is the main finding from two studies presented at the recent European Society for Medical Oncology annual meeting.

The survey of patients found that most don't understand how immunotherapy works, and the survey of doctors found that many working outside of the cancer field are using information on survival that is wildly out of date.

When a patient is first told they have cancer, counseling is usually done by a surgeon or general medical doctor and not an oncologist, said Conleth Murphy, MD, of Bon Secours Hospital Cork, Ireland, and co-author of the second study.

Non-cancer doctors often grossly underestimate patients' chances of survival, Murphy's study found. This suggests that doctors who practice outside of cancer care may be working with the same information they learned in medical school, he said.

"These patients must be spared the traumatic effects of being handed a death sentence that no longer reflects the current reality," Murphy said.

After receiving a diagnosis of cancer, "patients often immediately have pressing questions about what it means for their future," he noted. A common question is, "How long do I have left?"

Non-oncologists should refrain from answering patients' questions with numbers, Murphy said.

Family doctors are likely to be influenced by the experience they have had with specific cancer patients in their practice, said Cyril Bonin, MD, a general practitioner in Usson-du-Poitou, France, who has 900 patients in his practice.

He sees about 10 patients with a new diagnosis of cancer each year.

In addition, about 50 of his patients are in active treatment for cancer or have finished treatment and are considered cancer survivors.

"It is not entirely realistic for us to expect practitioners who deal with hundreds of different diseases to keep up with every facet of a rapidly changing oncology landscape," said Marco Donia, MD, an expert in immunotherapy from the University of Copenhagen, Denmark, said.

That landscape has changed dramatically in recent years, particularly since immunotherapy was added to the arsenal. Immunotherapy is a way to fine tune your immune system to fight cancer.

For example, in the past, patients with metastatic melanoma would have an average survival of about 1 year. But now, some patients who have responded to immunotherapy are still alive 10 years later.

Findings From the Patient Survey

It is important that patients stay well-informed because immunotherapy is a "complex treatment that is too often mistaken for a miracle cure," said Paris Kosmidis, MD, the co-author of the patient survey.

"The more patients know about it, the better the communication with their medical team and thus the better their outcomes are likely to be," said Kosmidis, who is co-founder and chief medical officer of CareAcross, an online service that provides personalized education for cancer patients

The survey was of 5,589 patients with cancer who were recruited from CareAcross clients from the United Kingdom, France, Italy, Spain, and Germany.

The survey asked them about how immunotherapy works, what it

costs, and its side effects.

Almost half responded "not sure / do not know," but about a third correctly answered that immunotherapy "activates the immune system to kill cancer cells."

Similarly, more than half thought that immunotherapy started working right away, while only 20% correctly answered that it takes several weeks to become effective.

"This is important because patients need to start their therapy with realistic expectations, for example to avoid disappointment when their symptoms take some time to disappear," Kosmidis said.

A small group of 24 patients with lung cancer who had been treated with immunotherapy got many correct answers, but they overestimated the intensity of side effects, compared with other therapies.

"Well-informed patients who know what to expect can do 90% of the job of preventing side effects from becoming severe by having them treated early," said Donia, of the University of Copenhagen.

Most cancer patients were also unaware of the cost of immunotherapy, which can exceed $100,000 a year, Kosmidis said.

Results of the Doctor Survey

The other survey presented at the meeting looked at how much doctors know about survival for 12 of the most common cancers.

Murphy and colleagues asked 301 non-cancer doctors and 46 cancer specialists to estimate the percentage of patients who could be expected to live for 5 years after diagnosis (a measure known as the 5-year survival rate).

Answers from the two groups were compared and were graded according to cancer survival statistics from the National Cancer Registry of Ireland.

Both groups of doctors had a hard time estimating the survival of common cancers.

Non-oncologists accurately predicted 5-year survival for just two of the cancer types, while the cancer specialists got it right for four cancer types.

However, the non-cancer doctors had a more pessimistic outlook on cancer survival generally and severely underestimated the chances of survival in specific cancers, particularly stage IV breast cancer. The survival for this cancer has "evolved considerably over time and now reaches 40% in Ireland," Murphy pointed out.

