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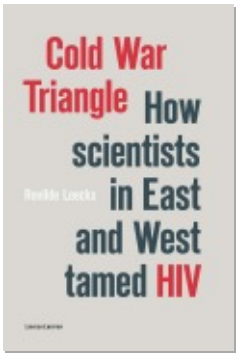
VI. From interferon to nucleosides



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In the Proceedings of the National Academy of Sciences (PNAS) it was speculated that this virus was at the origin of all cancers.[16] Erik was totally absorbed by this tantalizing hypothesis. If the cause of cancer was indeed a virus, a certain kind of RNA virus, then surely a way could be found to contain the virus and thus contain cancer. Discreetly, and without the help of any technician, he repeated all the biochemical experiments described in the *Nature* papers. He then validated these results with real life testing on mice. Building on the experience he had gained in Stanford, he used mice to grow a virus causing leukemia, then peel off the cancers and re-inject them into other mice to see if they would in turn grow cancers within ten days.

He was overjoyed that his "test tube" results confirmed there was indeed such an enzyme behaving as reverse transcriptase. This ritual would be repeated over and over, every time with different reagents to see whether any compound could inhibit the cancer cells. One day, he found a substance that is used against sleeping sickness in Africa, Suramin. It was a most curious experiment. It destroyed the virus in the test tube but had no effect on the cancer cells. His dream of finding a cure for cancer was instantly shattered, at least for now.

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Chapter VI
From interferon to nucleosides

The progress of science is strewn, like an ancient desert trail, with the bleached skeletons of discarded theories which once seemed to possess eternal life.

— Arthur Koestler

A first encounter with nucleosides

The dwindling interest in the induction of interferon suited Erik De Clercq very well. De Somer allowed him to broaden his interests and travel. Erik eagerly jumped on the occasion to go to Bulgaria in 1971 to attend an annual conference of the Federation of European Biochemical Societies (FEBS).

It was Erik De Clercq's first encounter with a relatively new organization at that time, FEBS, the brainchild of British biochemical societies. Most of the members of those societies had taken part in the famous International Union of Biochemistry (IUB) congress held in Moscow in 1961. They still reveled in the fact that the congress had brought them into personal contact with so many of their counterparts. The problem was that the IUB congresses were held only every three years, with the next conferences to be held in New York and then in Tokyo. Such long-distance travel was not easy for younger biochemists who found it hard to keep up with foreign colleagues. So the idea of organizing a Federation of European Biochemical Societies (FEBS) began to germinate within the Oxford and Cambridge societies. They conceived a platform in 1964 with annual congresses, alternating between countries in the East and West. An important principle was that political, national and territorial considerations would be ignored.

De Clercq was invited to Varna, a seaside resort on the Bulgarian Black Sea Coast, where the 1971 FEBS conference was held. Advertisements

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had promised a "Communist Riviera" with golden beaches, so he took his wife Lili along. Reality was rather different. The grayness and dirt matched the images of gloom and doom that filtered through other stories about Eastern Europe.

It was nevertheless in Varna that De Clercq met one of the most prestigious American chemists, Bill Prusoff, who was based at Yale University. Prusoff had acquired quite some fame for the nucleosides drug he had synthesized in 1959. It was supposed to be a cancer fighting agent, but a biologist, Ernest C. Hermann, later discovered it was in fact an antiviral. But it was the chemist who synthesized the drug, not the biologist, who would be hailed as the *father* of the first antiviral drug, a nucleoside. And thus, Prusoff entered medical history.

It was also in Varna that Erik De Clercq met David Shugar, the head of the Biophysics Department at the University of Warsaw. Shugar was an important player in the organization to bring scientists from East and West together. He had organized the first FEBS meeting. The meeting in Warsaw in 1964 was attended by more than a thousand scientists. It was considered nothing short of a miracle to bring so many distinguished scientists together in a country behind the Iron Curtain.

