

# THE CHAIN

# REACTION

Inspired by his father's role in the discovery of penicillin, Daniel Chain has his mind set on finding a treatment for Alzheimer's disease

By Bernard Dichek

**WHEN DANIEL** Chain invited a colleague of his father to breakfast in the fall of 1996, the young biology researcher didn't expect the meeting to lead to the founding of a biotech start-up.

"I asked Keith Mansford for his honest evaluation of an idea I had for treating Alzheimer's disease," recalls Chain, who, at the time, was studying the memory mechanism of snails at Columbia University. "I told him that if he thought the idea was totally crazy, I would stick to my snails, but he got very excited about it."

Mansford, a seasoned pharmaceutical executive who worked for many years with the British Beecham-SmithKline Group, urged Chain to go straight from the New York City restaurant to see a patent attorney. Before they parted, he even insisted on signing an improvised confidentiality agreement on the back of a paper napkin.

"I wanted him to be able to declare that no one else knew about the idea so that he would have no trouble registering the patent," Mansford tells *The Jerusalem Report*, noting that the patent for a medical therapy Daniel Chain's father had invented was something the young biologist's father had bristled over for many years.

The patent that had eluded Daniel's father, Prof. Sir Ernst Chain, was for one of the greatest medical discoveries ever made – penicillin.

For his role in establishing the curative properties of penicillin, Chain did receive the 1945 Nobel Prize for Medicine, together with Sir Alexander Fleming and Sir Howard Florey. However, the administrators of Oxford University, where Chain and his colleagues developed

the drug during World War II, ignored Chain's advice and failed to file for patent protection. Consequently, after an American drug manufacturer registered various patent claims, Oxford did not share in the profits – and even had to pay hefty royalties to the US patent holder for processed penicillin that its researchers required for their own experiments. (See *The true penicillin hero* on page 35.)

Daniel Chain did heed Mansford's advice, and quickly applied for a patent.

Over the 15 years that have passed since then, many of Chain's prescient ideas about developing drugs for Alzheimer's have become widely accepted. A cure has yet to emerge, but he is now the CEO of a Wall Street-traded company, Intellect Neurosciences, Inc., that boasts a large portfolio of promising patent-protected technologies for the treatment of Alzheimer's and other neurological conditions.

Chain, 55, has had his share of ups and downs, with some of the latter bringing to mind the frustrations faced by his father, a Berlin-born Jewish refugee who arrived penniless in Britain in the early 1930s and was often at odds with the British establishment.

Chain's first challenge was finding investors. Other than Mansford, few people thought his idea, based on removing beta-amyloid from the brain using monoclonal antibodies, could work. "At the time, there was a raging battle in scientific circles about the underlying cause of Alzheimer's," Chain tells *The Report*, noting there was skepticism both about beta-amyloid being the culprit



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and about the prospect of using monoclonal antibodies to prevent the build-up of plaque in the brain.

**BUT SOON** after Chain applied for his patent, scientists at several leading pharmaceutical companies began to think along similar lines. Chain's invention, he realized, had valuable potential. To commercialize his discovery, he set up a company, scraping together enough to get started from a small trust fund his father had set up out of the proceeds of his Nobel Prize. Rather than stay in the United States, where he had come for post-doctoral studies at Columbia University in collaboration with Nobel Laureate, Prof. Eric Kandel, he decided to return to Israel, where he had earned his PhD in biochemistry at the Weizmann Institute.

The move proved to be propitious, as venture capital funds in the late 1990s were pumping capital into the nascent Israeli biotech industry. With backing from large Israeli and American investment funds, Chain set up Mindset Pharmaceuticals in the Jerusalem Har Hotzvim Industrial Park. State-of-the-art lab facilities were installed and Mindset began gearing up for clinical experiments. Though this was his first business venture, Chain proved adept at acquiring early-stage technologies and drug candidates at a low cost in order to expand the company's portfolio.

Then, in 2003, disaster struck. The Israeli investment fund reneged on its pledge to provide the cash it had promised and the American fund was unwilling to continue without the participation of the Israelis. Mindset collapsed; the labs were closed, the staff was laid off, and Chain, who had poured his life savings into the company, was flat broke.

Chain considered going back to academia, but believed that he had come too close to succeeding to stop. However, he was unable to find anyone else in Israel willing to invest. Having lived most of his life in Europe, he was something of an outsider in the local business community. "On top of everything else, I needed to make an urgent payment for one of the technologies we had acquired or lose it and thereby forfeit almost everything we had achieved," he recalls.

Chain was reluctant to part from his teenage sons who remained in Israel, but felt that his only hope was to head back to the US to be closer to the Wall Street crowd. And when he arrived in New York in early

2005 a friend introduced him to a biotech industry pioneer who had been away from the business world for a number of years.

David Blech, the Brooklyn-born son of a rabbi, was a stock broker who had been enormously successful as one of the largest

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early investors in the US biotech industry and had founded almost 30 companies, many of which continue to be extremely profitable. Sadly, however, Blech's genius in identifying promising technologies was counteracted by the consequences of suffering from severe bipolar disorder and his compulsive gambling with the latter ultimately leading to his downfall, as he struggled to keep his companies afloat through illegal trading practices that resulted in a securities fraud conviction. At the time Blech met Chain, he was determined to make a comeback and was in a position to start again.