"These results are in line with what we had expected because most physicians' knowledge of oncology dates back to whatever education they received during their years of training, so their perceptions of cancer prognosis are likely to lag behind the major survival gains achieved in the recent past," Murphy said.

Sources

Conleth Murphy, MD, Bon Secours Hospital, Cork, Ireland.
Cyril Bonin, MD, general practitioner, Usson-du-Poitou, France.
Marco Donia, MD, PhD, University of Copenhagen, Denmark.

https://bit.ly/39XYpoZ

Bronze Age Mystery Surprise: Milk Enabled Massive Steppe Migration

Bronze Age migrations coincided with the adoption of milk drinking

From the Xiongnu to the Mongols, the pastoralist populations of the Eurasian steppe have long been a source of fascination. Amongst the earliest herding groups in this region were the Yamnaya, Bronze Age pastoralists who began expanding out of the Pontic-Caspian steppe more than 5000 years ago. These Bronze Age migrations resulted in gene flow across vast areas, ultimately linking pastoralist populations in Scandinavia with groups that expanded into Siberia.

Just how and why these pastoralists traveled such extraordinary distances in the Bronze Age has remained a mystery. Now a new study led by researchers from the Max Planck Institute for the Science of Human History in Jena, Germany has revealed a critical

clue and it might come as a surprise. It appears that the Bronze Age migrations coincided with a simple but important dietary shift – the adoption of milk drinking.

The researchers drew on a humble but extraordinary source of information from the archaeological record – they looked at ancient tartar (dental calculus) on the teeth of preserved skeletons.

By carefully removing samples of the built-up calculus, and using advanced molecular methods to extract and then analyze the proteins still preserved within this resistant and protective material, the researchers were able to identify which ancient individuals likely drank milk, and which did not.

Dental calculus removed from the teeth of this individual showed evidence of dairy consumption. **Credit: Egor Kitov, Samara Valley Project**

Their results surprised them. "The pattern was incredibly strong," observes study leader and paleoproteomics specialist Dr. Shevan Wilkin, "The majority of pre-Bronze Age Eneolithic individuals we tested – over 90% – showed absolutely no evidence of consuming dairy. In contrast, a remarkable 94% of the Early Bronze Age individuals had clearly been milk drinkers."

The researchers realized they had uncovered a significant pattern. They then further analyzed the data in order to examine what kind of milk the herders were consuming. "The differences between the milk peptides of different species are minor but critical," explains Dr. Wilkin. "They can allow us to reconstruct what species the consumed milk comes from." While most of the milk peptides pointed to species like cow, sheep, and goat, which was not surprising in light of the associated archaeological remains, calculus from a couple of individuals revealed an unexpected species: horse.

"Horse domestication is a heavily debated topic in Eurasian archaeology," notes Dr. Wilkin. One site where early Central Asian milk drinking had been proposed was the 3500-year-old site of Botai in Kazakhstan.

The researchers tested calculus from a couple of Botai individuals, but found no evidence of milk drinking. This fits with the idea that Przewalskii horses – an early form of which were excavated from the site – were not the ancestors of today's domestic horse, as shown by recent archaeogenetic study. Instead, horse domestication – and the drinking of horse milk – likely began about 1500 kilometers to the west in the Pontic Caspian steppe.

"Our results won't make everyone happy, but they are very clear," says Professor Nicole Boivin, senior author of the study and Director of the Department of Archaeology at the MPI Science of Human History. "We see a major transition to dairying right at the point that pastoralists began expanding eastwards." Domesticated horses likely had a role to play too. "Steppe populations were no longer just using animals for meat, but exploiting their additional properties –milking them and using them for transport, for example," states Professor Boivin.

What precise critical advantage milk gave remains to be investigated. But it is likely that the additional nutrients, rich proteins, and source of fluids in a highly arid environment would have been critical to survival in the harsh and open steppe. "What we see here is a form of cultural revolution," says Dr. Wilkin, "Early Bronze Age herders clearly realized that dairy consumption offered some fundamental benefits and once they did, vast steppe expansions of these groups across the steppe became possible."

