On Cancer’s Trail

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The women in Stefanie Raymond-Whish's family have a history of breast cancer. Now the young Navajo biologist is asking why.

FLAGSTAFF, ARIZONA

Stefanie Raymond-Whish was 9 years old when her grandmother was diagnosed with breast cancer. A traditional Navajo who raised 15 children after her husband died in a car wreck, Raymond-Whish's ama' sa' ni seldom spoke about her illness. Even after her surgery, when she lived with the grandchildren and their mother, she always acted strong around the kids. It became a pattern: When Raymond-Whish was 13, her 38-year-old mother, Nellie Sandoval, was also diagnosed with breast cancer. And Sandoval was equally reserved on the subject. "My mother was really good about not appearing sick in front of us," says Raymond-Whish, now 32. "As a little girl, I knew about cancer, but didn't understand the impact of it at the time."

She understood it better by the time she was in college, in Flagstaff, Ariz., when a new tumor appeared in her mother's other breast. "When my mom had her recurrence, that's when it really hit me ... it was really upsetting. I went home to Farmington for her lumpectomy." Sandoval survived the disease, but not without a long struggle that included chemotherapy, radiation, and finally a double mastectomy. "My breasts were pretty mangled," says Sandoval, now 58. "So I said, 'Just get rid of them.' " Both Sandoval and her daughter have made breast cancer and its impact on Navajos the focus of their lives. Sandoval became an activist and filmmaker, working out of her papaya-colored home in Farmington, N.M. Raymond-Whish has taken her mission a
step further: She works as a molecular biologist at the University of Northern Arizona, searching for breast cancer's root causes. "Is there any difference in how breast cancer develops in Native Americans and non-Native Americans?" she asks. One possible - and provocative - answer is emerging from her lab at the university: uranium.

Scientists have long known that uranium damages human cells. But in over six decades of atomic health testing, no one had ever noticed that uranium, at low doses, can act like an estrogen. No one, that is, until recently, when Raymond-Whish and her coworkers observed some unusual effects in lab animals.

Uranium can be found in several of the Jurassic sandstones that lie beneath the Four Corners region like a wrecked layered pastry. The target of frenzied mining throughout the Cold War, uranium ore has been wrenched from the ground, pulverized, milled and tossed in tailings across the Navajo Reservation. Low-level radioactive waste has dissolved into groundwater, escaped onto dust particles and blown off thousands of passing trucks to settle uneasily on surface soils. Over 1,000 abandoned uranium mines pockmark Navajo lands, but only half of them have been reclaimed. Exposure to uranium and its daughter elements has been linked to lung cancer, kidney damage and bone disease in Navajos, and it is the suspected culprit in numerous other medical conditions, from degenerative nerve disease and birth defects to a variety of other cancers.

Raymond-Whish's research lab is tucked inside a neo-Grecian edifice on the Northern Arizona University campus. With her gloved hands in a ventilated booth, the white-coated scientist carefully measures out uranium in solution into small test tubes. The solution will be injected into dishes of cultivated human breast cells, donated by a nun who died of breast cancer in 1979. The MCF-7 cells, as they are known, have been kept alive by the Michigan Cancer Fund through 178 generations of cell division. They are famous among researchers for the properties they exhibit in lab experiments. For example, estrogen causes them to proliferate rapidly - exactly as it does in real-life breast tissue, which is why many women diagnosed with breast cancer have their estrogen-producing ovaries removed. Raymond-Whish wants to see if the cells react in the same way to uranium.

"What I'm really interested in is the development of the mammary gland," says Raymond-Whish, who at this point is just weeks away from finishing her doctoral dissertation. A former teen rodeo star in barrel racing, she once wanted to be a veterinarian. But
NAU didn't have a vet school, so she majored in zoology. That eventually landed her in the Discovery Research lab, where she studied the effects of pollution on tadpoles. She found she loved research. "It's like being a detective," she says.

