The Crohn Legacy: From Halitosis to Colitis and Beyond

Rebecca J. Anderson

On a hot summer day in 1956, Burrill Crohn was planting sweet corn in the garden of his country home in New Milford, Connecticut, when he was called to the phone *(1)*. The editor of the *Washington Post* informed him that President Eisenhower had been rushed to Walter Reed Army Medical Center and was about to undergo emergency surgery for an intestinal obstruction. The 72-year-old Crohn was not part of Eisenhower's medical team and knew nothing about the case, except what the newspaper editor told him. Soon, though, journalists representing other prominent newspapers, news agencies, radio, and television networks, and scientific organizations also called Crohn. He was one of the most prominent gastroenterologists in the country, and they all wanted to know what he thought about the President's condition and chances for recovery.

Credit: The Crohn Family

Dr. Burrill Crohn

Always Inquisitive

Burrill Crohn did not set out to be a gastroenterologist. During his medical school training at Columbia University, he was fascinated by biochemistry and carried out a research project that earned him a PhD in addition to his MD in 1907. He subsequently set up a small private medical practice in Manhattan, but in the mornings, he volunteered as a biochemistry laboratory assistant at Mount Sinai Hospital. Between routine laboratory tests, he had plenty of time for research, and the hospital offered a wide variety of intriguing clinical cases.

From 1913 to 1921 (before the discovery of insulin), Crohn spent much of his time studying the function and diseases of the pancreas. This work was largely driven by Crohn's desire to use a new toy that had been presented to him by a visiting physician. The device was a new type of rubber catheter for collecting upper intestinal bile. Crohn first used it to establish a "normal" baseline by collecting specimens

from himself. "Night after night at bedtime, I would swallow that 36-inch long rubber catheter, drink a glass of milk to stimulate pancreatic secretion, and go to sleep. In the morning I would aspirate the pancreatic secretions and the bile from my duodenum…every afternoon the secretions were tested and the normal pancreatic enzymes evaluated in the laboratory" *(1)*. He then compared those results with secretions collected from a series of patients with pancreatitis. His published monograph (*Studies in Pancreatic Disease,* 1915) earned him recognition as an expert on the pancreas.

Crohn also used the catheter to study liver diseases and took advantage of a new test for quantifying sensitivity to physical pain (called the Libman Test) while examining patients who suffered from peptic ulcers. He found a correlation between pain sensitivity and patients' awareness of their peptic ulcers. Patients who presented with gross hemorrhage were insensitive to pain. On the other hand, patients with a low pain threshold were more likely to seek medical treatment, and their peptic ulcers were managed more effectively. On the strength of his innovative findings regarding ulcer management, Crohn was inducted into the American Gastroenterological Association in 1917, and in 1922, he was appointed to head the new gastroenterology department at Mount Sinai Hospital.

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A caring physician, Crohn treated celebrities and ordinary patients with the same attentive bedside manners and exceptional expertise. To his siblings, Burrill was the big brother, a tower of strength who listened sympathetically to their problems, provided helpful advice, and generously offered assistance (2). Despite his demanding professional duties, he devoted Sunday afternoons to his children. Together, they explored all of the historical and cultural sites that New York City offered, and Crohn turned each field trip into an adventure. Climbing rocks in Central Park, they fought the British at the Battle of Quebec. When they made their way through hilly terrain, it became the Donner Pass.

The youngsters roamed freely in the hospital's laboratories, watching the laboratory technicians and playing with the experimental animals. His daughter recalls, "Often he would be called out to see a sick patient. But somehow he made time for me" *(1, 2)*. Sometimes, Crohn took her along on house calls.

Gut Instincts

When Crohn entered medical practice at the turn of the twentieth century, the small intestine was not a topic of much interest. His medical school professors advised the class to skip the textbook chapter on small bowel because "there are no recognizable diseases of the small intestine except, perhaps, tuberculosis" *(1)*. During Crohn's internship at Mount Sinai Hospital, his mentor always required that autopsies include a dissection of the small bowel because he insisted on being thorough, but "nothing of note was ever found" *(1)*.

