Kids with serious illnesses bounce back emotionally.
"I'M FINE, MOM"

SICK KIDS ADJUST WELL

BY ERICA LLOYD

Robert Noll had been interested—on an intellectual level—in coping and stress since he took a class as an undergrad at the University of California, Berkeley, with the famed psychologist Richard Lazarus. That was in the '70s—when both Berkeley and Lazarus did a lot of boat rocking. (Lazarus made waves by demonstrating that denial can actually help patients fare better.) As a young PhD clinical psychologist transplanted to Cincinnati in the '80s, Noll wanted to help kids cope with serious illness. So he designed a study with colleagues at the University of Cincinnati, Ohio, to measure how kids with cancer (excluding those with brain tumors) were getting along. From that, he figured, he’d build a case for developing intervention strategies. He had no idea he’d end up rocking some boats himself.

The Cincinnati group assumed they would find that the kids, all of whom were undergoing chemotherapy, were seen by their peers as being more sensitive and isolated and having fewer friends. The researchers’ next step would be to find out why: If it was because of the way the children looked from the treatments, they’d design school interventions; if they were depressed, cognitive behavioral therapy might be appropriate. So they conducted evaluations in the children’s homes. Then they went into the schools and talked to the kids’ peers. Without revealing that the study’s purpose was to determine how a sick child in a class was faring, they asked all of the children questions like, “Who are your three best friends?” In another exercise, kids cast their classmates in a mock play whose characters demonstrated traits such as disruptiveness, bossiness, politeness, or leadership ability.

The researchers asked the teachers to evaluate their pupils, as well.

The results came in, but Noll didn’t find what he’d expected. The kids with cancer weren’t perceived as being any more withdrawn, depressed, or isolated than their peers. No one could have slipped through the cracks. This was a comprehensive study—nearly every child in that region of Ohio ages 8 to 15 with cancer (94 total) had participated.

“It was,” says Noll, “a grand, noble experiment that yielded not much.”

So they tried again with another disease. “We thought, Sickle cell—that’s an excruciatingly painful disease. Well find something there,” Noll says. But the results were the same. When it came to social and emotional adjustment, the kids were all right.

Noll, who is now Pitt’s chief of developmental and behavioral pediatrics, reapplied methodology to study kids with juvenile rheumatoid arthritis and kids with hemophilia. He got the same results. He has studied thousands of children, and except in cases where a disease affects central nervous system functioning, like neurofibromatosis or brain tumors, he has found that children with serious illness adjust well. (A colleague in Buffalo, N.Y., used Noll’s methodology to study very short children and found they, likewise, aren’t any less well-adjusted than their taller peers.)

“Kids are inherently hardy,” Noll says, adding that adults are more prone to experience depression as a result of an illness than children are. How can this be? Noll has a theory.

Referring to teenagers, he asks, “Why do these kids get pregnant? Why do these boys drive 100 miles an hour? What they were thinking about is the pleasure of the moment.”

“When 15-year-olds are diagnosed with cancer, they don’t say, ‘Will I be able to have children or go to college?’ They say, ‘When will I be able to go to class again?’” And this behavior, Noll says, is “inherently protective” in the sense that it helps kids bounce back.

“As we start to get older, into our 20s, we start to think long-term. Adults with chronic illnesses don’t stay in the moment. Kids do.”

Although it makes perfect sense to him today, Noll was surprised by the results of his initial classroom study. So was everybody else. The Cincinnati group had assumed that the children with cancer would have ongoing adjustment problems—that’s what the literature had predicted.

But Noll takes issue with how other studies of children with chronic illness have been carried out. For one, he avoids questioning kids in the hospital—a place associated with dismal memories such as lumbar punctures and chemotherapy treatments. Other contextual cues are key as well, he says, like the order in which one asks the questions. He points out, for example, that a researcher might ask a sick girl whether or not she is able to get out as much as she used to. Imagine she says, “No.” If the next question is “Are you sad?” she is more likely to say “yes” than if the researcher had first asked whether she was sad.

(Noll has observed, however, that mothers of children with chronic illnesses are a vulnerable group. Mothers, more than fathers, are at risk of internalizing children’s experiences and suffering from depression.)

Noll doesn’t pretend that kids with serious illnesses don’t face emotional and social issues. But if a normally pleasant kid is acting out or pulling back, perhaps there’s a good reason. Perhaps the prednisone has made him irritable. Perhaps she’s scared of another difficult procedure. Helping kids and parents address specific issues can make both feel better.

One recent day at Children’s Hospital of Pittsburgh, Noll mentions that he has been asked to consult on a case of a boy with a chronic illness who seems depressed. The boy’s doctor wants to know: “Should I prescribe an antidepressant?” Noll’s response: Wait to find out if the boy’s mood has something to do with his hospitalization or illness that can be remedied or if it’s a real, long-term condition.
WRECKING BALL

THE HEAVY EQUIPMENT BEHIND GLIOMA INFILTRATION  |  BY JOE MIKSCH

It's got to be tough for a physician to tell a patient that the cause for the headaches, blurred vision, and failing coordination is a glioma, an extraordinarily aggressive form of brain cancer. It's hard to give anyone bad news. What's harder still is when the patient discovers that of the 20,000 Americans who get that diagnosis each year, fewer than half live another 18 months.

Glioma cells worm their way into tissue throughout the brain. They seem to end up everywhere at once, rendering the cancer incurable, immune to the art of the surgeon, the radiologist, the immunologist, and the chemotherapist. Tame a Hydralike tumor in one region, and another grows back in its stead. Sitting in his immaculate Hillman Cancer Center office, Shi-Yuan Cheng says, "That's the big problem, invasiveness. Because the tumor is so invasive, it's hard to do anything." Cheng's research has resulted in a deeper understanding of how gliomas so effectively invade. They have at the ready the biological equivalent of a horde of wrecking balls, he's learned. He has some ideas about how to stop them from advancing.