The lab’s discoveries have already demolished the conventional wisdom on the properties of uranium. Not only does the heavy metal appear to alter mammary cells at very low doses, but it also seems to interfere with normal hormonal signals. Sometimes the uranium follows the same pathways as estrogen, but sometimes it doesn't, which means it's triggering other endocrine responses as well. "We don't yet know the mechanism of how uranium is affecting these cells," Raymond-Whish says, "but we do know an estrogen receptor is involved. We see it in both animals and MCF-7 cells."

Although the work in Raymond-Whish's lab is considered pure research science, it is impossible to sift it from the real-world context of her family, her culture and her beliefs. Breast, uterine and ovarian cancers have risen steeply in Indian country since the advent of uranium mining. Having watched her grandmother and mother suffer, and now with two kids of her own, 14 and 4 years old, Raymond-Whish can't help but wonder if she's next in line.

But while Raymond-Whish's intimate acquaintance with cancer may harm her credibility as a dispassionate scientist, it may also propel her to help make startling discoveries where no one else has thought to look.

The lab's investigation started several years ago, when Northern Arizona University became part of a team that received a five-year grant from the National Cancer Institute. The project is designed to address community health care, so the local Navajo elders had a few suggestions. They told the scientists they wanted to know more about the health effects of uranium pollution.

"So I started adding uranium to the drinking water of my lab animals," recalls physiologist Cheryl Dyer, who was Raymond-Whish's faculty advisor at the time. "And because I'm an ovarian physiologist, I wanted to see what happened in the ovary." Uranium has long been known to be radioactive and toxic, but no one had ever looked at its effects on follicle counts, or the number of "pre" eggs - eggs in the ovary that have not yet been released for fertilization. Dyer and Raymond-Whish found that
the number of pre-eggs declined with low exposure to uranium, and that the mice developed heavier-than-normal uteruses. Normally, a toxic chemical will cause an organ such as a kidney to shrink, not expand. "I said, 'Whoa, what is going on here?'" says Dyer. "I started to wonder if there were other heavy metals that cause these changes, and it turns out cadmium does the same thing. That's when a light bulb went off in my head. Cadmium is an estrogen mimic." All those decades of lab work with atomic elements, and "they had completely missed the boat on estrogen mimicry."

Raymond-Whish was the lead author of a paper showing the unexpected effects of uranium on mouse follicle counts, uterine weights and accelerated puberty. "Drinking Water with Uranium below U.S. EPA Water Standard Causes Estrogen Receptor Dependent Responses in Female Mice" was published in December in Environmental Health Perspectives, a peer-reviewed journal put out by the National Institutes of Environmental Health Sciences. Raymond-Whish concluded that uranium acts as an estrogen, and she recommended that Navajo girls and women be followed closely for reproductive cancers. In conversation, Dyer makes her opinion clear: The U.S. Environmental Protection Agency should lower its drinking water standard for uranium from 30 micrograms per liter to 20 micrograms, the Canadian standard. But Dyer and Raymond-Whish are tip-toeing out on a treacherous scientific limb by suggesting policy changes that are based on controversial data.

Raymond-Whish's work and its results have landed her in the middle of a scientific and regulatory quagmire. It's one thing to regulate a chemical known to be toxic at high doses; it's entirely another to suggest regulating minute levels of a substance that is readily found across a large swath of the American West. Many communities, not just those on the reservation, are affected by uranium. Recent tests in Colorado, for example, revealed that 37 cities and towns in the state depend on drinking water that exceeds federal levels for uranium and its daughter nuclides.

**Uranium is not just an emotional issue** for Raymond-Whish, but for the tribe as a whole. The legacy of mining the element on the 27,000-square-mile reservation is so deeply and collectively felt that the Navajo Nation banned it altogether in 2005 in the face of globally rising ore prices. During the '40s and the Cold War period, the U.S. government used yellow cake - or milled
and concentrated uranium ore - to build nuclear weapons. The government stopped buying the ore for weapons in 1971, but the commercial nuclear energy market picked up the slack until the early 1980s. Only about a quarter of all U.S. uranium miners were Native American - Laguna, Hopi, Zuni and Ute as well as Navajo. But Native Americans have been disproportionately affected: Their tribal lands are still contaminated, and former miners suffer illnesses and deaths for which many families are still awaiting compensation.