Despite the lack of known intestinal ailments, Crohn was always curious and developed a keen gut instinct. A popular catch-all abdominal diagnosis at the time was "chronic appendicitis." It covered all sorts of vague, unexplained, and neurotic abdominal pains and discomfort, including an inflamed gut. Over and over, surgeons removed a healthy appendix (often missing by inches a mass in the adjacent small bowel). One day on hospital rounds during Crohn's residency, his chief of service presented a case of "chronic appendicitis." Crohn paid close attention as his chief described the patient's symptoms to the residents, but something about this case aroused his doubts. After hospital rounds, Crohn went back to re-examine the patient's belly and noted a faint line that looked like a surgical scar. When asked, the patient confirmed that years earlier his appendix had been removed. Any question in Crohn's mind about "the fanciful diagnosis of chronic appendicitis was dispelled then and there. The disease never existed" *(1)*.

That was the first of many cases Crohn investigated because he thought the standard diagnosis seemed illogical. Rather than accepting medical dogma, he followed the trail of evidence, and his inquisitive mind and methodical research served him well. Most of these enigmatic cases involved the digestive system. In addition to pancreatitis and hemorrhagic peptic ulcers, he studied bulimia, pica, dyspepsia, trauma-

induced intestinal ulcers, and gallstones. He published his findings, which made significant contributions to explain the etiology of those disorders and honed his expertise in gastroenterology. He once lamented, "It has been my misfortune (or perhaps my fortune) to spend most of my professional life as a student of constipation and diarrhea. Sometimes I wished I had chosen ear, nose, and throat as a specialty rather than the tail end of the human anatomy" *(1)*!

In 1930, Crohn examined a 17-year-old boy who exhibited a fever, diarrhea, and a tender, palpable mass in his abdomen. Tuberculosis was still a common disease, and harkening back to his medical school training, Crohn initially diagnosed intestinal tuberculosis, the only known explanation for an irritable bowel. Fortunately, new diagnostic tests had become available, and Crohn systematically conducted skin, eye, and sputum assays. All were negative for tubercle bacilli. The chest X-ray was also negative. Having exhausted all of his noninvasive options, Crohn wanted to conduct exploratory surgery to examine the boy's intestines directly.

Crohn accumulated 1000 cases over the course of his medical practice, and regional ileitis emerged as a common type of inflammatory bowel disease, second only to ulcerative colitis. It affected people across all cultures and economic groups.

At that time, there was no treatment for intestinal tuberculosis, and A. A. Berg, his surgical colleague and friend, initially refused to operate. Earlier, at the Trudeau Sanitarium, Berg had been persuaded against his better judgment to operate and resect the bowel of five patients with intestinal tuberculosis. Two patients were made worse, 2 died, and he did not know the outcome of the last patient—and never wanted to know.

Crohn persisted. He showed Berg his patient's test results, which had convincingly ruled out tuberculosis. Reluctantly, Berg agreed to operate. He found an inflammatory mass and removed the terminal 12–16 inches of the boy's ileum. In the laboratory, Crohn subjected the excised specimen to every available assay, scrutinizing stained sections for hours, but found no trace of tubercle bacilli. He concluded that the boy's ailment represented a new and previously undocumented medical condition, which he initially assumed was probably extremely rare. However, within 2 years, Crohn and his colleagues accumulated 14 such cases, all with the same clinical characteristics.

These cases had baffled the hospital staff, who speculated that the cause might be intestinal tuberculosis or actinomycosis (a disease characterized by granulomatous lesions), but they could not establish a definitive diagnosis. Some of those patients had been lying in the wards with their condition growing progressively worse for lack of an effective treatment—in the process developing fistulas (openings) in the gut wall.

