Cystic Fibrosis

HANNAH: In the 1950's, little is known about the cause of cystic fibrosis. But the signs of the disease are clear: "Chronic cough, repeated pneumonia… and a tremendous appetite, but poor weight gain,"[1] writes a doctor in the *New York Times*. The chance of a kid with cystic fibrosis living past five, he says, is fifty-fifty.[2] Plus, the short lives kids do have are mostly miserable. Long stretches in hospitals, and a near-endless chain of inhalers and antibiotics and terrible lung infections.[3]

Today, things are much different for kids with cystic fibrosis, or, as most people call it: CF. But to find out *how* different, I wanted to see for myself. So, on a Sunday morning in October, I make the hour-long drive from Toronto to Oshawa to visit Mac Robertson and his family. He's 14 now. But he's been a CF patient at SickKids since he was 18 months.

Before I open the door, I already know Mac is doing well. He's one of the lucky ones. His doctor told me that. His dad told me that. And yet, when I meet Mac, I'm stunned:

HANNAH (Talking to Mac): Now I'm looking across the table at Mac, and I have to say, you look like one of the healthiest children I've ever met.

MARTY: He's just under six feet tall. He's one hundred and sixty five pounds. He's a big boy. He's very healthy.

HANNAH: That's Marty, Mac's dad.

I learn that Mac plays elite baseball. He's got his sights on the majors. And he's a great student. But the most amazing thing Mac tells me is this:

MAC: Sometimes, I'm gonna be honest, I forget I even have it. It's like when I'm doing something with my friends, I just don't pay attention to it at all.

HANNAH: Things aren't perfect, of course. He still takes fistfuls of digestive enzymes a day. He still comes to SickKids a few times a year. And he still needs to be careful about his meds. But his quality of life? His health? They're both amazing.

But why is that? How did we get from the grim reality of the 1950's to Mac Robertson?

And what does SickKids have to do with it?

[MUSIC]

Welcome to SickKids VS, where we take you to the frontlines in the fight for child health. I'm Hannah Bank. And this is SickKids VS Cystic Fibrosis.

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[1] Rusk, Howard A. "War on Cystic Fibrosis: Study of New Voluntary Health Agency And the Disease It Seeks to Overcome." *New York Times*. October 13, 1957.
[2] Van Dellen, Dr. T.R. "Cystic Fibrosis Kills." *Toronto Star*. November 16, 1957. (Note: This doctor says most patients die by age three.)
[3] Rusk, Howard A. "War on Cystic Fibrosis: Study of New Voluntary Health Agency And the Disease It Seeks to Overcome." *New York Times*. October 13, 1957.

ACT ONE

HANNAH: Now, before we go too deep into the history of CF research, you should probably know a bit *about* CF. Here's how SickKids doctor and CF expert, Felix Ratjen, explains it.

DR. FELIX RATJEN So, It's a genetic disease. So it's basically a disease you're born with. Your parents usually don't have the disease because we call it a recessive disease, but with where each of the parents will carry the gene defect. But if you just have one copy of it here, you're perfectly healthy. And what it does is that in all the organs where secretions that are being produced are important, such as the lungs, but also the pancreas and the liver, these secretions are thicker and don't carry enough water. And if they're thicker, then it's more difficult for the body to get those secretions out. So they sit and that then in the airways and then it's more easy for this mucus to become infected with bacteria. And these bacteria then can cause damage to the lung.

HANNAH: But what's that like exactly? How does it *feel* to have CF, to live with it every day?

This is how one woman explains it for a SickKids documentary in 1985.

SUSAN: There is a certain flavor to your decisions, the decisions you make. The life goals you set are all set within the limits of the disease.

HANNAH: That's Susan McKellar. She is first treated at SickKids in 1967. In 1985, at the age of thirty, she becomes the first woman in Canada with CF to give birth to a child.[4]

Susan is exceptionally lucky. But by 1985, patients across Canada are doing better. In fact, most are now expected to live into their 20s.[5] Because while doctors are still far from a cure, they're much better at diagnosing CF and managing its symptoms.

Around this time, organizations like Cystic Fibrosis Canada are also well established.[6] There's hope. There's research. And excitement builds as teams across the world race to find the gene responsible for CF. But the task is daunting. And tedious. Dr. Francis Collins, a geneticist in Michigan, says it's like finding a needle in an eight-ton haystack.

But Collins is up to the challenge. And so is SickKids. Because not only does SickKids have the biggest CF clinic in the world,[7] it's got brilliant geneticists like Drs. Lap-Chee Tsui and Jack Riordan, who are leading the effort to find the gene. Their team is focused and relentless, working night and day.