Despite the tribal ban, at least five companies are seeking state permits in New Mexico to mine lands just off the reservation, including on tribal allotment land. In Arizona, 700 individual mining claims were filed in 2005. The prehistoric sea and river beds that run underground from Naturita, Colo., to Grants, N.M., and across to Moab, Utah, still hold an estimated 600 million pounds of low-grade ore. But for every 4 pounds of uranium extracted, 996 pounds of slightly radioactive waste is left over, in piles, in pits and eventually in the soil, arroyos and underground aquifers.

Some Western tailings piles, like those outside of Monticello, Utah, or Grand Junction, Colo., have been cleaned up. But those on tribal lands have fallen through yawning bureaucratic and regulatory gaps. It's estimated that up to 25 percent of unregulated water sources on the Navajo Reservation exceed federal drinking water standards for uranium. And many families still haul water from these wells, despite warnings by health providers and advocacy groups.

In her lab experiments, Raymond-Whish applies concentrations of uranium that match those of water supplies in parts of the Four Corners, at or slightly above the current EPA standard. She will treat the mammary cells - which come bathed in a red wash of nutrients that resembles weak Kool-Aid - twice in nine days with differing doses. She will then collect the breast cells, extract their protein signatures, and use a tedious process to examine differences in the number of their estrogen receptors. She will also feed rats different mixtures of uranium-tainted water and examine their mammary glands for altered development. She will compare those results to rats fed a well-known synthetic estrogen, diethylstilbestrol, or DES, and to rats that have drunk plain tap water. She'll look for changes to the mammary glands' terminal end buds, lobules and milk ducts, changes that may make them more prone to breast cancer. The work is controversial, and its implications, both for the science of breast cancer and for the treatment of past and future mining pollution, could be profound.
Like Marie Curie over a century before, Raymond-Whish is both repelled and fascinated by the heavy element’s mysterious abilities to alter living cells. In some respects, Raymond-Whish and Curie are not dissimilar. Curie, a Polish Jew working in anti-Semitic France, was the first woman to teach at the Sorbonne. As the first Navajo to be awarded a Ph.D. in the Biology Department of NAU, Raymond-Whish displays a confident ease in navigating a different dominant culture. Like Curie, she is driven by an unrelenting curiosity.

If it was a difficult journey from being Rookie of the Year in barrel racing to creating stunning presentations on heavy metals, Raymond-Whish doesn't show it. She moves through the fluorescent-lit lab in a quiet, deliberate fashion, her long, shiny hair neatly in place.

"I like it that you're working on something no one knows the answers to and you're finding the answers," says Raymond-Whish. She grew up in Colorado and New Mexico with her siblings, stepfather and mother, who was a high school guidance counselor before becoming a breast-cancer activist. Forty-four percent of Navajos do not graduate from high school, but Raymond-Whish's mother made sure that she did. "Everybody's saying it's a big deal for me to get a Ph.D. For me, nothing less was expected than, 'You're going to college.'"

The lab work is routine - even tedious - but it's also demanding and consuming. She is tired. With her oral defense looming before a committee of distinguished faculty, she doesn't slow down. In the mornings, she drops her two kids at school. Her husband, Bryan, a Wichita Indian, works nearby in the university's admissions office. She shuttles from the tissue culture room down a long linoleum-floored corridor to the animal histology lab with its wide-screened computer that magnifies mouse ovary sections 40 times over. Scrolling across the screen to count the follicles is her least favorite job. "I get motion sick," she says. The ovaries dominate the screen like giant pink potato chips, lightly salted.

The science of endocrine disruptors, which studies chemicals that mimic hormones, is a little over 10 years old and still rife
with skeptics. It has only been in recent years that very low doses of chemicals - in the parts-per-billion range - have been measurable. (A part per billion is the equivalent of one kernel of corn in a corn-filled silo 45 feet tall.) But natural hormones do their work at these very low levels in the human body. One theory holds that certain environmental chemicals, both natural and man-made, can bind to and deceive the hormone receptors.

