directs training efforts for the wellness center, acknowledges that OSU has a lot of ground to make up to become a preeminent medical research organization. "The [psychiatry] department has zero history of NIH [National Institutes of Health] grants," he says. "But we've got four in review right now." In addition, the center's first two addiction medicine fellows start this summer, and he hopes to have six in the next cohort.

Beaman says he left the University of Arkansas in 2015 and returned to his alma mater because the medical school had made addressing the state's mounting opioid crisis a priority. "Our mission is to train primary care physicians to work in rural and underserved areas," says OSU's Kayse Shrum, who became the youngest and first female president of an Oklahoma medical school when she was promoted into the job in 2013. "And that's where the [addiction] crisis is most acute. So we began hiring psychiatrists with expertise in addiction medicine."

Shrum and Beaman also benefited from serendipity. The medical school at their

State Attorney General Mike Hunter (left) joins Oklahoma State University medical school President Kayse Shrum (right) to announce a settlement.

archrival, the University of Oklahoma (OU) in Norman, is known nationally for its efforts to combat cancer and cardiovascular disease, and last year its faculty members could boast of 105 NIH grants. (OSU has one, a capacity-building grant to study adverse childhood experiences.) But in 2016, OU officials decided addiction medicine was no longer a priority and ended the training program.

"We lost our funding, and I retired after 25 years there," says emeritus professor William Yarborough, who ran the program. "Meanwhile, OSU was ramping up its program. So once [the state and Purdue] reached a deal, there really wasn't anybody else at the table," says Yarborough, who is president of the Oklahoma Society of Addiction Medicine.

Beaman's department has swelled from three to 20 faculty members in the past 3 years, and he expects the settlement and the endowment to accelerate that growth. "There are three or four people who I anticipate being able to hire almost immediately," he says. "And I'll also go on the road. Maybe I'm being a Pollyanna, but who wouldn't want to be part of what I hope will be the first sign of the end of the country's opioid epidemic?"

The settlement creates an endowment that is likely to generate less than $10 million a year in new spending. That new pot is dwarfed by the $500 million that NIH will spend this year on its new Helping to End Addiction Long-term Initiative, launched in April 2018. And even that amount, public health advocates say, is minuscule compared with the magnitude of the opioid epidemic and the pressing need for treatment facilities, medical providers, and prevention.

Cheryl Healton, dean of public health at New York University in New York City, praises Oklahoma Attorney General Mike Hunter for negotiating a deal that funnels most of the money to those needs. "That's a far cry from the tobacco settlement," she says, referring to the $126 billion tobacco companies have paid out to date to 46 states under a 1998 agreement.

For many years Healton led a national public antismoking campaign financed by the massive settlement. State officials were given the power to allocate the money as they saw fit, however, and less than 1% of it has gone to tobacco prevention programs, even as tobacco companies continue to spend billions each year on marketing their products.

Healton says there's an urgent need for a similar, sustained national public education campaign to combat the opioid epidemic. The best chance for that, she says, is a well-focused, master settlement of the pending opioid cases, something that a federal judge in Ohio has tried to pull off, so far unsuccessfully. Absent that, Healton worries that any deals struck by individual states and localities could wind up being too little, too late, to save many lives.

"Compared with tobacco, the use of opioids is likely to grow," she warns. "And it's up to all of us to be a countervailing force." ■

HUMAN EVOLUTION

Moderns said to mate with late-surviving Denisovans

Genomes from New Guineans suggest mixing, perhaps as recently as 15,000 years ago

By **Ann Gibbons**, *in Cleveland, Ohio*

The elusive Denisovans, the extinct cousins of Neanderthals, are known only from the scraps of bone and teeth they left in Siberia's Denisova Cave and the genetic legacy they bequeathed to living people across Asia. A new study of that legacy in people from New Guinea now suggests that, far from being a single group, these mysterious humans were so diverse that their populations were as distantly related to each other as they were to Neanderthals.

In another startling suggestion, the study implies that one of those groups may have survived and encountered modern humans as recently as 15,000 to 30,000 years ago—tens of thousands of years later than researchers had thought. "A late surviving lineage [of Denisovans] could have interbred with *Homo sapiens*" in Southeast Asia, paleoanthropologist Chris Stringer of the Natural History Museum in London, not a member of the team, said in a Skype interview at the annual meeting of the American Association of Physical Anthropologists here last week.

Researchers already knew living people from a vast area spanning the Philippines and New Guinea to China and Tibet have inherited 3% to 5% of their DNA from Denisovans. The leading scenario had suggested that as modern humans swept out of Africa, they first encountered Neanderthals and mated with them; hence, all people in Europe and Asia now have 1% to 3% of their DNA from Neanderthals. The ancestors of Asians then met Denisovans 50,000 years ago or so and acquired additional DNA from those archaic people.

