Baseball causes cancer.

Yep, heading out to the old ball yard and watching nine innings: nothing but trouble for the lungs. Such was the conclusion of a decades-ago epidemiological study regarding the causes of lung cancer. Smoking seemed to play a role, too. That nasty little habit came in number two in the cause-and-effect game.

"Cigarette smoking was the second-most-highly correlated factor that they asked about," says Bernard Goldstein, dean...
of the University of Pittsburgh Graduate School of Public Health (GSPH). “Going to baseball games was the first. You’re describing a phenomenon that has a lot to do with the old days. Going to a baseball game, you were just assailed by smoke. And lots of sports fans were smokers.”

That’s the value of one particular study without the work of investigators toiling away in labs— an incomplete glimpse of the big picture. You realize something is up pathologically speaking, but you’re still, more or less, swinging at curveballs in the dark.

Regardless, smoking is bad for you. Check. Not as bad as baseball, perhaps, but still. …

It has long been known that carcinogens in cigarette smoke mutate DNA, leading to cancer. But recently, a team of Pitt researchers got further inside smoking and cancer. They found that not only is the smoker’s DNA sequence scrambled— kind of like letters being rearranged in a word— cell division is thrown into disarray. That’s more like the chapters of a book being mixed up, with the first half of Chapter 1 followed by the second third of Chapter 5. And whereas mutations affect the functioning of one gene, chromosomal instability affects a whole host of genes.

When damaged by cigarette smoke, DNA strands are broken, chromosomes are either torn apart or elongated, and the resulting imbalanced cells don’t die like they should. They keep on reproducing.

So smoking’s reach is more profound than we knew, affecting us on the most fundamental level as it sends cells spiraling out of control.

A couple of Pitt researchers have stepped into this vortex, hoping to learn how such knowledge might one day change cancer prognoses.

In the early 1970s, Harvey Gollin, a non-smoker in the grip of a lymphoma that would prove fatal, was abed in suburban Chicago. At that time, his daughter, Susanne, was pursuing a bachelor’s degree in biological sciences at nearby Northwestern University.

The two often talked about how the world worked, and Susanne learned from these conversations. As a young girl interested in biology, she’d immersed herself in books on tropical fish to understand what was going on in her father’s aquarium. (An attempt to rear angel fish hatched in the tank didn’t work out so well. “I think we overfed them and contaminated the water with bacteria,” she says, looking back.) In high school, she cultured plant tissue in media she made. (The commercial stuff wasn’t available.)

Harvey, an obstetrician, and his wife, Pearl, a pediatrician, encouraged their daughter’s inquisitive nature. They’d do things like arrange visits north to the University of Wisconsin, Madison, so that Susanne could learn about plant tissue culture from professors there.

But shortly before Harvey Gollin’s death in 1974, his daughter had become the teacher. “I was taking genetics classes, and this was when amniocentesis was beginning,” Susanne Gollin recalls. She is now a professor of human genetics (in GSPH), of otolaryngology and pathology (in the School of Medicine), and director of the University of Pittsburgh Cancer Institute (UPCI) Cytogenetics Facility. “My father the obstetrician very much wanted to learn everything I knew about genetics,” she says. So as the doctor lay in bed, his daughter taught him.
“I really believe that, subconsciously, I went into cancer genetics as a result of my father enjoying genetics so much and my father dying from cancer,” she says today.

“My goal is to help somebody else’s mother or father so other young people don’t have to go through what I went through in college.”

Gollin joined the faculty of the University of Pittsburgh 18 years ago. As a PhD researcher, she focuses on head, neck, and oral cancers. If diagnosed early, these cancers can be treated, but if discovered in later stages, the five-year survival rate ranges from 15 to 30 percent. Gollin is determined to make these cancers into chronic rather than acute illnesses.

On a beastly hot August morning, a bespectacled Gollin, wearing a loosely constructed orange blazer, sits in her cool office at the GSPH building. Her bookshelves are stuffed with cytogenetics texts, and her walls are dappled with photographs of former students, lab cohorts, colleagues, and sundry candid shots of family and friends (including President Bill Clinton). The composed Gollin chooses her words carefully, asking on occasion to restate an answer. Yet she readily talks about her family, and is even more forthcoming when it comes to her work.

In her early days at the University, she encountered data that showed certain tumor cells seemed unaware that they should have 46 chromosomes—no more, no less. In cells she studied, harvested from head and neck cancers, the chromosomes numbered as high as 100.

So there’s a correlation between a cell having too many chromosomes and that cell becoming cancerous, she noted. Gollin was witnessing evidence of a correlation Bavarian biologist Theodor Boveri had suggested in 1914. If she could only figure out why this happened.