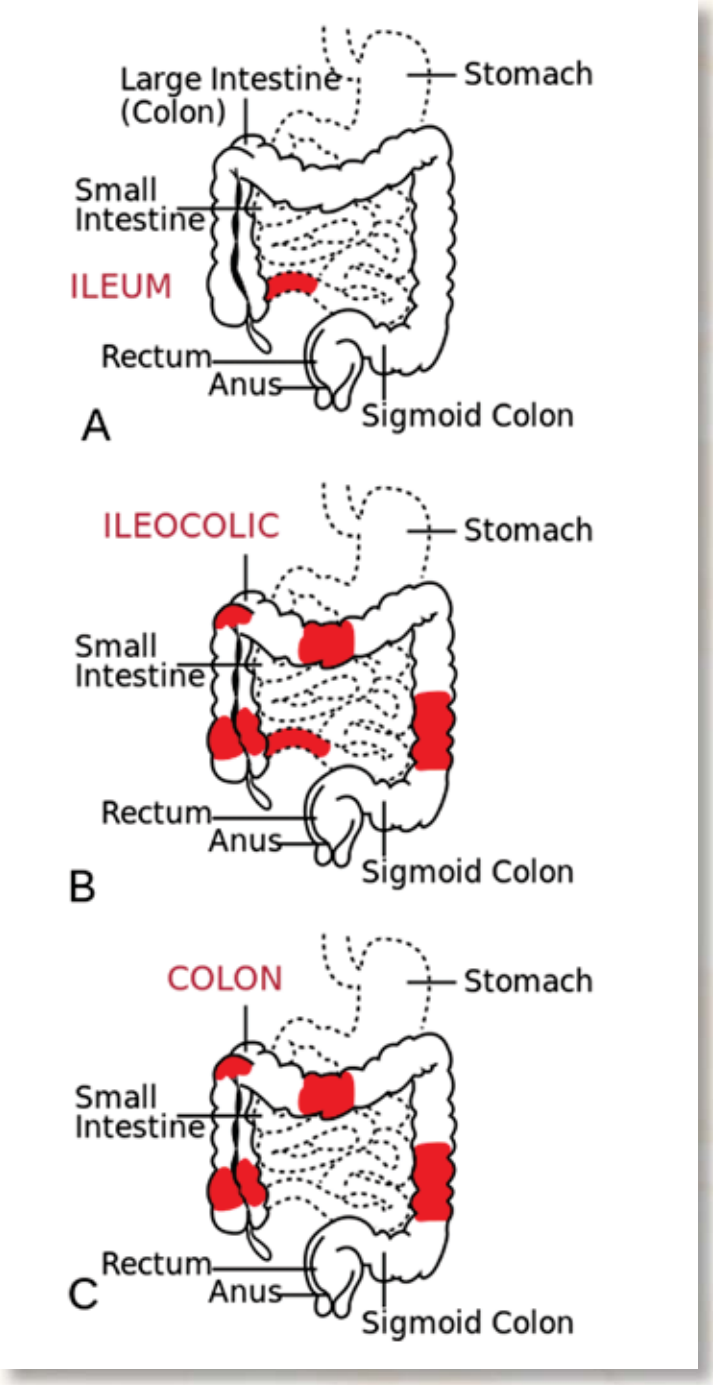
After the test results ruled out tuberculosis in these patients, Berg operated on them. In one patient, Berg removed eleven fistulas in the abdominal wall and cured the patient in a single operation. From the symptoms, surgical observations, pathologic analysis, and successful post-operative recoveries, Crohn and his pathology colleagues concluded that they were dealing with a previously undefined disease. They called it "regional ileitis" and Crohn proceeded to share their findings with the medical community.

In May 1932, he traveled to New Orleans and read his paper, "Regional Ileitis: A New Clinical Entity," at the annual meeting of the American Medical Association. Crohn explained, "Regional ileitis is an inflammatory or granulomatous disease of the small bowel, characterized by fever, diarrhea, abdominal pain, and fistula formation. It is essentially a disease of youth, slowly progressive and disabling"*(1)*. In October, Crohn, Leon Ginzburg, and Gordon Oppenheimer published their findings in *JAMA (3)*. This seminal paper, which listed the authors in alphabetical order, would be widely referenced.

The Mayo Clinic immediately reviewed their files and found previously overlooked cases of ileitis. Within a year, regional ileitis was being discussed in Germany at an international meeting of surgeons. The introduction of endoscopes and higher resolution radiographic images facilitated the diagnosis. Radiologist John Kantor described the "string sign," a narrowing of the intestinal lumen that appears as a thin string on barium radiographs, and which is now generally recognized as a characteristic sign of regional ileitis. Crohn accumulated 1000 cases over the course of his medical practice, and regional ileitis emerged as a common type of inflammatory bowel

disease, second only to ulcerative colitis. It affected people across all cultures and economic groups.