Blech, impressed with Chain's ideas, came up with an initial \$2 million to help Chain found a new company, Intellect Neurosciences. The money was enough to extricate Mindset from Chapter 11 and purchase several of Mindset's assets, including the intellectual property that was about to expire without funding.

**JOINED BY** two former employees of Mindset, Chain quickly set to work to revive the programs that had been on hold for three years. This included initiating clinical trials for a promising new drug for various neurological conditions known as OX1. To advance the development of OX1, Chain was eventually able to partner with a large company, ViroPharma, which provided Intellect with a \$6.5 million upfront payment. Under the deal, Intellect stands to receive up to \$120 million in milestone payments and royalties.

Chain also put together a string of successful business deals and licensed his original discovery regarding monoclonal antibodies for Alzheimer's to several global

pharmaceutical companies. In addition, Chain diversified the company's approach to treating Alzheimer's by acquiring a vaccine technology that may be able to prevent the outbreak of the disease as well as lessen the impact on patients that are symptomatic.

But then, early last summer, the company hit one bump in the road after another. In May, Blech was again convicted of stock market fraud. Chain was not in any way involved, but the company had lost a major investor.

Next, during the summer, after the US Patent and Trademark Office granted Intellect a much-awaited patent, there was another disappointment. The milestone was supposed to trigger a \$2 million payment from Pfizer, one of the pharmaceutical company licensees, but Pfizer failed to meet its commitment. In October, Intellect filed a lawsuit against Pfizer.

But most disappointing was the failure of bapineuzumab in a clinical trial for Alzheimer's. Bapineuzumab was a drug co-developed by Johnson & Johnson and Pfizer based on Chain's idea. He was somewhat consoled by the fact that most experts concluded that the drug was given to patients whose disease was too far advanced to show benefit as a result of treatment.

"Importantly, biomarkers indicated that the drug had successfully engaged the target, resulting in lowered amyloid plaque load and reduced neuro-degeneration," says Chain, pointing out that an improved clinical trial design could yet lead to more positive results.

Despite these setbacks, Chain continues to forge ahead, and has started to work on a new generation of drugs that he hopes will ultimately translate into effective medicines.

"His tenacity reminds me of his father," recalls Mansford, who collaborated with Ernst Chain in the 1950s and 60s. "He has the same enthusiasm, the same refusal to bow down to what seem to be insurmountable obstacles."

Mansford also shares Chain's belief that his insight into the underlying mechanisms that cause Alzheimer's will eventually lead to a major therapeutic breakthrough. When Mansford is asked how it was that no one prior to Chain had thought of something that now seems fairly obvious to the scientific community, he smiles. "Most things that now look obvious weren't obvious when they were discovered," he says. ■



WIKIPEDIA

Professor Sir Ernst Chain

A close examination of the historical facts indicates that the lion's share of the recognition for the discovery of penicillin ought to go to Ernst Chain

## The true penicillin hero

**BEFORE PENICILLIN**, there was no known cure for infectious diseases – the leading cause of death everywhere in the world. Today, thanks to the iconic story of Alexander Fleming accidentally noticing that a mold in an unwashed Petri dish had destroyed bacteria, most people credit him with the breakthrough that led to this miracle drug.

But a close examination of the historical facts indicates that the lion's share of the recognition ought to go to Ernst Chain. Fleming did indeed publish a scientific paper in 1929 indicating that a mold, *penicillium notatum*, was capable of destroying bacteria, but he did not believe that the substance would be sufficiently chemically stable to have medical value. For more than a decade, neither Fleming nor anyone else thought it was worth the effort to test penicillin's curative properties on animals.

Enter Ernst Chain, a chemist who fled Nazi Germany in 1933 at age 27 and was eventually recruited as a disease-control researcher by the Oxford University medical school. After a rigorous search through medical literature, Chain came across Fleming's paper. Defying the objections of his department head, Howard Florey, who advised Chain to prioritize other substances, Chain tested penicillin extract on infected mice in 1940.

After witnessing the recovery of the mice, Chain spearheaded a year-long effort to purify enough penicillin for use on humans; and in 1941, after penicillin was shown to be effective on a human patient, the British medical establishment jumped on the bandwagon. Fleming suddenly renewed his interest too, and

Lord Beaverbrook, a newspaper baron and a patron of St. Mary's hospital where Fleming worked, made sure the media spotlight shone in the Scot's direction.

Fleming, a senior physician at a high-profile London hospital, seemed well cast for the hero's role, while Chain, a German-Jewish refugee laboring behind the scenes in a lab at a time when anti-Semitism in Britain was well-entrenched, was pushed aside. In 1945, after penicillin had played a decisive role in treating the battle wounds of the Allied troops, both Fleming and Florey were knighted. Chain was ignored.

After the war, Chain moved to Italy, where he continued to pioneer research on antibiotics, helping to develop the broad-spectrum semi-synthetic penicillins that are still widely used today and assisting China and other countries in the improvement of their production methods.

Chain, whose sister and mother perished in the Theresienstadt concentration camp, was an active Zionist. He regularly lectured in Israel and served on the board of the Weizmann Institute.

In the 1960s, Chain returned to England, where he was finally knighted in 1969. He died in 1979, without ever truly receiving the recognition he deserved for developing the therapy that has saved more lives than any other in medical history. Only now, with his son, Daniel, in the public arena as a biotech entrepreneur tackling Alzheimer's disease, is the story of Ernst Chain resurfacing. The Chain name may yet rise to the top of the medical pantheon.

**B.D.**