Here began Gollin’s search for the root cause of chromosomal instability, a phenomenon that allows cells to grow like kudzu, without regard for cellular convention and likely to bypass the DNA repair process. DNA’s repair system either fixes problems that arise during cell division or kills the mutated cells, cleaning out the cellular garbage and voiding misfit cells. If these types of cells are allowed to live and divide again and again they become cancerous tumors.

Boveri glimpsed this phenomenon while Woodrow Wilson was president. In the early part of the last century, the biologist studied sea urchin eggs and worms. Under his microscope, he noticed that cancer developed when abnormal numbers of chromosomes were present in a cell. Chromosomal imbalance in one cell, he predicted, would be enough to engender a cancerous tumor. As the muddled cell divided, it would produce similarly flawed daughter cells. Thus the process would continue, evolving into cancer. He was essentially right, but his work drifted into obscurity until the ’90s. Boveri was long on theory, but short on proof.

Rather than blaming baseball, Gollin and her colleagues, notably William Saunders, chose to follow Boveri’s lead in understanding cancer.

Boveri’s work was premised on the assumption that the rhythm of cell division is the key to understanding cancer, says Graham Hatfull, chair of the Department of Biological Sciences. He adds that such an understanding is key to controlling the disease.

Referring to the collaboration, UPCI Director Ronald Herberman says that’s the way things are supposed to happen in research.

“It’s a great example of the type of synergies that occur when you do this type of match-
making or interaction amongst faculty doing things within very different areas of expertise," he says. Herberman was instrumental in recruiting Gollin to come to Pitt from the University of Arkansas for Medical Sciences. Her charge upon arriving in Pittsburgh was to head a facility created to provide cytogenetics expertise, to apply her deep understanding of the chromosome, to a variety of clinical programs and cancer researchers. She did that well, Herberman says. Then she went on to do much more by pursuing the most elemental causes of cancer as her research mission.

"As often happens with the faculty I bring in, we have one particular need in mind, but once they're here, and they become part of the environment and see the opportunities, they evolve in directions that none of us had the wisdom to foresee initially," Herberman says.

In other studies, Gollin has gone on to pinpoint a specific chromosome band that she believes plays a primary role in the proliferation of head, neck, and oral cancers. In nearly half of these cancers that Gollin has studied, she found that chromosomal band 11q13 appears 10 to 40 times as often as it should. Extra copies of 11q13 are also seen in breast, lung, and bladder cancers and in all cases are indicative of a poor prognosis. In head and neck cancer in particular, the overall survival rate has hovered around 50 percent for decades; the unlucky 50 percent have a particularly high concentration of 11q13.

In 2002, Gollin's lab mapped 11q13 and, in the course of that effort, discovered a new gene that is found in abundance in oral cancer cells.

Gollin recently discovered and subsequently mapped the breakpoint regions on 11q13, places where the chromosome snaps, leading to extra copies of the band. These breakpoints, called fragile sites, are susceptible to all manner of abuse—including alcoholic beverages, the human papilloma virus (long associated with cervical cancer), and tobacco smoke.

You might say that Gollin and Saunders' team is swinging for the fences; it's one to watch. When Saunders' lab explored the role of cigarette smoke in chromosomal breakage, grad student Li Luo found that one or two puffs of a cigarette was enough to cause irreversible changes. Cultured cells were exposed to an R.J. Reynolds-cigarette-smoke condensate equal to that produced by about 4 percent of a cigarette. That miniscule amount—with its thousands of carcinogenic compounds—was enough to cause breaks in both DNA strands, a situation that can lead to chromosomal imbalance.

It happens like this: When a cell prepares to divide, its DNA is copied and crammed into identical copies of each chromosome. Under normal circumstances, each of two "daughter" cells created during this process possesses a full copy of the parent cell's genetic material. When smoke is introduced into the mix, this elegant little display of cellular reproduction is thrown into disarray. Chromosomes are torn apart, creating what are called anaphase bridges and leaving incomplete, broken chunks of genetic information—either that or they don't divide at all and remain stretched and misshapen. Anaphase bridges have been correlated with chromosomal instability in cancer cells.
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But now, says Saunders, they’ve established a concrete, observable link between smoking and anaphase bridges, a well-known source of mutations and, subsequently, cancer.

The good news is that antioxidants have been shown to halt this process. The bad news or, rather, the incomplete news is that so far this recourse has been successful only in the lab.

“Chemically, there are certain ways of resisting or preventing DNA damage,” Saunders says of antioxidants. “I can show you quite readily in the laboratory things that are common in food (vitamin C, beta-carotene, vitamin E) that actually prevent DNA damage. But that doesn’t necessarily mean those treatments are going to prevent cancer.”

