Serendipity, politics, and crystal structures, or how I became a protein crystallographer

Alexander Wlodawer✉

Macromolecular Crystallography Laboratory, National Cancer Institute at Frederick, Frederick, MD 21702, USA

✉Macromolecular Crystallography Laboratory, National Cancer Institute at Frederick, Frederick, MD 21702, USA,
e-mail: wlodawer@nih.gov

Many things that influenced my scientific career were due to serendipity, politics, or both. Their roots go back a long way. For example, my mother's parents did not believe that women needed higher education, thus instead of going to a medical school (her original choice) she studied biology (that could be done in secret). She graduated from the University of Warsaw in August 1939 and her first real job was as a completely unqualified nurse in a Syberian gulag. I was born just after my parents returned to Poland in 1946 and, according to a story that my mother told me, after two years of staying at home with me she was ready to do anything else – for example, to become a scientist. Thus she joined the group of Włodzimierz Niemierko (her former undergraduate advisor) in the resurrected Nencki Institute of Experimental Biology. That decision was important not only for her future career (she climbed all rungs of the academic ladder), but also for my own future. I cannot say that I remember that occasion too well, but apparently at the age of four I went to Professor Niemierko (who was then the director of Nencki) and offered my future services subject to successful graduation from kindergarten, school, and university. Little did I know that I would actually accomplish that goal.

Another serendipitous event in my life happened when I was in the tenth grade – I was selected to become a member of the Polish delegation to a meeting of the American Junior Red Cross (held on the occasion of its hundredth anniversary in the United States). The luck was with me – English was not taught in my school, but my parents insisted early on that I study the language, so I did not have much competition in the selection process. The meeting that took place in the summer of 1962 was an event that truly changed not only my own life, but also the lives of many other participants. A visit to the White House hosted by President Kennedy (Fig. 1) was truly inspiring, and a visit to the United Nations headquarters in New York provided an impetus for another young participant, Ban Ki-moon, to become a diplomat who now occupies the most important office in that same building. My own goal was set – I would finish my school and university and go to the United States for graduate studies.

Figure 1. In the Rose Garden of the White House, Washington DC, August 20, 1962. President John Kennedy and General Alfred Gruenther, the head of the American Red Cross, are addressing international delegates to the Junior Red Cross meeting. My younger self is indicated by an arrow.

However, when the time came to choose the direction of university studies, I abandoned the idea of life sciences and decided to study physics. I did that for three years, until in 1966 I had to select my specialization. That was, however, the first year when Professor David Shugar started a new program in biophysics in Warsaw. Thus I joined the first class (of 10) and decided to work on my master's thesis in no other place than the Nencki Institute. My supervisor of record was Włodzimierz Kozak, but in reality it was his wife, Bella Harutunian, who taught me how to open the craniums of poor cats (with a dental drill) and insert electrodes into their visual cortex. That was not exactly physics, so I was not even surprised when two years later my application to work on my thesis at Nencki was denied (with a friendly advice to pick up my diploma before anybody would notice).

That was the time when many young people in Poland became very active politically and when secret groups were discussing how to improve socialism to the point that it would actually deliver on its promises. I joined such a group together with a number of currently well-known political figures (who, of course, even now are doing best by being members of the opposition). My enthusiasm to become politically active was tempered by the realization that people with my ethnic background should not try to change the political system of Poland too much, or they would be declared enemies of the state. Unfortunately pessimists are the ones winning all bets, as became clear in March 1968.

That was another milestone in my life. By then I was already accepted to a graduate program in neurobiology at the University of Iowa and my aim was to finish my master's thesis on time in early 1969. However, I barely avoided arrest for my slightly illegal activities and decided that it would be best to leave the University (and Poland) as soon as possible. Both Shugar and Kozak were very helpful when I was writing my master's thesis that did not contain much experimental data, and both were quite gentle with me during the final exams. What I did not know was that Kozak himself would disappear from Poland a few days later, so in a sense I was quite lucky. By the summer of 1968 I was ready to depart on a one-way ticket, minus my citizenship.

However, nothing was simple, and for reasons that were never explained to us, my parents and I could not get the travel documents that were necessary for emigration. Thus I had to do something in the so-called meantime, but there were not too many places that would employ a recent graduate who already applied for permission to leave. Fortunately there was an exception – the Nencki Institute was an oasis of sanity in those difficult times and I was offered a part-time technical position, funded by American money. In that way, I unexpectedly fulfilled my early promise to Professor Niemierko. I don't know if I accomplished much during the several months of work at the Institute, but while being there I applied for doctoral studies in two universities in California – UCLA and CalTech.

Our travel documents finally arrived in March 1969 and we all went to Sweden, where my mother had scientific contacts due to her previous work in that country. Upon arrival in Stockholm I learned that my application to CalTech was never considered since I had been unable to send them the $10 application fee, but that I was not only accepted to the Molecular Biology program at UCLA, but was even given a stipend. Thus it was not Iowa, but California, and not neurobiology, but molecular biology. The only problem was how to get there.

Due to some rather obscure American rules I could not apply for a US visa in Sweden, but that was possible if I were to go to Italy. Thus my next step was to fly to Rome, file visa applications, and wait. In another serendipitous development I was hired as a completely unqualified technician in a laboratory in the Istituto Superiore di Sanita. The head of the laboratory was Rita Levi-Montalcini, who some years later became a Nobel laureate, and the area of studies was a small protein called nerve growth factor. I became completely fascinated by this hormone that directs the growth of neurons. Again, it was not clear to me at all that this would become important much later.

