Cystic Fibrosis Discovery Hailed As A Medical Milestone

Hospital for Sick Children

The discovery of the cystic fibrosis gene by researchers at The Hospital for Sick Children in Toronto and the University of Michigan leads to improved health care and global scientific knowledge.

Sixteen years ago, Grant Boyle's birth was a familiar routine in a world of medical challenges and sickly children. Like other parents, John and Marylynn Boyle of Toronto were thrilled to learn their firstborn child was healthy.

But 13 months later, it became obvious that Grant was not thriving. Though they knew he wasn't well, he suffered from symptoms that parents unfamiliar with cystic fibrosis wouldn't have recognized. The baby's skin had a salty taste, he wasn't gaining weight as he should and he suffered from a constant bowel dysfunction.

When his parents started down the diagnostic path that would lead to The Hospital for Sick Children in Toronto, John Boyle says, "We didn't know anything about cystic fibrosis, including any of the symptoms connected with the disease."

> *Cystic fibrosis, a debilitating inherited disease that is usually manifested in children and affects approximately 1 in 2,000 live births in North America, often results in premature death. In the U.S. about 1,000 new cases are identified each year.*

As Grant's parents discovered, the defective gene blocks chloride transport, and as a result of this gene defect, the body produces an abnormally thick mucus that affects the lungs. The disorder is often a precursor to life-threatening lung infections.

John Boyle would learn that he, along with millions of others in North America, are unknowing, symptomless carriers of cystic fibrosis. He also would learn that nothing a parent does causes the disease.

Grant was born in the same month in 1989 that the cystic fibrosis gene was isolated and characterized at The Hospital for Sick Children, Canada's most research-intensive hospital. The University of Toronto-affiliated hospital is the largest pediatric academic health science center in Canada and one of the largest in the world. Its clinicians are widely known for treating a huge number of patients with cystic fibrosis.

Researchers Isolate Mutant Gene

Thanks largely to the world-class research team of scientists and physicians, the defective gene responsible for cystic fibrosis was found in human chromosome No. 7. Before the discovery, scientists knew that the faulty gene was somewhere in the 22 pairs of autosomal chromosomes, not the x or y sex chromosome. But Lap-Chee Tsui, Ph.D., Jack Riordan, Ph.D., and others in collaboration with the University of Michigan's physician-geneticist Francis Collins, M.D., and his research team, took the research to a new level when they cloned and sequenced a gene encoding a protein known as cystic fibrosis transmembrane regulator, or CFTR. They found a mutant form of the CFTR gene known as Delta 508, which causes about 70 percent of the clinical incident of the disease.

During eight years of intensive research, they narrowed the field from an enormous pool of genes — now known to number about 30,000 along the DNA molecule. The discovery provided the first structural evidence that the defective CF gene leads to a malformation of the protein that regulates chloride transport across epithelial cells. This milestone discovery of the cystic fibrosis gene was a supreme example of how research can benefit people worldwide and lead to better health care.

"During the collaborative research, looking for the CF gene was somewhat like looking for a needle in a haystack. When the gene's position was found, it set the stage for the development of CF carrier tests," says Stuart D. Howe, Ph.D., director of business and partnership development at The Hospital for Sick Children.

The discovery has enormous impact on families worldwide. The breakthrough opened the door to a screening test to identify people who unknowingly carry the defective gene and pass it along to their children.

Diagnosis, Treatment and Testing

Grant's diagnosis started with a sweat test to assess the salinity of his skin. When the first test was negative, his parents were relieved, but when it was run again, it confirmed the baby had cystic fibrosis. His father, though not affected by CF, is a carrier of the Delta 508 gene.

"I was in Ottawa on business when I learned I was Delta carrier. I didn't recognize the connection with CF," John Boyle says. "I thought the test results had something to do with the heart." Back home, the reality that Grant has cystic fibrosis, hit hard. "When I read that CF affects the lungs, is always fatal, and that it typically happens when children

are young, I fell apart inside."
When Grant spent a week at The Hospital for Sick Children while his medications were adjusted, two life-changing things happened. First, Marylynn Boyle learned she was pregnant with her second child. "By then I knew there was a one-in-four chance that the unborn baby would have CF. I wasn't terribly concerned, but everyone around me was worried," John Boyle recalls.