Reference: "Dairying enabled Early Bronze Age Yamnaya steppe expansions" by Shevan Wilkin, Alicia Ventresca Miller, Ricardo Fernandes, Robert Spengler, William T.-T. Taylor, Dorcas R. Brown, David Reich, Douglas J. Kennett, Brendan J. Culleton, Laura Kunz, Claudia Fortes, Aleksandra Kitova, Pavel Kuznetsov, Andrey Epimakhov, Victor F. Zaibert, Alan K. Outram, Egor Kitov, Aleksandr Khokhlov, David Anthony and Nicole Boivin, 15 September 2021, Nature. [*DOI: 10.1038/s41586-021-03798-4*]

https://bit.ly/3B7yEOW

Non-toxic technology extracts more gold from ore

Study shows new chloride-based process recovers 84% of gold compared to the 64% recovered with traditional methods.

Gold is one of the world's most popular metals. Malleable, conductive and non-corrosive, it's used in jewelry, electronics, and even space exploration. But traditional gold production typically involves a famous toxin, cyanide, which has been banned for industrial use in several countries.

The wait for a scalable non-toxic alternative may now be over as a research team from Aalto University in Finland has successfully replaced cyanide in a key part of gold extraction from ore. The results are published in *Chemical Engineering*.

Traditionally, once gold ore is mined from the ground, it's crushed to a powder and passed through a series of tanks in a process called leaching. Cyanide is then used to separate the gold from the ore into the leached solution.

With the new process, the leaching and recovery process is done with chloride, one of two elements in table salt.

"Until now, no one has developed a good method for recovering small amounts of gold from industrial chloride solutions," says Ivan Korolev, a researcher on the project and doctoral candidate.

"With our process, the amount of gold we've been able to recover using chloride is as high as 84%. In comparison, using the standard cyanide process with the same ore yielded only 64% in our control experiment," he explains.

Called electrodeposition-redox replacement (EDRR), the new process combines the best of two common methods for extracting leached gold: electrolysis, which uses electric currents to reduce gold or other metals present in the leaching solution, and cementation, which adds particles of other metals to the solution to react with the gold. Professor Mari Lundström and University Lecturer Kirsi Yliniemi, from Aalto University's School of Chemical Engineering, are behind its development.

"With EDRR, we apply short pulses of electricity to create thin layers of metal—in our case copper—on the electrode and cause a reaction that encourages gold to replace the copper layer by layer," says Korolev. "The method has low energy consumption and doesn't require the addition of any other elements."

Industry-level collaboration

The research was conducted as part of a broader EU sustainability project called SOCRATES, and the work was done in collaboration with Finnish mining-technology giant Metso Outotec. Most of the experiments were performed at the company's research center in western Finland.

"Collaborating with Metso Outotec allowed us to develop the method in a way that's much closer to real-world implementation," says Korolev. "We started with about 9% recovery, but it then grew to 25%, and soon we were hitting 70%—sometimes we even achieved close to 95%."

"It's one thing to do an experiment like this on a small scale, but nobody had ever done it at the scale that we have done. We showed that even though our method is still really new, there is a lot of potential for making it a successful alternative to the traditional industrial process," he says.

"The extraction methods of the past have always left some valuable metals behind. Now, as demand for metals grows all the time, even these small amounts are important," he says. "I think we can still increase the yield with our EDRR technology. Perhaps we cannot reach 100%, but I believe we can hit the 90% mark or more."

"It would be great to see a mining company interested in this technology and willing to test with their ore on site."

Korolev has a very personal interest in the project too. Born in the Siberian mining town of Kemerovo, he grew up seeing both the

positive and the negative sides of the industry. When studying mining engineering—first in Russia and then in several European universities—Korolev became interested in metallurgy and the recovery of waste materials.

"The extraction methods of the past always left some valuable metals behind. Now, as demand for metals grows all the time, even these small amounts are important," he says. "I think we can still increase the yield with our EDRR technology. Perhaps we cannot reach 100%, but I believe we can hit the 90% mark or more."

More information: *Ivan Korolev et al, Electro-hydrometallurgical chloride process for selective gold recovery from refractory telluride gold ores: A mini-pilot study, Chemical Engineering Journal (2021).* *DOI: 10.1016/j.cej.2021.132283*

https://bit.ly/3Dc5hvx

Devonian Phacopid Trilobites Had Unique Hyper-Compound Eyes

Hyper-compound eyes hiding an individual compound eye below each of the big lenses

by Enrico de Lazaro

Phacops geesops, a trilobite species that lived during the Devonian period; the animal's eyes consist of 200 single lenses each, spanning six small facets, which again form one eye each. **Image credit: Brigitte Schoenemann.**

Trilobites are extinct arthropods that dominated the faunas of the Paleozoic Era. Since their appearance 523 million years ago, they were equipped with elaborate compound eyes.