I came to Los Angeles in the summer of 1969 and started my graduate studies a day after my arrival. That was the year when a young scientist moved from CalTech to UCLA to become an assistant professor. His name was David Eisenberg and I became one of his first graduate students. David decided to establish at UCLA a new area of investigations, namely protein crystallography. That was barely a decade since the first protein structures had been determined by Max Perutz and John Kendrew and only a few places in the world were engaged in such studies. I certainly did not plan on becoming a crystallographer when I started my graduate work, but I was very quickly converted and realized that this should be the field worth specializing in.

For the next 4 ½ years I was trying to solve the crystal structure of rabbit muscle aldolase – clearly an important enzyme. I cannot say that the work was going too well and there was no structure by the time I was ready to write my thesis. However, it was still possible at that time to graduate without solving a protein crystal structure and by publishing only a single paper [1], thus finally Ronald Reagan's signature was put on my Ph.D. diploma (he was then the governor of California). When I was at UCLA I tried to interest David in nerve growth factor, but he did not bite.

My next move was to look for a postdoctoral position. I was offered an opportunity to work with Martha Ludwig in Michigan, but since I knew that there were no mountains worth climbing in that state, I declined. On the other hand, Brian Matthews at the University of Oregon must have learned about how little experimental data was presented in my Ph.D. thesis, so he very politely turned me down. But my luck somehow held – I got in touch with Eric Shooter, one of the major players in the nerve growth factor field, who was a professor at Stanford University. Eric became interested and promised to support my quest for the structure of this protein, but since he did not have funds to support me, he made a deal with Keith Hodgson, who at that time was starting to develop synchrotron radiation as a source of X-rays for protein crystallography. Thus I could work on both methods development [2,3] and structure solution.

The summer of 1974 was the most successful period in my career as an experimental crystallographer. I crystallized not only nerve growth factor [4] but also two other proteins, L-asparaginase and monellin (at that time, just crystallization of a protein was sufficient for a full publication). However, development of a synchrotron beam line as a source of X-rays was a much slower project, and thus I did not have any equipment to collect X-ray diffraction data at Stanford. I ended up flying regularly to Oregon, so Brian Matthews was stuck with me despite his earlier decision.

My next move to the National Bureau of Standards in Maryland was a direct result of another serendipitous event, namely meeting Hal Wyckoff, a well-known crystallographer from Yale University. Hal and I had many conversations about building crystallographic instruments so, without my knowledge, he recommended me as a suitable candidate to develop

Figure 2. The retroviral protease [7,12] team at the NCI laboratory in Frederick, Maryland in 1988. Left to right: Jonathan Leis, A.W., Maria Miller, J. K. Mohana Rao and Mariusz Jaskólski.

a neutron diffraction facility. Considering the fact that the only trained American macromolecular neutron crystallographer had just quit that job, I again did not have many competitors, was selected, and moved to Gaithersburg, Maryland.

Working at NBS I was trying to balance two requirements – developing a neutron diffraction station that utilized a completely unique detector (that was what I was paid for) [5], and continuing my work on the structures of nerve growth factor and asparaginase (in my "free" time). Fortunately David Davies assigned to me a corner of his laboratory in the attic of a building on the Bethesda campus of the National Institutes of Health, and there I struggled, without much apparent success.

The 1978 Congress of the International Union of Crystallography was going to take place in Warsaw, so I decided to make an attempt to attend. I was by then both a US citizen and a civil servant, so I thought that maybe I had a chance to obtain a visa. Indeed, a visa materialized a few days before the meeting, largely due to the efforts of Jerome Karle, who later received his Nobel Prize (but was at one time banned himself from visiting Poland as a punishment for forcing the government to issue visas to undesirable elements such as myself). While in Warsaw I met Tom Blundell, one of the top English crystallographers of the younger generation. Tom and I discussed the nerve growth factor stalemate in considerable detail and came to an understanding – his laboratory would take over the project, but I would be kept in a supporting role. That agreement held for the next 13 years – that was how long it took to finally determine the structure of this very small protein. The results were worth it, though – the structure, published in Nature in 1991 [6], elucidated a brand new fold that included a cystine knot, later found in many other important proteins. Tom held his part of the bargain and I was included as a coauthor of that paper, even though by then we were more competitors than collaborators.

There were many other serendipitous events in my scientific career, some of which led me to study the structures of proteins encoded by the human immunodeficiency virus [7,8] (Fig. 2), or interacting with it [9]. That is, however, a different story that has already been told [10,11]. And Poland was becoming a very different country – I was no longer considered an outcast, but maybe even an asset. My second trip to Poland

Figure 3. Two co-organizers of the first MultiPole meeting that took place in Warsaw in 2011 and brought together over 200 structural biologists with Polish roots from all over the world. Mariusz Jaskólski, my closest collaborator throughout the last 30 years, is standing on the right. A follow-up meeting was held in 2015 and it was equally successful.

in 1986 resulted in establishing scientific collaborations that continue until this day, and the subsequent visits have become quite routine (Fig. 3). Despite my very short tenure at the Nencki Institute, I am considered to be its alumnus and I feel welcome during every visit to that dynamic and successful scientific institution. History has indeed made a full circle.

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