By the time President Eisenhower was rushed to Walter Reed Army Medical Center, the disorder had become well recognized by the medical profession, but Crohn was the only one who still called it regional ileitis. Everyone else called it Crohn's disease. No wonder every reporter in the country wanted Crohn to comment on the President's prognosis.



The three most common sites of intestinal involvement in Crohn's disease are ileal, ileocolic, and colonic.

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Based on the President's symptoms, Crohn surmised that the obstruction was a late manifestation of longstanding ileitis *(1)*. Eisenhower had suffered from gastrointestinal distress for decades. While serving in the Panama Canal Zone as a newly commissioned officer in 1922, he experienced episodes of abdominal pain and weight loss *(4)*. Convinced that the problem was appendicitis, he persuaded doctors in Denver to perform an appendectomy in 1923. Subsequently, he underwent a series of thorough diagnostic evaluations. While investigating his severe intestinal symptoms in 1949, doctors saw some "irregularity of caliber of the small bowel" in an X-ray *(4)*. However, it was not until a month before his surgery in 1956 that an X-ray revealed a picture of his terminal ileum typical of Crohn's disease. His periodically inflamed ileum had healed, and scar tissue in the intestinal wall led to the obstruction *(1, 4)*.

Eisenhower's medical team confirmed Crohn's disease as the diagnosis through direct observation during surgery and later microscopic examination of the diseased terminal ileum. They successfully bypassed the diseased segment by anastomosing the intestine above the obstruction with the transverse colon. The president made a rapid and full recovery.

Pharmacologic Intervention

In the days before regulatory oversight of pharmaceuticals, peddlers hawked patent medicines, reinforcing the public's widely held but misguided belief that a daily bowel movement was the key to a happy life. Elixirs and pills were promoted as a remedy for spring fever, tiredness, poor blood, and depression, but most of these concoctions were a mixture of vegetable compounds (including castor oil) that were predominantly laxatives. The main ingredient in Carter's Little Liver Pills was the cathartic, bisacodyl.

Constipation was not a serious medical concern. Diarrhea was. A primary symptom of ileitis and colitis, diarrhea caused dehydration, electrolyte imbalances, and abdominal pain. Crohn saw so many cases in his long career that he once exclaimed, "When I die, I hope to be sent to a Heaven where even the angels are constipated" *(1)*.

In the decades before the introduction of anti-inflammatory drugs, surgery was a common treatment for Crohn's disease. Crohn's first ileitis patient (the 17-year-old boy) was well for 25 years

after Berg's operation, and then he developed only a mild recurrence. In many other cases of Crohn's disease, surgical intervention gave permanent relief from symptoms. But it was a radical treatment, and there was a limit to how much small bowel could be removed if symptoms recurred.

The results from all of these experiments supported his view that breath odor was not produced locally in the mouth or pharynx, but rather from metabolism and subsequent respiratory excretion.

Current pharmacological treatment of Crohn's disease is aimed at symptomatic relief. Treatments of choice to induce remission and manage acute recurrences of inflammation are systemic glucocorticoids such as budesonide or prednisone. Remission can be maintained with immunomodulatory drugs (such as mercaptopurine and azathioprine) and broad-spectrum antibiotics (such as metronidazole and ciprofloxacin), which manage inflammation and infection, respectively. For moderate to severe Crohn's disease, as well as in patients who become refractory to the first-line drugs, TNF inhibitors such as infliximab (Remicade®) or adalimumab (Humira®) have proven effective alone and in combination with azathioprine/mercaptopurine. Because the cause of Crohn's disease is unknown and there is no cure, it remains a fertile area for pharmacologic research. Crohn's disease now affects about 500,000 people in the United States, and two of the top three best-selling drugs in the world in 2013 were anti-inflammatory drugs (adalimumab and infliximab) used to treat Crohn's disease.

In Search of Bad Breath

The elucidation of Crohn's disease established Crohn as a premier gastroenterologist, and he was in great demand as a speaker. He was flattered when a dental association invited him to speak at a meeting in New York in 1941, but he struggled to find a topic in gastroenterology that would be of interest to dentists. Finally, he settled on the perfect subject: bad breath.