These receptors are the signal towers that trigger - or prevent - cellular responses that govern everything from metabolism to sex. Artificial chemicals scramble the signals. They appear to be interfering with normal cellular communication and altering how and when the cells, glands and organs develop. Endocrine disruptors have been implicated in obesity, infertility and the timing of puberty as well as in cancer. When many older women stopped taking synthetic estrogen a few years ago, breast cancer rates in this country dropped for the first time in 40 years. DES, the control substance used by Raymond-Whish, was given to pregnant women to prevent miscarriages up until 1971. Their daughters, who were exposed to it in the womb, have been stricken with unusual reproductive cancers, and recent studies have shown an increased risk of breast cancer as well.

Typical carcinogens cause a cell's DNA to mutate, eventually leading to cancer. Radiation causes the fragile chains of DNA to break, also leading to errors and mutations. Scientists know a lot about these two types of cancer-causing agents. But endocrine disruption is far more mysterious.

Which is why scientists like Raymond-Whish find themselves at a unique moment in science, just as the traditional models of understanding disease are shifting. The field of breast cancer research in particular is driving the debate. Chemicals such as atrazine and DDT (an herbicide and a pesticide, respectively), plastics - such as the bisphenol A compound found in Nalgene that was banned from baby bottles this spring in Canada - and now uranium, are challenging and confounding scientists seeking to understand the actions of chemicals in the human body.

In the dynamic field of environmental health, toxicologists - who study traditional dose-response curves of carcinogens - and endocrinologists - who study extremely low levels of chemicals that do not always follow expected linear curves - frequently disagree. Because it is not yet known exactly how chemicals like uranium act upon cells, some scientists flatly dispute Raymond-
Whish's findings. "Uranium is not plausibly linked as an endocrine disruptor," says toxicologist Margaret Ruttenber, director of the environmental health studies program of the Colorado Department of Public Health and the Environment. "There is an absence of a known mechanism."

Louise Canfield, director of the Native American Cancer Research Partnership at the University of Arizona, says: "My personal opinion is that obesity and other lifestyle factors are key risks (for breast cancer), along with access to care. Uranium in drinking water is a health hazard for sure, but I'm not sure it's a primary cause of cancer."

But others consider the work groundbreaking. "This is a science of subtlety," explains Andrea Gore, a neuroendocrinologist at the University of Texas, Austin, and former advisor to the National Science Foundation. "(Dyer's and Raymond-Whish's) work is consistent with other good labs. People criticize the field of endocrine disruption because we don't always understand the mechanisms, but the effects are still real. This is why animal studies are so important. The responses we see in lab animals can happen in humans, because we share the exact same hormones. The estrogen receptor is similar."

Still, more evidence is needed before scientists concede a link between uranium and breast cancer in humans. "You can make a very strong case with animal studies, but it will never be definitive," says cancer expert Joaquin Espinosa, professor of molecular, cellular and developmental biology at the University of Colorado, Boulder. "You hope that nature would have done the experiment for you out there at some point. You need to show that real people are affected."

But epidemiological data on the reservation is hard to come by. For one thing, it's difficult to sort out reliable cancer statistics and their changes over time. Some Navajo elders consult only medicine men, so some cancers go unreported. Cancer itself is translated in Navajo as Lood doo nadziihii, "the sore that does not heal." Some patients do not seek treatment, nor do they even speak of the disease for fear of wishing it upon their families, according to Fran Robinson, a nurse oncologist at San Juan Regional Medical Center in Farmington. Until recently, the Indian Health Services kept haphazard records in which diagnoses
went unconfirmed and doctors came and went. For a variety of reasons, including instances of abuse of trust by researchers, the Navajo Nation guards its own data as closely as any member of the former Soviet bloc.