While most of them possessed apposition compound eyes, comparable to the compound eyes of many crustaceans and insects living today, trilobites of the suborder Phacopina that lived 390 million years ago developed the so-called schizochroal eyes — atypical large eyes with wide lenses and wide interspaces in between. New research shows that these compound eyes were highly sophisticated systems — hyper-compound eyes hiding an individual compound eye below each of the big lenses.

"Most trilobites had compound eyes similar to those that are still found in insects today: a large number of hexagonal facets form the eye. There are usually eight photoreceptors under each facet," said Dr. Brigitte Schoenemann, a researcher in the Department of Zoology, Neurobiology/Animal Physiology and Biology Education at the University of Cologne, and her colleagues.

"Comparable to the image of a computer screen, which is built up from individual pixels, an image is built up from the individual facets. In dragonflies, there are up to ten thousand individual facets." "In order to produce a coherent image, the facets must be very close together and connected by neurons."

"However, in the trilobite suborder Phacopina, the externally visible lenses of the compound eyes are much larger, up to 1 mm in diameter and more. In addition, they are set farther apart."

In the new research, Dr. Schoenemann and co-authors analyzed X-ray images taken by Wilhelm Stürmer, an amateur paleontologist and a pioneer of X-ray analyses in fossils during the 1970s.

The researchers found that the facets in the schizochroal eyes of the phacopid trilobites are less numerous than in most trilobite eyes, but can reach diameters of 2 mm and more, and there are wide interspaces in between.

They found that below each of the these large lenses sits a small complete individual compound eye — so in total there results a hyper-compound eye, with several tens, in cases hundreds of compound eyes in one eye-system.

**** "Each phacopid had two eyes, one on the left and one on the right," Dr. Schoenemann said.***

**** "Each of these eyes consisted of about 200 lenses up to 1 mm in size."***

**** "Under each of these lenses, in turn, at least 6 facets are set up, each of which together again makes up a small compound eye."***

**** "So we have about 200 compound eyes (one under each lens) in one eye. These sub-facets are arranged in either one ring or two rings."***

**** "Underneath sat a foam-like nest that was probably a small neural network to process the signals."***

According to the team, the hyper-compound eyes of the phacopid trilobites may have been an evolutionary adaptation to life in low light conditions.

"With its highly complex visual apparatus, it may have been much more sensitive to light than a normal trilobite eye," Dr. Schoenemann said. "It is also possible that the individual components of the eye performed different functions, enabling, for example, contrast enhancement or the perception of different colors." "So far, such an eye has only been found in the trilobite suborder Phacopina," she said.

"This is unique in the animal kingdom. In the course of evolution, this eye system was not continued, since the trilobites of the suborder Phacopina died out at the end of the Devonian period 360 million years ago." The discovery is reported in a paper in the journal *Scientific Reports*.

B. Schoenemann et al. 2021. A 390 million-year-old hyper-compound eye in Devonian phacopid trilobites. Sci Rep 11, 19505; doi: 10.1038/s41598-021-98740-z

https://bit.ly/3DbbHe2

Sneaky Mutations Are Helping Malaria to Avoid Detection And Spread in The Body

new strain of Plasmodium falciparum, is able to avoid a common way we detect it.

Tessa Koumoundouros

Malaria still relentlessly plagues parts of the world. It killed more than 400,000 people in 2019, most of them babies and toddlers. In areas of Africa, it's even rivaling COVID-19 deaths, where the coronavirus pandemic has severely interrupted prevention and treatment efforts.

Now, to make matters worse, it looks as if a new strain of the primary parasite responsible for the disease, *Plasmodium falciparum*, is able to avoid a common way we detect it.

New research led by Ethiopian Public Health Institute's immunologist Sindew Feleke has shown nearly 10 percent of malaria cases are missed across Ethiopia's borders as a result of at least one of the mutations helping the parasite evade rapid diagnostic testing (RDT).

