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Feeling like a lucky passenger

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Successful people are sometimes said to have been in the right place at the right time. Most likely, the trajectory of a career arc is more about purposeful pursuit than place in space, but high achievers may cultivate pattern recognition skills that enable them to know a launch pad when they see one. Fortune may not smile on them any more than anyone else, but they have taught themselves to feel that it just might. So they are flexible, open to new ideas, and willing to take risks.

This is one way to describe a transformational mindset, and D. Ashley Hill, MD, FCAP, is a case study.

Dr. Hill is chief of pathology and an associate professor of pathology and immunology and pediatrics at the Children's National Medical Center in Washington, DC. A pediatric pathologist with a primary interest in the developmental basis of pediatric embryonal neoplasms, Dr. Hill is the director of pathology operations for the International Pleuropulmonary Blastoma (PPB) Registry, founded by physicians and scientists who have been working with PPB for more than 20 years.

PPB is a rare malignant tumor of the lung primarily affecting infants and young children. Early detection dramatically improves outcomes in this disease, which appears to have a strong genetic component. PPB was identified as a distinct clinicopathologic entity in 1988 by Louis "Pepper" Dehner, MD, now a professor of pathology and immunology and pediatrics, at the Washington University School of Medicine in St. Louis. At the time, Dr. Dehner was working with Jack Priest, MD, at the Children's Hospitals and Clinics of Minnesota. Physicians and scientists at the three institutions maintain the registry and collaborate in research.

Dr Hill worked with the PPB registry when completing her anatomic pathology residency and pediatric pathology fellowship under Dr. Dehner, who had returned home to St. Louis to practice at Wash U.

"As fellows, we would handle and look at patient cases and sit with him when he examined these tumors," Dr Hill said. "They were very unique. It was as if each case was trying to tell us something. Each case would be a learning experience."

Dr. Hill spent a couple of years as an attending pathologist at St. Jude Children's Research Hospital in Memphis before returning to St. Louis. By this time, the researchers were increasingly focused on two characteristics of PPB: it appeared to run in families and the context in which is appeared (fast-growing tissue) had to be significant.

"We were thinking that advances in genetic technology might allow us to do a linkage study to figure out which chromosomes or parts of chromosomes are shared among those who have the disease," Dr. Hill said. "Something on that shared piece of chromosome might tell us what was predisposing these kids to cancer. Not being a geneticist but knowing a few, I set up some appointments with people at Wash U and pitched the idea of trying to find a gene in this rare cancer."

Grants were written and donations obtained; researchers extracted the DNA and sent it to the core facility at Wash U for genotyping. "A total of 4,000 markers across all 22 autosomes would be used to try and find the common link," Dr. Hill said. The data were ready for analysis, but their statistical geneticist was out on medical leave.

"I knew the answer was in there, but I didn't know how to get to it," Dr. Hill said, "and I was lamenting this fact to the mothers of children who were in my son's junior kindergarten class." One of those mothers happened to be a child neurologist who was doing linkage studies. She shared her laboratory, her software, and her student assistant. There, Dr. Hill asked the computer to analyze the DNA of four families with multiple affected family members. "Out came a graph that said every affected member of these four families shared a region on chromosome 14," Dr. Hill said. "So I did a *PubMed* search, putting in the name of the gene (Dicer 1*)* and 'lung,' and sure enough, a couple of years ago a researcher had knocked out Dicer in the lining of the airways of the lung epithelium and the lungs had developed cysts. That made a lot of sense to me, because the first stage of PPB is cysts. I printed out the paper and took it to Pepper and said, 'What do you think about this picture?' and he said, 'That's it.'"

They sequenced 11 different families and each had unique genetic mutations in the DICER1 gene, a huge breakthrough, although not the end of the story. "It's one thing to know something and another to prove it," Dr. Hill said. "You have to be sure, and then you have to figure out how to tell the families." They opted to describe progress on the Web sites (www.ppbregistry.org and www.ppbgeneticstudy.org.)

The genetic link and the rarity of the disease, which affects 25-35 children worldwide every year, made PPB both a challenge and an opportunity. Dr. Dehner's group started thinking about holding a meeting for families of children in the registry, where they could share experiences and donate blood for genetic analysis. The first PPB Family Weekend was held in St. Louis in August 2006. "We ended up having 24 families from 17 states meet on a Friday night in St. Louis," Dr. Hill said. "Everyone came with kids in tow; these are usually young families and sometimes more than one child is affected by the diagnosis. There were 100 people or so, 45 kids from 6 months to 26 years." The meeting was dynamic translational research in action.

Everyone who came to the family meeting donated blood for the research, and those who couldn't come sent samples through the mail. As of today, almost 70 families from the registry are participating in the research.

The family meeting was transformational for just about everyone present. Families of children with a rare disease had the first opportunity to meet others who shared it; researchers bonded with patients. "I had seen their names on reports, talked to some parents on the telephone, but seeing them and the kids in person and how they deal with things, learning how hard it really is, put a burden of responsibility on the research team to really try and do something, " Dr. Hill said. "It was a very important event."

A second family weekend took place in Bloomington, Minnesota, in August 2008, and the third meeting will be held in August 2010, in Washington, DC.

"There is something propelling this story along," Dr. Hill said. "I feel like I'm a lucky passenger. Some decisions were mine, but some of it came from taking advantage of opportunities. Some of it was fortuitous; I ran into the right people at the right time, and the door was open. I found people who could and were willing to help. I had tremendous mentorship along the way."

No doubt. But Dr. Hill has also been able to recognize when she was in the right place and to act at the right time.