The New Mexico State Tumor Registry keeps statistics on cancers by county, including those on the New Mexico portion of the reservation, which is also where many uranium mines were located. In her published paper, Raymond-Whish cites registry data from the late 1970s showing a 17-fold increase in childhood reproductive cancers there compared to the U.S. as a whole. These are extremely rare cancers that are related to hormone systems. Another study looking at registry data from 1970-1982 showed a 2.5-fold increase in these cancers among all Native Americans in New Mexico. (Although these statistics are not broken down by tribe, most of the Native Americans in the state are Navajo.) A 1981 paper showed a possible link between incidents of birth defects in families and the proximity of those families to uranium mine tailings. The sample sizes of the first two studies were too small to draw solid conclusions, and the birth defects study was flawed, cautions Charles Wiggins, director of the Tumor Registry. He plans to re-examine childhood cancer statistics this fall, using new data gathered since 1982.

Overall, Native Americans in New Mexico actually suffer less cancer than the rest of the country, including about half the rate of breast cancer. But even as breast cancer rates in the U.S. have leveled or dropped slightly in recent years, they continue to grow among Native Americans, and the rate has increased more steeply over the past three decades. Breast cancer is the number-two killer (after heart disease) of Navajo women and the most common cancer found in Navajos. (In the U.S. as a whole, lung cancer is the most common cancer.) Navajos with cancer also suffer higher mortality rates due to poor access to medical care. One study found that between one-third and one-fifth of Navajo breast cancer patients receive substandard care. Relatively more young Navajo women get breast cancer, although much of this can be explained by demographics: Navajos have a younger population than other groups. To the doctors working on the reservation, the anecdotal evidence is disturbing. "When we see women in their 30s with breast cancer, it really knocks everyone for a loop," says physician Tom Drouhard, who has been practicing in Tuba City, Ariz., for 30 years. "Our ladies come in with later stages and higher death rates. It's hard to say what the trends are. All of these tumors are multi-factorial, and uranium could be another thing thrown at it. We are very paranoid about the situation with uranium. We had uncovered tailings five miles from Tuba City for 20 years. It's a reasonable concern."
Two other hormonally active cancers, uterine and ovarian cancers, have doubled or tripled in New Mexico Indians since 1970 while remaining essentially the same for Anglos and Hispanics. But although lung cancer in the Navajo population has been authoritatively linked to uranium exposure, it's harder to make the case for other cancers.

"It's a tough nut to crack," says Wiggins. "The rise in breast cancer everywhere almost certainly has to do with hormones more than anything else. Is something going on with hormones and hormone receptors? Our data is not going to make or break any one hypothesis, because there are a zillion factors going up or down. But you have to take seriously any proposition anyone comes out with, because we just don't have answers yet."

It's difficult to trace a disease to an environmental exposure that may have occurred years earlier. And so far, cancer cases have not been mapped in concert with drinking water sources. "Is there more breast and reproductive cancer here?" asks Dyer. "Yes, but you can't localize it geographically. It would be nice to establish a connection between where people are getting sick and where they drink their water. It's hard to get the data. It's frustrating."

One major effort is currently under way to do just that, but the sickness in question is kidney disease, not cancer. This five-year, $2.5 million study, a collaboration between the University of New Mexico Community Environmental Health Program, the Eastern Navajo Health Board and the Dine Network for Environmental Health, is being funded by U.S. Health and Human Services. The team is compiling illness data from 1,300 Navajos, backed up by urine and blood samples, and then overlaying the results on a map of 160 drinking wells that have been studied for uranium, arsenic and other contaminants. Preliminary data from 550 residents and 100 wells have already shown that living within .8 kilometer of an abandoned mine is a significant predictor of kidney disease and diabetes. Although the science linking uranium with kidney disease is solid, it's never before been demonstrated on a real-life map showing proximity to mines, says Chris Shuey, an environmental scientist at the Southwest Research and Information Center. Once the kidney data are in, the researchers might look at cancer next, he says.
Of course, Navajos are not the only population exposed to uranium. What about breast cancer rates in other areas with better data?