What's more, an ability to hide from test kits could easily give this mutated strain enough of an advantage to spread. "False-negative results were common in multiple sites and will lead to misdiagnosis and malaria deaths without intervention," said University of North Carolina's infectious disease researcher Jonathan Parr. "This is a serious problem for malaria control efforts and a reminder that pathogens are very capable of adapting to survive."

P. falciparum is the most common and deadliest of parasites responsible for malaria in humans. Spread by mosquitoes, the parasite infests human red blood cells to clone itself within. These blood cells eventually burst, sending floods of parasites into the bloodstream, causing waves of fevers and other nasty symptoms. Much of the disease's management revolves around reducing human contact with the blood-sucking insects.

Rapid diagnostic testing for malaria has helped Ethiopia – Africa's second-most populous country – make great strides against the disease in the last decade. With around 345 million sold annually, the most common rapid test detects antigens the parasite releases into the bloodstream. This is primarily histidine-rich protein 2 (HRP2), but the test can also be triggered by the closely related HRP3. But some *P. falciparum* have mutations where the genetic instructions coding for the proteins (pfhrp2 and pfhrp23) have been deleted.

Studying the blood samples of over 12,500 patients along Ethiopia

borders with Eritrea and Sudan, Feleke and team discovered these genetic variants had caused false-negative results for just under 10 percent of tests. This is double WHO's minimum criteria for triggering a change in national diagnostic strategy.

"We also found signs that RDT-based testing and treatment are driving a recent rise in pfhrp2 deletion mutation prevalence, allowing parasites to escape detection, " explained Parr.

While the mutations themselves were entirely random, this inadvertent selective treatment is allowing the parasites with either deletion in both the genes or sometimes just one gene or the other to flourish and spread.

The researchers mapped the sequences around the deletions for evidence of evolutionary pressure. This revealed pfhrp2 likely rapidly spread from a single, recent point of origin, with 30 of 31 strains forming a related cluster.

But pfhrp3 has been around longer, present in samples from 2013, and there are a number of different deletion patterns, suggesting it had multiple origins.

Unfortunately, other testing options are not as straightforward, and RDT that works by detecting other molecules produced by the parasite have not performed as well.

The team notes the way they picked up deletions in their study means they would have missed those who are asymptomatic, and they only sampled three sites, so they have not captured a complete picture of what these strains of malaria are doing yet. But evidence from Sudan, Djibouti, and Somalia suggest that the Horn of Africa may already be heavily infiltrated by the mutant *P. falciparum*.

"New tools are needed to support surveillance of [gene] deletions, determine their true prevalence and understand the forces impacting their evolution and spread," the team wrote in their paper.

The deletions are also present in South America, where RDT is not common. So they could be conferring some other evolutionary advantage, too, Feleke and colleagues suspect. It's possible that pfhrp2 does too. There is some evidence that pfhrp2 is involved in inflammation seen in severe malaria.

"People infected by pfhrp2/3-deleted parasites may have less severe disease and therefore be less likely to seek treatment, increasing the likelihood of onward transmission," explain the researchers.

But they can't yet rule out the possibility that its surrounding genes, also impacted by the deletion, are what's driving the parasite to become fitter. One of the flanking genes called EBL-1 is involved in *P. falciparum*'s invasion of red blood cells.

"Surveillance across the Horn of Africa and alternative malaria diagnostic approaches in affected regions are urgently needed," said Parr. This research was published in *Nature Microbiology*.

https://bit.ly/3A2qhcV

The decreasing cost of renewables unlikely to plateau anytime soon

Early price forecasts underestimated how good we'd get at making green energy

Doug Johnson

Past projections of energy costs have consistently underestimated just how cheap renewable energy would be in the future, as well as the benefits of rolling them out quickly, according to a new report out of the Institute of New Economic Thinking at the University of Oxford.

The report makes predictions about more than 50 technologies such as solar power, offshore wind, and more, and it compares them to a future that still runs on carbon. "It's not just good news for renewables. It's good news for the planet," Matthew Ives, one of the report's authors and a senior researcher at the Oxford Martin Post-Carbon Transition Programme, told Ars.