Before the 1989 gene discovery, parents were alerted to the possibility of having a baby with cystic fibrosis only if they already had an affected child. But as a result of the breakthrough cystic fibrosis gene discovery, doctors can identify carriers and conduct genetic tests on unborn babies to offer parents a prenatal diagnosis. The sophisticated diagnosis shows if the fetus has a known mutation of the cystic fibrosis gene. At the 12-week mark in her pregnancy, Marylynn Boyle was tested and learned the baby did not have cystic fibrosis.

The genetic screening not only provided knowledge of the baby's health, it also unleashed enormous comfort and joy for the family. James, the baby Marylynn was carrying when Grant was diagnosed with cystic fibrosis, is now 14. The couple's third child, 8-year-old Jacklynn, does not have cystic fibrosis, but genetic testing has determined she is a cystic fibrosis carrier.

There was a second thing that happened during Grant's stay at the hospital. "By the end of the week, I saw many kids far sicker than Grant," John Boyle says. "At the end of the week, I actually felt jubilant when I realized that, when compared to other children, Grant is fairly healthy. Because the CF team is exceptionally proactive and dedicated, they have helped Grant live life to the fullest."

Grant continues to do just that. But when he was 12 cystic fibrosis caused his lung to collapse. The event was extremely alarming, John Boyle says. "CF kids may look normal one day, but the following day they may be ill or dead because of a time bomb inside of them."

When Grant lost the function of his lung, John Boyle asked the hospital staff if there was someone they could call. "They humbly replied that when it comes to CF children, other hospitals call them. We felt privileged to have this extraordinary CF team working for us."

Worldwide Impact

Today, children and parents throughout the world benefit from the CF testing. The Hospital for Sick Children and the University of Michigan entered an agreement that allows the hospital to manage international licenses while the University of Michigan manages licensing activities in the United States.

"The decision to license non-exclusively has encouraged competition among diagnostic laboratories," says David Ritchie, Ph.D., senior technology licensing specialist at the University of Michigan. "Seventeen companies are producing CF testing kits, about half are not on the market yet but expect to be in the next five years."

Licensing of the cystic fibrosis testing occurred in 1994, and in the last four years the licensing has become profitable, allowing both institutions to reinvest in new research. With every diagnostic kit sold, a small percentage of each net sale is returned in royalties. Patent protection was established for the gene, the protein derived from it and the mutation. Numerous non-exclusive licenses for the diagnostic test have been granted in Canada, the U.S. and Europe.

"The widely available CF diagnostic testing offers valuable 'yes or no' information. Families now have the opportunity to make intelligent decisions about deciding to have children and, depending on the test results, what the risks might be," Ritchie says. Now that newborns are automatically tested for cystic fibrosis, the technology has had a direct

impact on the licensing of the test."If you want to do CF testing, use of the Delta 508 mutation must be included in the testing panel because it is present in 70 percent of CF patients," Ritchie says.

CF research was funded in the U.S. by Cystic Fibrosis Foundation of America, the Howard Hughes Medical Institutes and the National Institutes of Heath. In Canada, funding was received from several government and private grantors including the Canadian Institute for Health Research, formerly the Medical Research Council, and the Canadian Cystic Fibrosis Foundation. Royalties derived from the Delta 508 tests are shared with a number of the grantors.

Today, Grant Boyle is an outgoing 16-year-old high-school student. His father says he goes full tilt. Last summer he spent a month in Africa with a humanitarian organization. "He's a great musician, a professional actor and fully connected with life," John Boyle says. "He doesn't think about his CF much, which is a lesson for his parents."

Still, if it hadn't been for the hospital's CF clinical care and research, combined with life saving drugs and physical therapy, it might be a different story.

"The hospital has superb technology driven clinical care, and outstanding CF research and empathetic skills," says John Boyle. "As parents we demand the best care for our kids, and as CF parents, we are grateful that the hospital is gifted when it comes to CF research and knowledge."

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