A healthy woman in her mid-20s shouldn’t die on the operating table from an appendectomy. Instead—through anesthesia—she should have a pain-free operation and awaken hours later.

First, the anesthetic should kick in, causing her to fall into a deep sleep. This state, as expected, would stop her breathing, so a tube would have to be inserted through her mouth, past the vocal chords, and into her lungs. Machinery would then breathe for her throughout the operation. That should happen.
There was no reason to anticipate any deviations during this young woman’s appendectomy. But after she was sedated, there was a problem. Swollen tonsil tissue, which was undetectable during the preoperative examination, prevented insertion of the tube—she was suffocating. Every passing minute presented a greater risk for brain damage. After 10 minutes, she would be dead. With the heart monitor beeping ever more slowly in the operating room, the anesthesiologists resorted to rarely practiced invasive techniques. The steady drone of the heart monitor chronicled the ending to this sad episode.

That patient’s medical emergency—an unanticipated difficult airway management—occurs once in every 2,000 operations. As an assistant professor and director of the University of Pittsburgh School of Medicine’s simulation center for the anesthesiology/critical care medicine department, John J. Schaefer III provides training to prevent these fatalities, a tricky job: “If I have to open a hole in your throat, how do I go practice that?” he asks.

Before 1990 there was no straightforward way. But in the early 1990s, a simulator for airway management, costing around $250,000, became available. Schaefer’s enthusiasm for the teaching tool turned to frustration. He found it complicated to run. That made it difficult to create clinical scenarios similar to the appendectomy patient’s plight or more frequent airway problems caused by conditions such as cancer or obesity. Not helping matters was the price tag. “If I have to open a hole in your throat, how do I go practice that?” he asks.

Schaefer in 1996 decided to put his under-graduate engineering degree to use. For months, he would head down to his basement after dinner, push aside the toys of his preschool children, and tinker with creating an easy-to-use, portable, low-cost simulator. He ran into a glitch. “I was stuck on one part of it, how to make the vocal chords close.” None of the materials he tried generated an accurate portrayal of the vocal chords closing. He didn’t know what to do. The answer lay at his feet. “I saw one of my kid’s toys—these [oversized plastic] keys—lying on the floor, and I grabbed them and used [the ring] section of the keys to actually fix the last thing.”

A prototype was born, complete with real-life effects such as tongue and throat swellings, a stiff neck, and changing respiratory rates. “I recreated the anatomy of the airway,” he says proudly. His toy-store effects were more lifelike and easier to program than the pricey simulators.

With his “sounding board” and collaborator, René Gonzales, Schaefer secured a patent in less than a year on the cost-effective design and parts of “AirMan.” Next, the physicians partnered with Laerdal, Inc., which manufactures Resusci Anne, the widely used CPR simulator.

Two years of AirMan testing recently concluded at facilities throughout the world. Schaefer liked the results. In recreating the tragic circumstances of the appendectomy patient, he has seen first-year anesthesiology residents take steps that would have saved her. Experts believe AirMan holds enormous promise for addressing training issues related to medical mistakes and could improve the fate of thousands of patients each year.

AirMan is now on the market for about $10,000. The University, in part through Laerdal grant money, will buy three AirMan models and eight “SimMan” simulators, which combine the features of AirMan; a more sophisticated model of Resusci Anne, called Recording Anne; and a full cardiac simulator.

AirMan sales may someday pay for his children’s college tuition, yet Schaefer is more excited that he has developed an effective teaching tool: “It will allow other people to learn well, and that should save lives.”

---

**FERTILE PREPARATIONS**

**IMMUNE CELLS IN THE UTERUS**

**BY DOTTIE HORN**

For 14 days a month, the uterus is busy—anticipating an arrival. Once the uterus is almost ready, its guest, a fertilized egg heading toward it, grows into a cluster of cells called a blastocyst. The uterus’s final preparations ensure that when the blastocyst arrives, it finds a nourishing environment...
in which to grow into a fetus.

Sometimes, however, this normal reproductive process goes awry. Julie DeLoia, assistant professor of obstetrics/gynecology and reproductive sciences, postulates a scenario. Say the blastocyst arrives at the right moment, but the uterus isn’t ready because of some malfunction, so the blastocyst cannot implant itself into the built-up uterine lining, or it implants but then withers away. Could the inability of the uterus to make the necessary preparations be a cause of infertility? Up to 20 percent of infertile couples are diagnosed with female infertility for which no explanation can be found. Hoping to find answers, DeLoia is trying to decipher the steps involved in creating a receptive uterus.

Some of the preparatory steps are already known, in general terms. The endometrium lining the uterus puts out a signal that brings immune cells, known as leukocytes, to the uterus from elsewhere in the body. As the endometrium prepares, it steadily increases its number of leukocytes. They reach their highest point during the one-and-a-half to two-day period when the uterus is ready for the blastocyst. During this receptive phase, 25 to 30 percent of all the cells in the endometrium are leukocytes—at other points in the cycle, they make up as little as 10 percent of endometrial cells.

Why does the uterus beef up its supply of immune cells? The answer may involve the placenta, which starts to grow as soon as the blastocyst implants. “The placenta is like a cancer. It chews up the lining of the endometrium; it chews away the blood vessel so that it’s bathed in blood,” says DeLoia. The leukocytes may keep the placenta from invading too far into the endometrium.

As part of its preparations, the uterus subdues the endometrial immune cells. The blastocyst, which inherits half of its genetic material from the father, would be attacked and rejected by the leukocytes—if it were anywhere in the woman’s body but the uterus. “If you transplant a kid’s skin to his mother’s skin, that would be rejected quite quickly and vigorously; so it’s a unique situation in the uterus,” says DeLoia. On the other hand, the immune cells must be active enough to respond to bacteria and other pathogens that might enter the uterus through the reproductive tract.