Then, in 1987, a team in London announces that they've found the gene. It's a massive leap forward, a victory for science and a triumph for everyone with CF.

Lap-Chee asks the London team to share their data so he can confirm their findings. But they refuse. The next day the British press runs a story on the discovery.

Lap-Chee can read the entire sequence of the gene in the newspaper photo. It's wrong.

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[4] Wright, David. *SickKids: The History of the Hospital for Sick Children*. Chapter Fourteen, page 312.
[5] Lindgren, April. "Geneticists hold out hope for troubled families." *Ottawa Citizen*. February 14, 1986.
[6] https://www.cysticfibrosis.ca/about-us/cystic-fibrosis-canada
[7] Dunlop, Marilyn. " 'Curtain of silence' hid hunt for deadly cystic fibrosis gene." *Toronto Star*. 08 Sep 1989. A20.

Soon, the rest of the world knows it's wrong too. For many scientists and CF families, it's a crushing blow.

Research teams drop out of the race. But Lap-Chee and Jack's team persists. And so does Francis' team in Michigan.

The two teams start collaborating. Now, there are around 20 researchers involved across two countries.[8] Progress is slow, but steady. And then, things get quiet—and secretive. By 1989, not even the SickKids geneticist-in-chief knows what's going on. He describes it as a "curtain of silence."[9] That's because the scientific journal has forbidden the teams from sharing their discovery until it's published. Which means something's coming. Something big.

CTV NEWS CLIP (BROADCASTER): Good evening. There was jubilation at a Toronto news conference today and with very good reason. A team of Canadian and American scientists has made a stunning medical discovery. They've identified the defective gene that causes cystic fibrosis. This morning, they discussed their breakthrough after receiving a standing ovation at the news conference. The discovery offers hope for those affected by the hereditary disease.

CTV NEWS CLIP (LAP-CHEE): We think we have isolated the gene responsible for cystic fibrosis.

HANNAH: That's Lap-Chee.

CTV NEWS CLIP (FRANCIS): You can think of this, if you will, as analogous to climbing a mountain that's never been climbed before.

HANNAH: And that's Francis.

HANNAH: For families of children with CF, this is a moment of celebration. All the research, all the fundraising, all of it has led to this. But lost amidst the joy is a more sobering truth. This is a scientific breakthrough, not a cure. And while scientists now know the gene responsible for CF, known as the CFTR gene, they still don't understand what it does, or how it works.

To answer these questions, Lap-Chee, Jack, and their colleagues need help. Someone with expertise in chloride channels and electrophysiology, the science of electrical activity inside the body's cells and tissues.

That someone is Dr. Christine Bear. She's hired in 1988 to help take the discovery further.

Because if they can figure out *how* cystic fibrosis works, they just might be able to figure out how to stop it.

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[8] http://discovermagazine.com/2013/september/14-doorway-to-a-cure

[9] Dunlop, Marilyn. " 'Curtain of silence' hid hunt for deadly cystic fibrosis gene." *Toronto Star*. 08 Sep 1989. A20.

ACT TWO

HANNAH: Although much remains unclear about how CF works, Christine is sure of one thing: It has something to do with salt.

DR. CHRISTINE BEAR And we knew that CFTR - the gene - the protein that's made by the gene, the CF gene, exists in sweat ducts. So that was one of the first clues that people used to determine whether a kid, a child, had cystic fibrosis. Their skin was very salty.

HANNAH: In fact, the salt-CF connection has been long-established. And there's been research on the subject, too. Much of that is thanks to Dr. Paul Quinton, a Californian electrophysiologist who himself has CF. Throughout the 80's, he runs a series of interesting experiments on salt and CF. On himself.[10]

DR. CHRISTINE BEAR: And what he did is he would cut out segments of skin, his own skin, like his back looked like an incredible road map of potholes because he would pull out segments of his own skin and do electrophysiology studies on his skin and compare with skin from other samples that had been taken for medical purposes.

HANNAH: He discovers there's a difference between how chloride—a component of salt—moves through the sweat ducts of CF patients.

It's a start. But Christine still has lots of work to do. Fortunately, she's got some help, including Jack Riordan, one of the discoverers of the CFTR gene.

To begin, Christine, Jack, and their team must study the protein in the cystic fibrosis gene. So they can focus on the basics, to really understand *how* it works. And that means making heaps of protein.

They take CFTR genes and jam them into big, bulbous cells harvested from armyworms. And those cells turn into factories, pumping out tons of protein. Then they isolate the protein, so they can study it by itself. And study it they do—over years and years.

They discover that the CFTR gene produces a protein which regulates the movement of water and chloride in the body. In CF patients, it's dysfunctional. Chloride and fluid don't flow freely, creating a buildup. Which leads to salty skin, and an accumulation of thick, sticky mucus in the lungs, pancreas, and digestive system.