Until the late 1930s, halitosis was attributed primarily to decaying teeth, necrotic abscesses of the pharynx, infected tonsils, obstructed nasal passages, nasal deviations, and periodontal disease. "Even before serious consideration, these explanations did not make sense to me"*(1)*. Improvements in oral hygiene, which minimized the role of teeth, gums, and the pharynx in persistent halitosis, reinforced his skepticism. He also noted a publication by Marion Blankenhorn who had studied a patient with a complete stenosis of the esophagus following laryngeal cancer surgery. Blankenhorn inserted garlic directly into the patient's stomach via a gastrostomy tube, and the patient developed a distinctive garlicky breath *(5)*.

To prepare for his dental conference lecture, Crohn decided to conduct his own research and obtained a small grant from a toothpaste manufacturer to follow up on Blankenhorn's observations. With no previous experience, Crohn first had to master how to classify and quantify odors. He adapted a sniff test devised by scientists at the Massachusetts Institute of Technology for assessing industrial smells and classified breath according to type (sweet, acrid, pungent, and repulsive/nauseating) and intensity (from very faint to overpowering).

In his first experiments, Crohn asked test subjects to chew onions or garlic-loaded salami without swallowing. The odor remained on their breath for only a short time. Next, he intubated a willing subject and placed a solution of garlic or onions directly in the stomach. The subject passed the sniff test during and shortly after intubation, but a few hours later, his breath was overpowering. Like Blankenhorn, Crohn concluded that mouth exposure is not responsible for bad breath. Rather, food must pass through the intestinal tract, be absorbed into the bloodstream, and undergo metabolism in the liver. Those smelly metabolites eventually reach the lungs and are expired.

To further test this hypothesis, Crohn studied two subjects who were patients in his wards. One patient was recovering from a colostomy to treat ulcerative colitis. Crohn inserted a capsule of garlic into the patient's stoma and within hours his garlic breath was obvious to the nurses on the ward. The other patient had undergone gall bladder surgery, and a drainage tube had been inserted into his bile tract. When Crohn gave the patient garlic either orally or rectally, he could detect the distinct odor of garlic in the bile

drainage the next day. Later, the odor also appeared on the patient's breath.

Crohn repeated these experiments with whiskey—deciding it was time to jump in and serve as his own test subject. After rinsing his mouth or gargling with Scotch, Crohn noted the odor of whiskey faded within ten minutes. In his next test, he downed six shots of Scotch at bedtime. His friends did not need to be sniff test experts to whiff his whiskey breath the next morning.

The results from all of these experiments supported his view that breath odor was not produced locally in the mouth or pharynx, but rather from metabolism and subsequent respiratory excretion. He suspected that fats or fatty substances were the odiferous substances, but he was not equipped to isolate them. (Investigators subsequently identified the garlic metabolites as organosulfur compounds.) Nevertheless, when his findings were published, Crohn became an overnight expert on halitosis (6). Patients flooded to his office wanting relief from real or suspected bad breath.

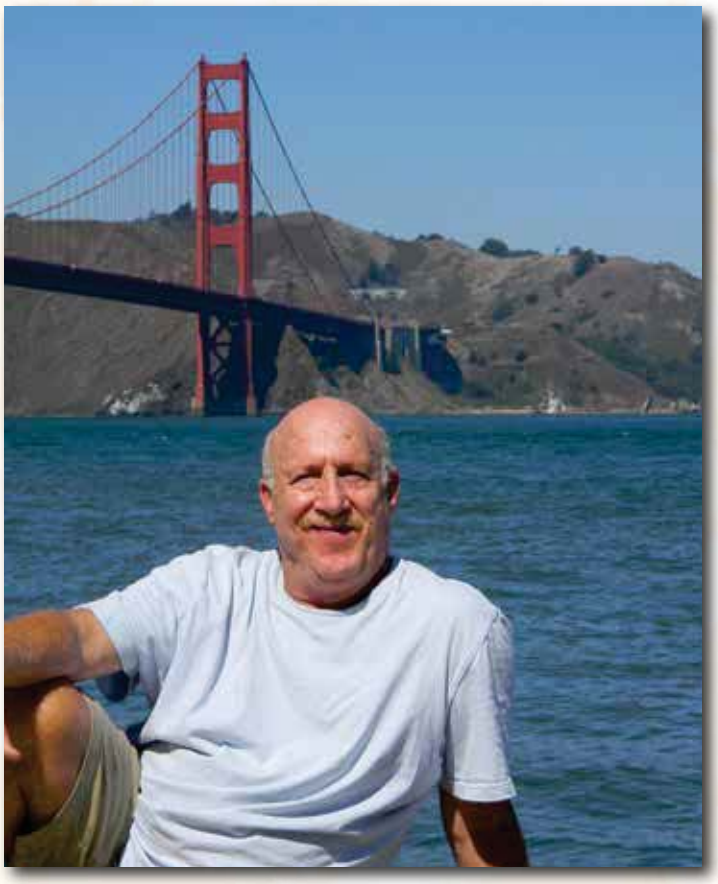
Steve willingly returned to the clinic again and again to donate additional samples of his blood. Same result. He became known as "the man who can't catch AIDS"