DeLoia’s research suggests that in infertile women this normal process of recruiting and subduing the immune cells is out of kilter.

One study showed that the immune cells of infertile women were present in different quantities and acted in different ways than in fertile women. DeLoia is now asking a series of questions to pinpoint more precisely what must happen—leukocyte-wise—to get the endometrium ready. Among her questions: By what signals are the leukocytes recruited to the uterus? How are they subdued once they arrive? She suspects that estrogen—the hormone that is released by the ovary and controls much of female reproduction—plays a role. Immune cells, however, do not respond to estrogen, so DeLoia believes intermediary agents are at play.

She is trying to identify these intermediaries. She approached her search by taking biopsies from the endometria of fertile women when the uterus was receptive to the blastocyst. She removed all the immune cells and treated the remaining tissue with estrogen. The tissue gave off several signaling compounds that act upon immune cells. DeLoia now wonders if the cells that normally make these signaling compounds are somehow impaired in infertile women.

Ultimately, DeLoia hopes to provide new treatment options for women who have unexplained infertility. Her work might also someday help women who don’t want to become pregnant. She hopes to develop a new form of contraception that works by turning the endometrium into an environment hostile to the blastocyst. However, those are long-term goals; for now, there are many more experiments to conduct. “We’re chipping away at it,” she says. “Solved and science aren’t words that go together.”

A human embryo at eight weeks
Schizophrenia Unlocked

DNA Chips Tag Culprit Genes

BY ERICA LLOYD

This woman has hugged her only daughter once. That was when her daughter was 63 years old.

Her life is a string of paradoxes. She’s kind and generous, would do anything to help another. You needn’t even ask. Yet she trusts few and is sure that others disdain her—probably, they are plotting against her. Her sense of humor delights with its irreverence, though when she is not telling jokes, she’s likely to be whispering about the “theys” who run things. Usually, she is nervous. Often, she is terrified.

What’s happening inside her mind is an infuriating mystery to her family. It’s a mystery to doctors as well. The precise cause of her disorder, schizophrenia, is up for grabs. Doctors define it by symptoms, which they place in functional categories. Impaired motivation and decreased emotional expression—such as reluctance to embrace a loved one—are classified as “negative” symptoms. Delusions, hallucinations, and thought disorganization they consider “positive.” Disturbances in certain types of memory and intellectual function are the “cognitive” symptoms. A team of University of Pittsburgh faculty members believes it has identified the genes related to schizophrenia’s cognitive symptoms. Pat Levitt, chair of neuroscience, credits the team’s success to interdisciplinary collaboration and DNA microarray technology. It is clear, however, that the team would not have gotten far had they listened to the naysayers.

For the most part, scientists have studied genes one at a time. Then DNA microarrays came on the scene. The technology and its variants are commonly referred to as DNA chips or gene chips (the latter a trademarked name). By color-coding the binding of chemical base pairs, these little wonders offered the possibility of monitoring the expression of thousands of genes at once.

Applying the technology to an organ like the liver, which has only a few cell types, seemed to make a lot of sense. But using a DNA chip on brain tissue, which is composed of probably hundreds of kinds of cells—that seemed overly ambitious. Levitt and colleagues saw things differently. They thought the technology offered an efficient and industrial approach to studying a complex problem. It appears they were right. Moreover, they had the breadth of expertise to pull off the enterprise. Primary collaborators included Levitt (a PhD molecular and neurodevelopmental biologist), David Lewis (MD psychiatrist and systems neuroscientist), who provided neuroanatomical models, and Karoly Mirnics (MD neurophysiologist and computer scientist), who figured out how to structure the analysis.

People with schizophrenia experience it differently, notes Levitt. “Some hallucinate often. Some don’t seem to have this problem, but can’t plan. Some can plan, but can’t remember,” he explains. To make sense of what was assumed to be a disorder involving multiple genes, the Pitt team focused on the prefrontal cortex, a brain region that affects emotions and memory and has been implicated in schizophrenia. They divided genes into 250 functional gene groups, analyzing 8,000 to 10,000 genes on each chip. They saw differences in gene expression compared to controls in only five of the 250 groups.

People thought that the data would be highly variable, but most genes hadn’t changed,” says Levitt. After hundreds of hours spent in Levitt’s office teasing apart data sets, the researchers saw a common thread—there was something unusual about how subjects with schizophrenia encoded proteins that come together in nerve terminals to regulate synaptic transmission. These findings were not restricted to any one neurotransmitter, such as dopamine. Instead, they showed that the basic circuitry defining how information moves through the nervous system is different in those with schizophrenia.

Most notably, these patients tend to underexpress a gene called RGS4, which controls the “volume” of synaptic transmissions. The RGS4 gene helps our bodies suppress the duration of a signal telling us to experience emotions such as fear. Its decrease on the duration of a signal tells us to experience emotions such as fear. Its decrease is something unusual about how subjects with schizophrenia encoded proteins that come together in nerve terminals to regulate synaptic transmission. These findings were not restricted to any one neurotransmitter, such as dopamine. Instead, they showed that the basic circuitry defining how information moves through the nervous system is different in those with schizophrenia.

DNA chips are built by robotically tethering thousands of carefully arranged and known DNA “spots,” or nucleic acids, to a solid substrate. That array is then exposed to sample tissue. The chips work by recording the binding of chemical base pairs—A-T, G-C, and so on—the alphabet for the “Book of Life.” Using color-coding (red and green) on diseased and control sample tissue, scientists can determine if the samples express genes differently. No difference appears yellow.