The paper used probabilistic cost forecasting methods—taking into account both past data and current and ongoing technological

developments in renewables—for its findings. It also used large caches of data from sources such as the International Renewable Energy Agency (IRENA) and Bloomberg. Beyond looking at the cost (represented as dollar per unit of energy production over time), the report also represents its findings in three scenarios: a fast transition to renewables, a slow transition, and no transition at all.

Compared to sticking with fossil fuels, a quick shift to renewables could mean trillions of dollars in savings, even without accounting for things like damages caused by climate change or any co-benefits from the reduced pollution. Even beyond the savings, rolling out renewable energy sources could help the world limit global warming to 1.5º C. According to the report, if solar, wind, and the myriad other green energy tools followed the deployment trends they are projected to see in the next decade, in 25 years the world could potentially see a net-zero energy system.

"The energy transition is also going to save us money. We should be doing it anyway," Ives said.

Plateau, or no?

The cost for renewable energy has consistently dropped as the world started its transition away from fossil fuels. Solar, for instance, is now cheaper than the creation of new coal or gas-fired power plants, according to an International Energy Agency (IEA) report. However, several reports in the past have suggested that, at some point or another, the falling costs of renewables will begin to level out. For instance, the same IEA report suggests that offshore wind prices will begin to level off now.

However, another recent paper reviewed projections for the future of renewable resources and also found that much of the earlier research underestimated future cost reductions in the field. According to Ives, past reports consistently underestimate the technological advancements that are leading to the continued decrease in the price of renewables. Ives' paper suggests that the models used in these other forecasts have had two problems: they make assumptions about the maximum growth rates of renewables, and they use "floor costs," a point at which the prices can't fall further.

Ives' report focuses mainly on the process of technological advancement, which is part of what has made renewables cheaper. Renewables have routinely performed beyond the expectations of previous papers. "They've been getting these forecasts wrong for quite some time," Ives said. "You can see we've consistently broken through those forecasts again and again."

The Institute of New Economic Thinking report doesn't place a hard deadline on a cost plateau for renewables. Rather than there being a plateau caused by advancements, Ives said the greater likelihood is that the prices will decrease slower once things like solar and wind end up dominating the market. At that point, technological advances may very well still happen, but they might not be rolled out as frequently as they are now. "It's the deployment that slows it down," Ives said.

"Overly pessimistic"

This largely fits with IRENA's finding as well, according to Michael Taylor. He's a senior analyst with the group, which recently released its own report. According to Taylor, the group found that the cost-reduction drivers—improved technology, supply chains, scalability, and manufacturing processes—for solar and wind are likely to continue at least for the next 10 to 15 years. It's possible that previous forecasts were conservative in their estimations, he said.

"I would expect they're overly pessimistic," Taylor told Ars.

However, he noted that some issues might see the reductions slow down. The pandemic, for instance, disrupted global supply chains and made it harder to obtain some essential materials, like the polysilicon used in solar panels. There are also some barriers to

fully implementing renewables, such as oil and gas subsidies, public opinion, permitting, etc.

"Just on purely economic grounds, there are increasing benefits to consumers to be had by accelerating the rollout of renewable power generation," Taylor said. "We'd encourage policy makers to look very seriously at trying to remove the barriers that currently exist."

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Scientists Discover New Science of the Body's "Second Brain" – New Leads To Treat Irritable Bowel Syndrome

Revealing the Logic of the Body's "Second Brain" Scientists discover new science in the gut and, potentially, new leads on how to treat irritable bowel syndrome and other disorders.

Researchers at Michigan State University have made a surprising discovery about the human gut's enteric nervous system that itself is filled with surprising facts.

For starters, there's the fact that this "second brain" exists at all.

"Most people don't even know that they have this in their guts," said Brian Gulbransen, an MSU Foundation Professor in the College of Natural Science's Department of Physiology.

Beyond that, the enteric nervous system is remarkably independent: Intestines could carry out many of their regular duties even if they somehow became disconnected from the central nervous system.

And the number of specialized nervous system cells, namely neurons and glia, that live in a person's gut is roughly equivalent to the number found in a cat's brain.

"It's like this second brain in our gut," Gulbransen said.

"It's an extensive network of neurons and glia that line our intestines."

Neurons are the more familiar cell type, famously conducting the nervous system's electrical signals.