For the new study, an international team analyzed the complete genomes of 161 people from 14 groups in Indonesia and Papua New Guinea. In the DNA of 60 people from New

PHOTO: OKLAHOMA STATE UNIVERSITY CENTER FOR HEALTH SCIENCES

Some of the last Denisovans may have intermingled with modern humans on mountainous New Guinea or nearby islands.

PHOTO: DOZIER MARC/HEMIS.FR/GETTY IMAGES

Guinea, population biologist Murray Cox of Massey University in Palmerston North, New Zealand, molecular biologist Herawati Sudoyo of the Eijkman Institute for Molecular Biology in Jakarta, and their colleagues found an unexpected twist. The first Denisovan DNA discovered, from the cave in Russia, comes from a single population (which geneticists have labeled D0). But "Papuans carry DNA from at least two [other] Denisovan populations, called D1 and D2," Cox said in his talk, which was filmed in advance and played at the meeting.

When the team members analyzed the DNA with three statistical methods, they found that the two additional sources of Denisovan DNA came from populations so distantly related that they had diverged more than 283,000 years ago. The D2 population is even more distant from the Siberian Denisovans, having split off roughly 363,000 years ago. That makes those two populations almost as distantly related to each other as they are to Neanderthals, Cox says. "We used to think of Denisovans as a single group," says Cox, who suggests as an aside that the D2 group might even need a new name.

The D1 DNA isn't seen in people outside New Guinea, and it's found on large chunks of chromosome that haven't been mixed over time, suggesting it entered the modern human genome recently—about 30,000 years ago, and perhaps just 15,000 years ago. Cox's team suggests a group of Denisovans survived in the remote mountains or islands of New Guinea and mated with modern humans.

The finding of two Denisovan lineages in New Guineans adds to results reported in *Cell* last year by a team including postdoc Serena Tucci of Princeton University, who co-organized the session. They found that East Asians had two sources of Denisovan DNA, suggesting at least two mixing events. But they did not find evidence that New Guineans got Denisovan DNA from two sources.

The multiple encounters with Denisovans gave living people in Indonesia and Papua New Guinea 400 new gene variants, including an immune gene variant (*TNFAIP3*) and a gene involved in diet (*WDFY2*). "People are turning up in hospitals in Australia carrying this gene [*TNFAIP3*]; it has clinical implications for how they respond to autoimmune diseases," Cox said in his talk.

Not everyone is convinced by the late dates. "There are definitely multiple Denisovan populations, but the claim that they interbred 15,000 to 30,000 years ago is extraordinary," says population geneticist Benjamin Vernot of the Max Planck Institute for Evolutionary Anthropology in Leipzig, Germany.

"I'm skeptical," adds Cosimo Posth of the Max Planck Institute for the Science of Human History in Jena, Germany. He suggests that the hints of a recent mating could reflect an encounter of previously isolated modern populations rather than of moderns and Denisovans. In this scenario, modern humans mated with Denisovans, and then the modern populations diverged, with each branch retaining a different set of Denisovan genes. The moderns then reconnected, bringing the two sets of Denisovan DNA together again.

Whatever happened on New Guinea, it seems that Denisovans mixed with modern humans often. In a separate talk, Xinjun Zhang of the University of California, Los Angeles, reported that Tibetans also got their Denisovan DNA from two encounters. And population geneticist Alan Rogers of the University of Utah in Salt Lake City said that his analysis suggests Denisovans and Neanderthals themselves were the product of interbreeding. He used computational modeling to test different scenarios for how Denisovans, Neanderthals, and modern humans acquired each other's DNA. He concluded that the common ancestor of Denisovans and Neanderthals interbred with another extinct "superarchaic" member of the human family, possibly *H. erectus*, about 700,000 years ago or so. "There was an awful lot of mixing whenever hominins got together," he says.

The Denisovan findings add new urgency to the effort to find more than scraps of this mysterious hominin. At the meeting, paleoanthropologist Bence Viola of the University of Toronto in Canada described the first chunk of skull bone found of a Denisovan—a coaster-size piece of thick parietal bone from the back of the skull, found in Denisova Cave and containing Denisovan DNA. It suggests "a large individual, which fits with the [large] teeth" from the cave, Viola says. The bone offers guidance for paleoanthropologists sorting through specimens for Denisovans. "It raises many more questions than it answers, but I'm hopeful" that researchers will be able to link Denisovan DNA to more-complete bones, Viola says. ■