The team publishes its findings in 1992. It's another landmark discovery, and a major step forward in understanding the disease. But the paper is controversial. Many scientists are skeptical. And they're not shy about it.

DR. CHRISTINE BEAR: I would go to meetings and people would just kind of look at me and you kind of feel like there's this this wall of cloud around you because they didn't believe it.

HANNAH: There's a lot of soul searching as Christine defends herself to drug companies, and repeats the experiments, probing for weaknesses. But as the years go by, the truth prevails—and so does she. Research proliferates, and her own work grows more complex. She's not just looking at the CFTR protein by itself. She's studying how it functions in cells, in organs, in people.

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[10] https://www.nature.com/articles/460164a

By 2001, pharmaceutical companies are working on new drugs.[11] Drugs that treat the cause of CF, not the symptoms. It's exhilarating—but they're still years away from bringing anything to market.

In the meantime, there is still no cure for the 3,600 Canadian born with CF each year.[12] [13]

On August 28th, 2005, Mac Robertson is born. And he becomes one of those kids. But his parents, Marty and Tania, don't know it yet. He seems healthy.

TANIA: He was a big, chubby baby. He was twenty six pounds by six months.

HANNAH: But then he stops gaining weight. He develops this cough that just won't go away. And there's this:

TANIA: When he was a baby, I used to feed him and he would get really sweaty and I would kiss him and he would taste like nachos. He was so salty.

HANNAH: Tania's a physiotherapist. She knows the signs and symptoms of CF. She's even treated kids with CF at SickKids. She suspects Mac has it.

His diagnosis is confirmed at 18 months. And she and Marty are devastated.

MID-ROLL COMMERCIAL

ANDREW: Everything we're talking about in this podcast—the discovery of the CFTR gene, the discovery of what it actually does—they take time. And money. Some of that money comes from grants and governments. But a lot of it comes from people like you. So, if *you* want to help kickstart the next big breakthrough in kids' health, visit sickkidsfoundation.com/podcast to donate.

[11] https://www.vrtx.com/story/timeline-vertex-committed-advances-cystic-fibrosis-infographic
[12] Williamson, Doug. "CF sufferer grateful for every extra day." *The Windsor Star*. December 30, 2005.
[13] https://www.cysticfibrosis.ca/about-cf

ACT THREE

MARTY: I remember sitting in our basement at a time just in each other's arms, literally crying because of that. We had no idea what the future was going to hold.

TANIA: You have hopes and dreams for him, and all of a sudden this diagnosis could really much take a lot of that away, so it was quite scary and we were really upset.

HANNAH: But Marty and Tania don't surrender to despair. They get to work. And it is work. About three hours of treatment every day. Chief among them is percussive therapy. With cupped hands, they clap Mac's chest and back to loosen the mucus in his lungs. They call it Pat Pat.

MARTY: I do remember the very first time we did it. We literally had to hold him down and you're hitting your child and he was crying. And I remember doing it crying as well, because it was like, I can't believe I'm doing this to my son.

HANNAH: There are also masks to deliver antibiotics, masks to loosen mucus, puffers to help him breathe, enzymes to digest food, and peg flakes to keep him regular. But the family soon develops a routine. They learn to distract him during Pat Pat with the show *Go, Diego Go!* and the movie *Cars*. And Mac learns to adapt. The routine become part of his life, his everyday normal.

At SickKids, it's Dr. Felix Ratjen who supervises his care. And between the family's vigilance and SickKids supervision, Mac is doing well.

But, at this point, they're still treating the symptoms, not the cause. There's still no drug to do that. But it's not from lack of trying.

With the knowledge of how the CFTR protein functions, companies are now experimenting, trying to figure out how to get it functioning properly. But it's laborious, painstaking work. And it's not a one-size-fits-all approach. There are more than 1,700 different mutations in the CFTR gene.[14] A drug that works for one mutation probably won't work for another.

Still, Marty and Tania remain hopeful. And when Mac is five, they get wind of a trial for a new drug: Kalydeco. It's the first drug to treat the cause instead of the symptoms. And it's for CF patients with the mutation: G551D. Mac's mutation.

The initial results are fantastic. And the Robertsons are desperate to get Mac on the drug. But he must be at least six to participate in the study.

MARTY: And we were waiting for his sixth birthday and when his birthday actually rolled around. He actually, uh, they actually closed the study down because the results were so positive that, um, they wanted to get it, uh, out to Health Canada to be approved and then it would be eligible for everyone.

HANNAH: It's not until three years later that Mac finally takes Kalydeco. And when he does, his life is changed. Forever.