Cheng, an enthusiastic associate professor of pathology, leans forward in his chair—"Cancer is so fascinating," he says. "Cancer is the most incurable disease and the biggest challenge to the biologist." He has spent the better part of a decade delving into the knotty world of gliomas.

What makes gliomas so fiendish? Cheng would point you toward a protein called angiopoietin-2 (Ang2), a vascular growth factor found in uncommon abundance in the invasive edges of gliomas. Ang2, Cheng has discovered, turns on a set of enzymes that serve as a wrecking crew, destroying the material that connects one cell to another. Activated by Ang2, these enzymes, and plenty of them, essentially remodel the surrounding cell structure, creating room for tumors to grow. With that barrier torn asunder, glioma cells, and the blood vessels that feed tumors, are able to move into the freed-up space.

Cheng imagines the day when "glioma" needn't be read as "poor prognosis." He envisions new treatments, perhaps in the form of small Ang2-suppressing molecules circulating through the bloodstream to afflicated areas of the brain. Ideally, a treatment that inhibited Ang2 and its effects, including the wrecking crew, would keep the tumor from bulldozing forward.

In the mid-1990s, Cheng was a postdoctoral fellow working with Webster Cavenee, a professor in the University of California, San Diego's cancer genetics program and director of the Ludwig Institute for Cancer Research. With Cavenee, Cheng determined that a certain growth factor (VEGF) is a critical stimulator of blood vessel growth in brain tumors and that its overabundance could lead to robust growth of tumor vessels.

"We were one of the first in the world to demonstrate that VEGF was the molecule for angiogenesis, or blood vessel growth," Cheng recalls. He says this with a little self-deprecation, because scientists now know that VEGF isn't the only player in blood vessel growth in gliomas.

The entire process by which tumors grow is complex, Cheng says, referring to what he later learned about Ang2.

"One molecule cannot do it all. Many molecules act in concert. They're coordinated very, very, very well," he says.

Cavenee has followed Cheng's career—the last six years of which have been spent at the University of Pittsburgh. He praises Cheng for uncovering the fact that angiopoietins influence where cells go and how tumors overtake healthy tissue.

Cheng's work, he says, is likely to have important therapeutic value down the road. Perhaps it will one day give doctors the wherewithal to call off Ang2's deadly demolition crew.
THE UPSIDE OF RAGE

“A VERY AGGRAVATING PROTEIN”

BY ROBIN MEJIA

When everything known about a protein is bad, scientists might start to wonder why nature—evolution, that is—hasn’t gotten rid of it. It’s a question that was asked a few years ago in a review article about one cellular receptor. After describing its role in complications of diabetes, its tendency to propagate inflammatory responses, and its role in tumor growth, the authors noted that “it seems difficult to fathom how one receptor could be involved in an adverse manner... in so many and such diverse situations.”

The receptor—named RAGE, for receptor for advanced glycation endproducts—had been widely studied, but no one had looked at what it did in the lung. Tim Oury didn’t intend to either. The associate professor of pathology’s work on an enzyme that protects against pulmonary fibrosis was keeping him busy. Consults on asbestos damage were stacking up. (Literally. A small mountain of Fed Ex boxes with slides waiting to be reviewed greeted him on return from his family vacation last summer.) And there was the new test for PSA (prostate-specific antigen) levels that he’d patented and needed to move forward. RAGE wasn’t even on his radar screen until the receptor started turning up in his experiments. In fact, when he figured out what it was, the name seemed appropriate. RAGE had interfered with his experiments, and he’d already decided it was a “very aggravating protein.” It also turned out to be an interesting lead.

Oury quickly discovered in the literature that RAGE helps cause renal fibrosis. Fibrosis—be it of the lung or the kidney—is a disease in which normal healthy tissue is replaced with scar tissue. The scarring can interfere with the normal functions of the tissue, such as transferring nutrients and waste. (Imagine what it would feel like if your lungs were full of scar tissue, and you can see why Oury studies pulmonary fibrosis.) RAGE is present on epithelial cells, where it binds a variety of other proteins and ligands. In cases of renal fibrosis, if you stop RAGE from doing this, you can stop the disease. For example, if you give mice a soluble form of RAGE—which apparently binds ligands, keeping them away from the epithelial cells—it stops renal fibrosis in its tracks.

It was natural for Oury to hope that the same would hold true in the lung. Could he treat pulmonary fibrosis by targeting RAGE activity? He started experimenting with mice. “We gave them soluble RAGE and, lo and behold, it made the mice really bad. The exact opposite of the kidney.” Similarly, mice bred so that they didn’t produce RAGE in the lung promptly developed the disease.

The results were initially disheartening, but they’ve opened up a new avenue of research. Oury has gone on to show that RAGE is heavily expressed in healthy lung tissue, just as it is expressed in diseased kidney tissue. He now jokes that he has become remarkably accurate in his prediction of how RAGE will behave in the lung. He simply reads the existing literature on what the receptor does in other organs and hypothesizes that in the lung, it will do the opposite.

He’s a long way from translating his increased understanding of the protein into a treatment, but he’s aware of the implications of his findings. “If we can figure out why RAGE is high in the lung and not other tissues and can exploit it, I don’t think we can reverse the fibrosis, but maybe we can stop the progression.”

And his results are shedding light on an old question—that is, why a receptor that can do so much harm is still around. As the otherwise aggravating receptor’s role in lung health becomes clearer, Oury’s starting to think that perhaps we do need a little RAGE after all.