Susan Pinney is an epidemiologist at the University of Cincinnati. She and her colleagues looked at the population surrounding a nuclear processing facility in Fernald, Ohio, which operated between 1952 and 1989. The facility, which made fuel rods for nuclear power plants, was the site of numerous accidental releases of uranium into the surrounding air and water. As a result of a $73 million class action lawsuit in 1990 against National Lead of Ohio and the U.S. Department of Energy, the Fernald Medical Monitoring Project has accumulated 17 years worth of data on illnesses and exposures. Pinney examined the medical records of 8,770 people, including nearly 5,000 women, for a variety of cancers, and was able to model the exposure level of each individual. Her work is still being prepared for publication, and she declined to discuss it. However, a presentation of her preliminary, statistically significant findings last November to the annual conference of the Breast Cancer and the Environment Research Centers is now available on-line. Its provocative conclusion: "For women living within five miles of a uranium processing plant, degree of exposure to uranium particulates was related to risk of incident breast cancer."

A few months ago, Raymond-Whish held a traditional Kinaalda ceremony for her daughter, Darby, to mark her passage into puberty. One of the most important Navajo rituals, it celebrates fertility, the natural order and harmony with the earth through song and prayer. Raymond-Whish's mother was there along with dozens of other relatives, and Dyer from the biology department at NAU also attended. For Raymond-Whish, it was a happy, soulful event, but shadowed by the uncomfortable realities of her career in cancer research. From now until late middle age, Darby will produce the large pulses of estrogen that have been linked to breast and other cancers in so many women. And natural harmony, as her mother knows, is not what it used to be, especially now that pollutants are acting like even more estrogen in our bodies. Raymond-Whish can only hope that Darby's cells have the normal number of receptors, and that her genes and her environment haven't somehow conspired to reprogram her development.
"What does artificial estrogen do to the breast?" she asks. "It depends on the time of exposure. If you look at cells of a younger individual who's not yet through puberty, and you expose them to uranium, then that could promote earlier onset of puberty, earlier breast budding. And if they're exposed in the womb, you could be changing the way the receptors are expressed through life."

In breast cancer research in general, there is a fundamental shift from large epidemiological studies that look at women's current lifestyles and exposures to an examination of what the women were exposed to as children. "Most epidemiology starts with the moment a tumor is diagnosed," said Irma Russo, a molecular biologist at the Fox Chase Cancer Center in Philadelphia. "We need to look at when normal cells may have transformed many years earlier."

Suzanne Fenton, a research biologist at the U.S. Environmental Protection Agency, agrees. "We think one of the main drivers of breast cancer is what changes occurred in very early life to alter breast development. It's a fairly radical re-thinking."

Among other experiments, Raymond-Whish is exposing pregnant rats to uranium in order to track what happens in their offspring. When she tried this earlier with mice, the female pups exposed in the womb entered puberty approximately two days earlier, just as they did when exposed to DES. It's a subtle difference, but when combined with other real-life exposures, it may add up.

Explains Fenton: "It's important to remember that breast cancer risk is likely determined by a number of compounds interweaving with genetic factors and not just any one exposure."

Certainly, lifestyles on the reservation have changed in many ways over the past 50 years. "Once upon a time there was no diabetes here, no diverticulitis, no colon cancer," says physician Drouhard. "We are now exposed to the same things you are: plastics, fast food, obesity. Now everybody I know eats at Kentucky Fried Chicken." One way to learn more is by working with all those nose-twitching rodents in the lab. In the coming months, Raymond-Whish will repeat her experiments, prepare to publish again, and spend more time staring at the nauseating giant ovaries on the computer screen. The rats are euthanized before they actually get sick. Still, she says, they do have to offer up their organs to science. It's not easy for her to kill the animals.
"Culturally, it's an issue," she says. "But I'm searching for something that's going to help somebody or even lots of people. I always say, 'Thank you for your life.' "

Florence Williams is a 2007-2008 Scripps Fellow at the University of Colorado, where she is researching endocrine disruption and cancer. A former HCN staffer, she currently serves on the HCN board.

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