David Shugar had a warm heart for anything Belgian, perhaps due to the fact that Ghent University had awarded him an honorary doctorate.[1] The pipe-smoking Canadian had a tumultuous past. He had been charged in the early 1950s in connection with espionage activities. The affair was triggered by the defection of a cipher clerk in the Soviet embassy in Ottawa who accused Shugar of overly close contacts with Soviet diplomats. Even though he was never convicted of any wrongdoing, the investigations and the publicity damaged his career irrevocably. He was tarnished with the spy label despite being guilty of nothing more than "infatuation with communism."

After he moved to France, authorities there started to harass him, so he fled to Belgium. In Brussels, the wealthy Errera family and their legendary salon gatherings introduced him to the school of Jean Brachet and his nucleic acid chemistry.[2] Brachet influenced Shugar profoundly. Still, he did not feel safe in Belgium and the local police soon started questioning him as well. McCarthyism had long tentacles and only his native Poland could grant him a safe harbor. When he was offered a position at Warsaw

University, he gladly accepted and became perhaps the only scientist during the Cold War who fled from West to East.

Erik De Clercq and David Shugar became close friends. They immediately started to work out a plan whereby Shugar would send him polynucleotides to be tested and analyzed at the Rega Institute. Shugar, who was a physicist by training and a recent convert to biology, found the chemistry side of producing polynucleotides rather tedious and cumbersome. He suggested sticking to a simpler method of manufacturing. Why not synthesize nucleosides and put them to a test for interferon? De Clercq agreed reluctantly. He did not realize then how nucleosides were going to fundamentally change his future work.

A fateful meeting in Göttingen

Bernhard Witkop, Head of the Chemistry Department at NIH, had started a series of collaborations with Erik De Clercq, but liked to delegate many tasks. His deputy, Paul Torrence, regularly came to visit Erik in Leuven to see how things were progressing. This time, Torrence needed to stand in for his boss who was too busy preparing for a lecture in Japan. Witkop was meticulous to the extreme; he liked to read his text in classical Japanese.

Torrence arrived on the first day of May 1976. Leuven was primed for a festive May Day parade and the many red flags certainly made his visit to the Rega Institute very colorful. He wanted to rehearse the presentations he was preparing to deliver at a symposium in Göttingen that he would attend with De Clercq. They drove his old car at a leisurely pace so Torrence could enjoy the German landscape. Their destination was tucked between the Harz Mountains and the Weser River somewhere in the middle of West Germany. Seeing the centuries-old timbered houses behind the old town walls of Göttingen was quite a thrill for both. The little town, home to a famous university and several Max Planck Institutes, had fostered forty-six Nobel Prize winners.

Two of the Max Planck Institutes had selected about thirty chemistry researchers to spend a few days in Göttingen.[3] The small symposium on *Synthetic Nucleosides, Nucleotides and Polynucleotides* attracted some of the finest nucleic acid chemists from both the US and Europe, with only one medical doctor present, Erik De Clercq.[4] His friend Fritz Eckstein,

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with whom he shared a patent and several publications, was the likely instigator behind his participation.

De Clercq felt more at ease after spotting another friend, the perpetually smiling and pipe-smoking, David Shugar. They had established an intensive working relationship ever since they first met in Varna and had already published some twenty papers together. Shugar sent bright Polish researchers to the Rega Institute; it didn't hurt that they were female. They had given lectures at each other's universities. When De Clercq flew to Warsaw, it was immediately obvious that Shugar was in good standing with the communist authorities. In the airport, he was able to whisk his visitors through customs and immigration in no time. Despite his powerful connections, Shugar lived in surprisingly modest surroundings; in a small flat filled with books, not far from his lab.

David Shugar was well known in laboratories in both the East and West. With his Canadian passport and Polish residency card, he could easily navigate through the Iron Curtain. Thanks to his Jewish roots, he was also a welcome guest at the Weizmann Institute in Israel. The Israelis provided him with chemical compounds, the first nucleosides, that otherwise would be unavailable in Warsaw. Shugar developed a special bond with the head of the Weizmann Institute, Ephraim Katzir (Katchalski), a biophysicist who became the fourth president of Israel in 1973. Katzir also was his protector at times when the political climate in Poland turned anti-semitic. Shugar was a cross pollinator; he had quietly guided Erik's curiosity into the world of nucleosides. Both were now tackling the question of whether nucleosides could possess antiviral activity.