Because he knew the alimentary canal from top to bottom, Crohn was appointed to a panel of the American Medical Association to standardize the names of diseases of the gastrointestinal tract. In 1961, he chaired the committee of the American Gastroenterological Association that authorized and coded names of diseases of the abdominal digestive organs. Those panels established nomenclature that has now become standard at American institutions, but during the discussions, Crohn repeatedly stated his reluctance to incorporating his name into the lexicon. At an international conference in Prague, he rose to voice his objection to a resolution officially designating ileitis as Crohn's disease. He was ruled out of order, and the resolution was adopted unanimously.

The Other Crohn, the Other Disease

Sixty years after Burrill Crohn published his observations of the disease that bears his name, another member of the Crohn family made medical history. Stephen Crohn, the grandson of Burrill's brother, was increasingly puzzled why he remained healthy, while many of those around him died. In 1982, his business partner and lover, Jerry Green, died from a syndrome that had just been formally described by physicians and would later be coined AIDS. Over the next decade, Steve saw dozens of his friends become infected with HIV, develop the same symptoms, and die. In a life measured by funerals and memorials, he naturally worried that he had also become infected and frequently sought HIV testing. The results always came back negative and he remained healthy, but he constantly worried that the tests might be wrong.

Credit: The Crohn Family



Stephen Crohn

Intelligent and well spoken, Steve was a social activist. He marched with Martin Luther King from Selma to Montgomery and protested the Vietnam War. He found solace in Buddhism *(7)*. His pharmacology expertise—like many counterculture baby boomers—was limited to recreational drugs.

The focal point of his life had always been the fine arts. He trained at New York's Cooper Union, the

Biosketch:

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In the next issue of *The Pharmacologist...*

Dr. Anderson will be exploring a story on the "Great Dogsled Relay" that helped in treating a diphtheria epidemic in Alaska. Don't miss the exciting December 2014 issue.

Art Students League of New York, and City College of New York and became a talented painter and sculptor. He supported his passion for art through jobs in copyediting, magazine production, and interior design. His longest affiliation was as a proofreader for Fodor's travel guides *(7, 8)*. In the early 1980s, he operated a restaurant with Green in Los Angeles, but for most of his adult life, he lived in Hell's Kitchen, a rough-and-tumble working-class neighborhood on Manhattan's West Side. Naturally gregarious and fun loving, Steve maintained close relationships with his family. He remembered their birthdays, cheered them when they were sick, and joined them at the beach on summer holidays. He was the favorite uncle to his sisters' children *(2)*.

As more and more of his friends were struck down, though, Steve became increasingly conscious of every ache and pain. Could this be an early sign of AIDS? He walked faster than everyone else—so much to do, so little time *(2)*. An advocate of self-help, he boldly faced his fears, first through support and grief groups, and then, after earning a master's degree in social work from New York University in 1992, as a counselor to caregivers and AIDS patients. Still, against all odds, he remained healthy. He wanted to know why.

The Magic Missing Molecule

The Crohn family gathered every five years on Burrill's birthday *(2)*. Burrill's parents had instilled the importance of education and civic duty into their 12 children. A sizeable number of their descendants pursued careers in law or, like Burrill, in medicine. Steve consulted his medically oriented relatives, and they confirmed that he embodied an interesting case. Encouraged by them, Steve persisted—for years—telling anyone who would listen that he must have some sort of natural immunity to HIV. "Why won't anybody study me?" he complained in frustration to his sister *(2)*.