But the first clue that it's really working isn't all that dramatic. It's actually kinda funny.

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[14] https://www.cff.org/What-is-CF/Genetics/Types-of-CFTR-Mutations/

MARTY: Okay, so we talked about how Mac had to take the peg flakes. And basically, if we break it down, it's basically a big laxative. It helps him regulate his poop.

TANIA: And it draws water into the intestine.

MARTY: You can imagine, basically Mac all of a sudden gets on this pill and it literally turns on the salt channels and everything starts working properly and then you add a giant laxative in behind it. There were some issues where, you know, we were at the cottage and all of a sudden you'd see Mac running as fast as I've ever seen him run up to the cottage. And it's," Uh oh, I think I know what's going on here."

HANNAH: Mac does really well on Kalydeco. But his mutation accounts for only around 4% of CF cases.[15] Which means, in 2014, most kids with CF are *still* waiting for their wonder drug. The obvious next step is mutation delta F508. It's present in about 70% of people with CF. [16] One journal calls it the "holy grail of cystic fibrosis research." [17]

Finally, in 2016, a drug that targets the delta mutation is approved for use in Canada. It's called Orkambi. And it's what the world has been waiting for—a wonder drug that works for almost everyone with CF. Except that it doesn't work for almost everyone. At least not all that well. And neither does the next delta drug: Symdeko.

DR. CHRISTINE BEAR: The results were not spectacular. So, the average increase in lung function was less than half of what is a third of what people could see with Kalydeco.

HANNAH: It gets more frustrating. These new drugs are expensive. Like, really expensive. Kalydeco costs more than $300,000 a year.[18] Orkambi is around $250,000.[19]

Fights break out between insurance companies and CF activists, cash-strapped governments and the manufacturer for all three drugs.

Activists demand access. Insurance companies and provinces question the drugs' benefits. And the manufacturer insists the prices *need* to be high to recoup the hundreds of millions spent on research.

In 2016, Drs. Felix Ratjen, Christine Bear, and their colleague Dr. Janet Rossant come up with a plan to help. A way to predict how patients will respond to drugs like Orkambi, and a resource to spur future discoveries. It's called CFIT: The Cystic Fibrosis Individualized Therapy Program. And it works like this:

CF patients come to SickKids, where their nose is swabbed for nasal cells and blood is taken. Some of that blood is used to sequence the patient's whole genome. The rest is used to create stem cells.

DR. CHRISTINE BEAR: We are turning stem cells from a patient into their lung, intestine, bile duct and developing ways to test drug responses on all of these tissues from each person, with the final goal being that we can come up with predictive tools to predict whether or not they're going to be able to go on this drug. Or do they need to wait until another drug in development is would work better on them?

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[15] Verstraten, Katelyn. "The Miracle Drug, With a Catch." *The Globe and Mail*. June 21, 2014.
[16] https://med.stanford.edu/cfcenter/education/english/Genetics.html
[17] Maiuri, Luigi. "The Holy Grail of Cystic Fibrosis Research: Pharmacological Repair of the F508del-CFTR Mutation." Annals of Translational Medicine, May 2015, atm.amegroups.com/article/view/6357
[18] Verstraten, Katelyn. "The Miracle Drug, With a Catch." *The Globe and Mail*. June 21, 2014.
[19] https://www.cysticfibrosis.ca/our-programs/advocacy/access-to-medicines/orkambi

HANNAH: So, Christine can test drugs on patients' tissues—*without* them ever having to take the drugs. If one of the drugs works, it's powerful evidence for governments and insurance providers. If none do, they've got the tissues stored for future testing, when new drugs—and new combinations of drugs—come down the pipeline. CFIT is a research tool *and* a clinical tool. And it's not just for SickKids. It's accessible to CF researchers across Canada and around the world.

So far, the CFIT biobank has 96 different patients' nasal cultures and stem cells. One set is from a teenage boy in Oshawa: Mac Robertson.

I ask him why he donated his blood and tissues.

MAC: It not only benefits you as a patient, but it also benefits everybody else that has your disorder, disease or whatever it is.

HANNAH: Tania and Marty are equally enthusiastic about SickKids research. Their hope is that every kid with CF does as well as Mac.

MARTY: We want a pill what like Mac has in Kalydeco for everyone.

HANNAH: In the 1950's, most kids with CF didn't survive senior kindergarten. In the 1980's, they were lucky to make it to their thirties. Today, when families ask Felix how long their child will live, he can't give them a number. Because research is progressing. Treatments are improving.

The future is uncertain. And that's a good thing.

EXTRO

From SickKids Foundation, this is SickKids VS. Thanks for listening.

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