In Göttingen, every participant gave a presentation on their recent research. De Clercq's talk shed new light on fighting viral disease. Two well-known American scientists, John Montgomery from the University of Alabama and John Moffatt from the Syntex pharma company, were immediately interested in collaborating with the Rega Institute. With the exception of these few enthusiasts, most other chemists knew very little about antiviral drugs. Most of them believed that vaccines were sufficient to prevent virus infections and that there was no need for treatment.[5] They likened all viral diseases to a common cold: "if treated vigorously, it will go away within seven days, whereas if left alone it will disappear over the course of a week." Their knowledge did not extend

much beyond using Bayer's aspirin to treat the flu and quinine for fever suppression.

So Erik De Clercq's presentation linking certain nucleosides to antiviral activity was met with a mixture of awe and incredulity. One participant, a crude Russian from Novosibirsk, loudly protested. It only heightened the interest of the soft-spoken Czech scientist in the room, Antonín Holý. Years later, he wrote:

> Erik has by far the best chemical mind among the M.D.s I ever met; he correctly estimated the potential of nucleosides as antimetabolites acting against cellular parasites. This encounter developed into a friendship which has had a decisive role in my professional life. [...] In those days I had absolutely no knowledge of viruses, their life cycle and pathological manifestations and I presume that many of my contemporaries must have felt the same. After all, this knowledge was at that time rather scarce anyway. The pharmaceutical industry paid it but a formal interest [...].[6]

The Max Planck Institute was where Antonín Holý had spent the only postdoctoral stay in his life. Through his short annual trips to Göttingen, his home away from home, he had kept close contact with his friends, especially Fritz Eckstein. Everybody knew him as "Tony." This regular commute between Prague and Göttingen had been possible throughout the sixties until the *normalization* of 1970 imposed a travel ban in Czechoslovakia. It was only after a major East-West conference in 1975, the International Conference in Helsinki, that communist authorities began to relax the rules again.

Over the years, Holý learned to mimic the German accent so well, it was hard to believe he was a foreigner. His famous ear for classical music must have aided his linguistic skills. His favorite pastime on his trips to Germany was visiting hardware stores. His toolbox was his pride and joy. He was always curious to explore the latest in German tools, everything from a screwdriver to more sophisticated instruments that would be handy to pack in a suitcase.

Holý's topic, the chemical and biochemical aspects of L-nucleosides, remained anchored in De Clercq's memory. Many years later, these

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analogues became anti-HIV drugs. Holý did not speak about the political hardship in Prague, but instead he described the limitations imposed on his work at the IOCB.

Due to the scarcity of starting materials, he had to milk an African snake to get fresh snake venom and extract enzymes commonly used for analytical chemistry of nucleotides. Holý and his colleagues had also been toying with the idea of growing Japanese carnivorous plants whose digestive juices were reported to contain precious enzymes. Somehow, they had been overheard by helpful diplomats at the Czechoslovak embassy in Tokyo. Later, embassy packages with enzymes would mysteriously arrive at the Institute.

De Clercq was very touched by the quiet and dignified manner in which Holý coped with adversity. He promised that as soon as he was back in Leuven, his technician would send all kinds of reagents to Holý's lab to replace the expensive imports the Institute in Prague relied upon. In turn, Erik would ask whether his new friend, Tony Holý, could send some compounds to Leuven to be tested for antiviral activity. This became a standard request that De Clercq would ask of every chemist he would meet. These gifts greatly contributed to the Rega Institute's impressive collection of compounds.

De Clercq had also caught the attention of a British scientist from the University of Birmingham in the UK, Richard Walker. He kept quiet most of the time but had his eye on De Clercq as a possible co-organizer of NATO's Advanced Study Institutes. The institutes, in turn, would lead the way for some groundbreaking collaborations among the participating scientists.

Bringing compounds to life

Holý and De Clercq did not waste any time after their meeting in Göttingen. A very courteous correspondence began immediately once they were back in their labs. The first compounds from Prague to be tested for antiviral activity arrived in Leuven a few weeks later.