Glia, on the other hand, are not electrically active, which has made it more challenging for researchers to decipher what these cells do.

One of the leading theories was that glial cells provide passive support for neurons.

Gulbransen and his team have now shown that glial cells play a much more active role in the enteric nervous system.

In research published online on October 1, 2021, in the *Proceedings of the National Academy of Sciences*, the Spartans revealed that glia act in a very precise way to influence the signals carried by neuronal circuits.

This discovery could help pave the way for new treatments for intestinal illness that affects as much as 15% of the U.S. population.

"Thinking of this second brain as a computer, the glia are the chips working in the periphery," Gulbransen said.

"They're an active part of the signaling network, but not like neurons.

The glia are modulating or modifying the signal."

In computing language, the glia would be the logic gates.

Or, for a more musical metaphor, the glia aren't carrying the notes played on an electric guitar, they're the pedals and amplifiers modulating the tone and volume of those notes.

Regardless of the analogy, the glia are more integral to making sure things are running smoothly — or sounding good — than scientists previously understood.

This work creates a more complete, albeit more complicated picture of how the enteric nervous system works.

This also creates new opportunities to potentially treat gut disorders.

"This is a ways down the line, but now we can start to ask if there's a way to target a specific type or set of glia and change their function in some way," Gulbransen said.

"Drug companies are already interested in this."

Earlier this year, Gulbransen's team found that glia could open up new ways to help treat irritable bowel syndrome, a painful condition that currently has no cure and affects 10% to 15% of Americans.

Glia could also be involved in several other health conditions, including gut motility disorders, such as constipation, and a rare disorder known as chronic intestinal pseudo-obstruction.

"Right now, there's no known cause.

People develop what looks like an obstruction in the gut, only there's no physical obstruction," Gulbransen said.

"There's just a section of their gut that stops working."

Although he stressed that science isn't at the point to deliver treatments for these problems, it is better equipped to probe and understand them more fully.

And Gulbransen believes that MSU is going to be a central figure in developing that understanding.

"MSU has one of the best gut research groups in the world.

We have this huge, diverse group of people working on all the major areas of gut science" he said.

"It's a real strength of ours."

Reference: "Circuit-specific enteric glia regulate intestinal motor neurocircuits" by Mohammad M. Ahmadzai, Luisa Seguella and Brian D. Gulbransen, 30 September 2021, Proceedings of the National Academy of Sciences.
DOI: 10.1073/pnas.2025938118

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The Genius Idea for Making Drinks with Smoke-Damaged Grapes

Distillers are coming up with creative ways to use California wine grapes ruined by the smoke of wildfires.

Wayne Curtis

"Smoke taint" is the Marvel-caliber villain that's been stalking vineyards across the West the past few years.

It moves capriciously on the wind wending its way into valleys where it lingers in the company of wine grapes.

If those grapes are at a certain stage of maturity, the smoke and its noxious compounds pass through the grape skins, then bind with sugar molecules to create compounds called glycosides, making the smoke difficult to detect.

"If you pick a berry in the field, it tastes perfectly fine," says Nicolas Quille, chief winemaking and operations officer at Crimson Wine Group in California, which owns six wineries and nearly 1,000 acres of vineyards.

But smoke's villainy hasn't ceased; enzymes produced during fermentation break down the glycosides, releasing the noxious compounds.

"And at that point the flavors are revealed," Quille says.

This is not a good thing.

It's not as if a robust cabernet engages in an interesting duet with rustic mezcal and subtle phenolics harmonize with natural tannins.

"Some of those compounds are bitter," says Quille.

"In its worst effect, it's a like a cold ashtray." Or as another winemaker described it to *Wine Spectator* last year, the smoke manifests itself as a "acrid, bitter, charry finish."

Complicating matters, the process of revealing those flavors follows a vague timeline.

After her family's Napa Valley vineyard was briefly beset with smoke late in the 2017 season, Lindsay Hoopes of Hoopes Vineyard hoped for the best and made that year's harvest into cabernet.

All seemed fine during and after fermentation, and so the wine went into barrels for aging.

Two years later, after they popped the bungs, the stealth adversary resurfaced.

"We couldn't tell it had smoke taint until it was just about to be bottled," she says.

The variables affecting the extent of smoke taint are considerable.