Meanwhile, Bill Paxton, a British virologist, had arrived in New York to conduct postdoctoral research at the Aaron Diamond AIDS Research Center. Looking around the center for a research project, Paxton noticed that no one was studying people who were highly exposed to HIV but had not become infected. In 1994, he began contacting AIDS activists and asking for referrals of subjects who fit that profile. Within a week, a doctor associated with the AIDS community called and told him, "I have the perfect person" *(9)*.

Steve was the first subject to walk through Paxton's door, and they clicked instantly. Like Burrill, Steve had no qualms about being an experimental subject. He desperately wanted to help others and relished the opportunity to become part of his family's medical legacy. Paxton was impressed that although Steve had no formal research training, "he just had this empathy for science. He understood it" *(9)*.

The most satisfying thing to Paxton was that he could tell Steve, "You were right. You have this molecule missing. That is advancing science"

Paxton exposed samples of Steve's blood to HIV—thousands of times higher than the titer normally needed for infection—but Steve's lymphocytes remained virus-free. Suspecting a laboratory error, Paxton refined and repeated his tests. Steve willingly returned to the clinic again and again to donate additional samples of his blood. Same result. He became known as "the man who can't catch AIDS" *(10)*.

Scientists knew that T-helper lymphocytes (CD4 cells) carried a surface chemokine receptor, CCR5, that mediates HIV binding and entry into the cell. Paxton discovered that the gene that codes for

Comparison of Crohn's Disease Versus Ulcerative Colitis

	Crohn's Disease	Ulcerative Colitis
terminal ileum involvement	common	seldom
colon involvement	usually	always
rectum involvement	seldom	common
fever	common	in severe disease
abdominal pain	always	occasional
abdominal tenderness	always	occasional
rectal bleeding	rare	always
abdominal mass	common	never
obstruction/stricture	common	rare
fistulas	common	rare
inflammation	patchy, discrete ulcerations separated by segments of normal mucosa	continuous and diffuse
granulomas	common	never

the CCR5 receptor protein on Steve's CD4 cells was missing 32 base pairs (now called Δ32 CCR5). The deletion did not affect his health, but the deformed receptor prevented the virus from binding *(11)*.

Paxton soon found 12 additional people with the same defect, but Steve, with his outgoing personality, intellect, and keen sense of humor, was the most articulate and highly sought spokesperson. After the extreme sadness that he had experienced in losing so many loved ones, "he was proud of the miraculous gift of being able to provide the key to unlocking a mystery of AIDS" *(2)*. He personified and affirmed the hope that AIDS could be conquered.

The most satisfying thing to Paxton was that he could tell Steve, "You were right. You have this molecule missing. That is advancing science" *(9)*. The revelation about Δ32 CCR5 triggered a flood of clinical investigations worldwide *(12)*. Approximately 1% of the population in North America and Europe, like Steve, have the homozygous Δ32 CCR5 mutation and are resistant to HIV infection.

In 2006, clinicians in Germany transplanted stem cells with the Δ32 CCR5 mutation into Timothy Brown, a patient who was suffering from acute myeloid leukemia and was HIV-positive. The transplant prevented his leukemia from recurring, and the Δ32 CCR5 mutated cells cured his HIV infection *(13)*. The successful treatment of Brown (the "Berlin patient," the only documented case of an AIDS cure) opened new avenues for HIV/AIDS research and provided new evidence that AIDS could be cured. In 2007, the Food and Drug Administration approved maraviroc, the first CCR5 receptor antagonist, for the treatment of AIDS.

Watching these events unfold, Steve was thrilled: "Can you believe that this has happened *(2)*?" It was similar to the reaction of his great-uncle Burrill, who also watched in amazement as the intestinal disorder he first characterized became formally recognized and incorporated into the standard compendium of medical diseases. Each, in his own way, was extraordinary, a larger-than-life force of nature who contributed to breakthrough discoveries that have

significantly advanced medicine and improved the lives of millions of patients. But each was also a very ordinary man who enjoyed the simple pleasures in life, performed simple acts of kindness as a matter of course, and above all else was devoted to his family, the Crohn family.

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