They had to be mailed through a special clearance company that had been entrusted by the Belgian government to handle products from countries behind the Iron Curtain. The ideological divide of the Cold War and

its endless number of rules and regulations severely restricted trade between East and West.

In all Eastern bloc countries, one had to deal with the State Trading Organizations. These vast monolithic organizations of state employees were responsible for buying all products needed by the particular industry they represented. They also sold all products produced by that industry. Laboratory and research chemicals in Prague were channeled through Chemapol, while Koospol dealt with the food industry.

Basic necessities usually sailed through customs. Czech hops, critical to the brewing of Belgian beer, or Belgian milk powder destined for Czechoslovak cooperatives, were considered as such. Similarly, the compounds sent by a laboratory of the Academy of Sciences in Prague did not raise any suspicions.

Holý selected three compounds representative of structural classes of his nucleoside analogues. A few months later an enthusiastic letter arrived in Prague. Unbelievable as it might have seemed, one of these synthetic compounds was antivirally active.

Seventeen more nucleoside analogues followed shortly after. By April 1977, Holý and De Clercq were ready to announce their first discoveries. Their article about DHPA, a broad-spectrum antiviral agent, in *Science* was delayed until May of the following year when the patent was finally filed.

The discovery of the compound changed Holý's life dramatically. Prolific as he might be, he was considered an introverted loner at the Institute in Prague. His colleagues did not seem to grasp his superb creativity. The cooperation with Erik De Clercq and the patent they had secured had suddenly given him a focus to channel his talents: developing antiviral drugs. The possibility that the DHPA compound could be developed into a marketable drug gave him instant authority. His image improved greatly and allowed him to speak directly with the managers of *Lachema*, the pharmaceutical plant that held the communist government's monopoly in Czechoslovakia.

Meanwhile, another compound arrived for screening at the Rega Institute. It was sent by Richard Walker's lab; the Birmingham compound was named BVDU and had been synthesized as an irradiation-sensitizing agent. Could it also have antiviral properties? At first, De Clercq did not think much of it. He tested it with a vaccinia virus assay and found

nothing noteworthy. However, then his assistant tested it with a different virus and noticed the telltale activity with the cytopathogenicity method.[7] Human cells were grown in culture tubes. A dilution of the compound was added to one or more culture tubes, which were incubated overnight to allow time for the antiviral agent present to act on the cells. Then, all tubes were infected with the virus; if it was able to grow, it destroyed the cells. The areas of cell destruction indicated the extent of the cytopathic effect. If the antiviral in the dilution was working, the cells were protected so that no cythopathic effect was found.

"Compounds coming to life" meant that cells were protected! BVDU proved to be extremely active against herpes simplex.[8] Was the British BVDU compound similar to a discovery made at the Burroughs Wellcome plant in the United States?[9] Both compounds were tackling the herpes virus, a family of DNA viruses that have learned to play hide-and seek with immune cells. They cause latent infections that allow the viruses to remain in their hosts' bodies for life. Some herpes viruses are reasonably innocuous in healthy people and cause infections like cold sores, chickenpox and shingles. But in weaker and immune-compromised people, they can be deadly, while other members of the herpes family can cause cancer.[10] Richard Walker had been working along the same lines as Gertrude Elion at the Burroughs Wellcome facility but could not have possibly copied her. His compound had come alive in Erik's lab and received a new and thorough description of its mechanism in Leuven.

Had Richard Walker been inspired by a communist chemist from the GDR, an East German chemist, Peter Langen? Walker was also the editor of *Nucleic Acids Research* and Langen had written an obscure article in 1975 for his Journal. It was tucked away in the *supplement*, where it was not scrutinized by peer review. Langen had described the characteristics of the exact same compound but gave it the wrong chemical structure.[11] The description of the correct chemical structure earned Walker and De Clercq a joint patent for BVDU in 1978 and a moment in the limelight when Erik was invited to speak about this topic at a seminar in Prague.[12] A seminar, as fate would have it, organized by FEBS and chaired by the East German chemist, Peter Langen.[13]

Walker wanted to intensify his cooperation with the Rega Institute. He was rather annoyed that a great deal of Erik De Clercq's attention was