The distance from a fire and the amount of time the smoke lingers matters, as does the species of tree in the burning forests, the intensity of the fire and what part of the burn cycle is producing the smoke—the smoke compounds when a fire first ignites are not the same as when a fire smolders into embers.

Hoopes notes that the wildfires that affected her vineyard in 2017 and 2020 were strikingly different.

In 2017, the smoke arrived late in the growing season and was fleeting.

In 2020, the smoke settled earlier on in the growing cycle, then persisted.

A handful of enology labs are equipped to detect smoke taint in grapes using pricey gas chromatography-mass spectrometer analysis, helping wineries to decide whether to discard their harvest or proceed to make wine.

Following a string of active wildfire seasons, and a flood of grapes and wine sent for testing, labs got backed up and analyses delayed, sometimes for weeks, meaning that winemakers often had to make a go/no-go decisions about harvesting before the lab results were in.

And what to do if the lab discovered tainted grapes? Many wineries are covered by insurance and the damaged grapes are either discarded or left on the vines to rot.

Some are sold to bulk wine producers to make plonk, with the off flavors blended or sweetened away.

Others, however, are rescued by what amounts to smoke taint's kryptonite: distillation.

Hoopes was at an event in Kentucky shortly after she discovered that her 2017 vintage was spoiled.

She found herself seated near Marianne Eaves, a noted distiller and distilling consultant, formerly with Brown-Forman and Castle & Key.

Eaves was intrigued by the challenge posed by smoke taint.

Working with a pair of California craft distillers, Eaves made various products from the tainted wine, including gin, marsala wine and vermouth. "But the brandy really stood out," Hoopes said.

The distillate—stripped of the smoke taint after passing through the still—went into imported Cognac barrels for aging in 2019.

The brandy may be released as soon as next January under the Madame X brand.

Hoopes also acquired an additional trademark—Napañac—which she plans to allow others to use to establish an identity for brandy made in the Napa Valley.

The 2020 fire season was worse than 2017.

Smoke came earlier in the season and hung around longer.

"In 2020, the grapes were all hanging there for about two months while fires burned," Hoopes says.

"There was no way to feel confident." While some of the 2017 red grape harvest did make it into wine bottles, all of her red grapes harvested in 2020—along with some additional grapes added from nearby vineyards—were channeled into brandy production and will eventually hit the market as Napañac.

Smoke tainted grapes are also finding their way into a limited run of vodka produced by Hangar One in Alameda, California.

The Crimson Wine Group had previously worked with Hangar One to produce Fog Point Vodka, a grape-based vodka made with water collected from California fog using fog catchers.

Hangar One connected with Crimson after their 2020 harvest—about half of which was ruined by smoke—and took on some of their damaged grapes to try making vodka.

Eric Lee, Hangar One's distiller, said that the wine they started with had "almost no discernible smoke character," and by distilling it at the high proof used to make vodka, virtually all impurities had been stripped out.

Named Smoke Point, it has a rich, supple mouthfeel and fleeting, distant hints of honeysuckle and caramel, with just a hint of peppermint.

What it does not have is the taste of smoke.

Smoke Point was released in early September in California and "a handful of other states" at a suggested retail price of $50 a bottle.

(The web site refers to it as "smoke-tinged" rather than "smoke-tainted.") Proceeds from the sales will go to the California Fire Foundation, a nonprofit that supports firefighters and their families and communities.

About 2,400 bottles were produced.

"What interested us was the charity part," says Quille of Crimson Wine Group. "We could donate our time and our product to the firefighters.

The idea that we could make lemonade out of these lemons came after the fact."

While Hoopes Vineyard has invested heavily in learning how to make brandy from its grapes, don't expect to see regular releases of Napañac.

It's mostly a way to help cover losses when disaster strikes—Hoopes points out that it doesn't make sense to divert grapes that normally produce expensive, sought-after wine into brandy.

Add the additional expense of distillation and aging, and profits seem to recede even further.

"It's a project we make when Mother Nature comes in," Hoopes says. "You just never know."

This past summer was full of wildfire, the skies brown and the landscapes sepia.

But fortunately for vintners the largest fires were downwind—mostly to the east in the Sierra Nevada—and didn't affect the grapes.

"We're happy to have a normal season," says Quille.