He explains that when people take a lot of vitamin E— or other vitamins—in supplement form over long periods of time, their bodies make less of other antioxidants.

“It’s a two-edged sword: If you take too much of one type of antioxidant, you might suppress your own synthesis of other types,” he says.

Gollin tempers her optimism about potential treatments that will turn infamously aggressive cancers from mortal illnesses into manageable conditions:

“The rate of progress of research has exploded with genome sequencing; but, again, I believe that just the cell, let alone the human body, is so complex that it will be quite a while before we fully understand all of what’s going on in cancer cells.”

Her hope is that a new understanding of chromosomal instability will one day lead to screenings to find out who would respond best to a particular therapy. The work may help doctors tell whether a specific treatment is suitable for a person with certain genetic characteristics. Conversely, it could also be used to find out if the treatment a doctor is considering giving a patient would be too dangerous to administer, in light of the patient’s genetic makeup.

What’s the biology of quitting smoking?

“Never a bad idea,” says Saunders, noting that quitting is not, of course, a foolproof safeguard against cancer. Kicking the habit may allow cell division to return to normal, yet the damage done earlier remains. There is hope. As Saunders explains, our bodies have a mechanism for destroying cells with DNA damage. The caveat: “The more damage that is allowed to happen, the more likely a cell will escape this secondary protection, either by mutational loss of sensitivity or by chance,” he says.

Quitting, Gollin would say, is the best thing the 26 percent of Americans who smoke can do to protect themselves from cancer.

For 12 years, Gollin served on the Allegheny County Board of Health; she has also been involved with Tobacco Free Allegheny, an antitobacco agency funded with proceeds from the settlement of the federal government’s suit against tobacco companies.

“I’m very much in favor of smoke-free restaurants and bars,” she says. “It worked in California; it certainly could work here. Not just for the patrons, but also for the employees, because secondhand is almost as dangerous as firsthand smoke. When somebody is exposed to it possibly for an eight-hour shift, it’s really dangerous.”

The Graduate School of Public Health’s Goldstein appreciates her mind-set and efforts.

“She, personally, is someone who not only talks the talk, she walks the walk. Dr. Gollin took [the board of health position] as a challenge to be involved in all aspects of public health in the county. She is someone I tremendously respect.”

Acting on her concern for others, Gollin says, is a natural extension of her upbringing. She remembers dinnertime conversation with her pediatrician mother and her obstetrician father. She heard a lot of discussions like this: “I saw Mrs. So-and-so today; she brought her kids into my office.

“Oh, I delivered those children. How are they doing? How is she doing?”

“It was a very warm, caring environment,” Gollin says. She gets to Miami as much as she can these days to see her mother. Thirty years after Harvey Gollin’s death, Pearl Gollin is grappling with inoperable lung cancer.

“This brings it home every day,” says Gollin. “This is why I have my own personal crusade against smoking. In terms of public health, smoking is one of the very few preventable causes of cancer deaths.”

SECONDHAND MUTATIONS

Identify the nonsmoker.

Is she someone who’s never puffed herself or is she the person who doesn’t smoke and also very rarely spends time in the company of others as they puff away?

Stephen Grant takes the latter view. Labels aside, he believes that passive smoke is just as dangerous to aetus as a smoking mother.

Grant is a Pitt associate professor of environmental and occupational health and director of the toxicology facility at the University of Pittsburgh Cancer Institute. He reanalyzed data from three studies—one of which he coauthored—regarding the effect of cigarette exposure on fetuses. The initial analysis from these studies found little difference in the likelihood of umbilical cord mutation in mothers who smoked versus those who didn’t. But a premise behind the work didn’t sit well with Grant. Those studies lumped passive smokers together with mothers who had almost no exposure to cigarette smoke. Believing that a nonsmoker often exposed to secondhand smoke is, in essence, a smoker, he took another look at those studies. He determined that the pregnant women who actively smoked and the pregnant women who inhaled smoke is, in essence, a smoker, he took another look at those studies. He determined that the pregnant women who actively smoked and the pregnant women who inhaled smoke passively were equally as likely to have genetically mutated umbilical cord samples. His study was published in the online journal BMC Pediatrics.

To Grant, his reanalysis not only confirms the obvious—pregnant women should snuff out their cigarettes—but also suggests that women who may become pregnant should avoid exposure to secondhand smoke.

Because of the relatively small size of these studies, which involved 150 subjects overall, it’s not clear that Grant can generalize his reanalysis directly to the larger population. He recently completed a follow-up study of 300 newborns at Magee-Womens Hospital and is preparing it for publication with his collaborators. —JM