Interview to Prof. Istvan Hargittai
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# Alexander Varshavsky

Alexander Varshavsky (b. 1946, Moscow, Russia) is Smits Professor of Cell Biology at the California Institute of Technology in Pasadena, California. He moved to Caltech in 1992, after 15 years at MIT's Department of Biology in Cambridge, Massachusetts. He was born and educated in Russia, and was 30 at the time of his emigration to the U.S., in 1977. In Russia, and for a while at MIT as well, he studied the structure, replication and segregation of chromosomes. Over the last 27 years, the work of his laboratory focused on the ubiquitin system and related fields.

Dr. Varshavsky is a Member of the National Academy of Sciences of the U.S.A. (1995), the American Academy of Arts and Sciences (1987), the American Philosophical Society (2001), and Foreign Member of the Academia Europaea (2005) and the European Molecular Biology Organization (2001). He received, jointly with A. Hershko (Technion, Haifa, Israel), the Gairdner Award (Canada, 1999), the General Motors Sloan Prize in Cancer Research (2000), the Massry Prize (2001), the Merck Award (2001), the Wolf Prize in Medicine (Israel, 2001), the Horwitz Prize (2001), the Wilson Medal (2002), the Stein and Moore Award (2005), and the Lasker Award in Basic Medical Research (2000) (he shared the latter award with A. Hershko and A. Ciechanover). He also received the Novartis-Drew Award (1998), the Shubitz Prize in Cancer Research (2000), the Hoppe-Seyler Award (Germany, 2000), the Pasarow Award in Cancer Research (2001), the Max Plank Award (Germany, 2001), and the March of Dimes Prize in Developmental

Biology (2006). We had initial conversations in 1999 and in 2004 in Pasadena before we embarked on a more formal interview by e-mail during 2005.*

*I would like to ask you about your family background. You were born right after WWII, and for years there was hardship in Soviet society. How did the war impact your family?*

My mother Mary Zeitlin and father Jacob (Yakov) Varshavsky were acquainted before WWII, and got married in 1942. My mother's family was fortunate to be evacuated in time from Kharkov, a city in Ukraine that was overrun by the Wehrmacht in the Blitzkrieg offensive of 1941. My father graduated from the Chemistry Department of Moscow University two years before the war. He was drafted in 1941, joining a tank battalion of the retreating Soviet army, and was injured soon afterwards. A piece of shrapnel hit his kidney, and chronic damage ensued. He was never sent to the front again. That injury, bad as it was, was a stroke of luck, since few returned home among those who began as soldiers in 1941. Father's older brother Isaac was a military officer on a submarine based in Sevastopol, on the Black Sea. He was in combat from the beginning of war, and died two years later, in 1943, on a destroyer that was bringing him to Sevastopol's base and

Alexander Varshavsky's parents: Mary Zeitlin and Jacob (Yakov) Varshavsky in Moscow, 1950s (all pictures courtesy of Alex Varshavsky unless indicated otherwise).

*István Hargittai conducted the interview.

was sunk by a submarine. (In 1943, German submarines could still enter the Black Sea via the Danube river.)

*You went to school when Stalin was still alive. What was life like then? Were you much indoctrinated in ideology?*

The repression and physical hardships of life in the former Soviet Union were obvious to visitors from the West, especially during the first decades after WWII. But many denizens of Russia didn't see their lot this way, because they lacked a frame of reference. The Soviet regime's excellence in suppressing dissent relied in part on information blackout and incessant propaganda. As a result, many people didn't know that life in countries on the other side of the Iron Curtain was far better, freer than their own. Not everyone was duped of course. Native intelligence varies in outbred population, and some people perceived the truth of their condition even through the thickest of smokescreens. Russian-language radio broadcasts from the West were jammed but often not well enough, so a determined listener with a short-wave receiver could occasionally hear them. Those bits of truth about the nature of the Soviet regime became common knowledge (and even then largely amongst intelligentsia) only in the 1960s, some years after death of Stalin. The state's propaganda scored its greatest successes with children, whose trusting minds were particularly susceptible to lies. Besides, the adults were afraid to share misgivings, let alone hatreds, with their progeny. A cherubic kid might be innocent enough to chat at school about mom's and dad's conversations at home, with dire consequences for the entire family. I was a fairly typical Soviet youngster, and vaguely remember being enthusiastic about the Communist mythology, until early adolescence, when I started to notice inconsistencies in the official propaganda. Its main idea was that we, the Soviet people, were the luckiest people on earth.

*You lived the first 30 years of your life in the Soviet Union. People often posit this question to me as well: how one could survive the Communist system.*

The sheer cruelty of Communist regimes, in Russia at first and later elsewhere, had few parallels in history. But dictatorships age. Having killed a lot of its people and scared to death the rest of them, a senescing tyranny can afford a modicum of relaxation. By the time I had begun to understand

anything worth discussing, Stalin was long dead, and had been denounced by Khrushchev, a sidekick who clawed his way to the top and began a less bloody rule. I was born into a family of steady professional occupations (my mother a physician, my father a scientist), and was insulated from physical privation. But living in a Communist country was a psychologically difficult affair, easier for some, more trouble-prone for characters like mine, with hopes and reality on different planets. Such people trap themselves by their dreams. Before managing to escape from the Soviet Union in 1977, I had a few brushes with disasters that would have left me unable to become a scientist, had I not been lucky. One near-calamity, recounted below, stemmed from the writing of my first scientific paper. In all misadventures, the fault was mine, not the system's: the latter didn't hide but I still ran into it, daydreaming a pillow ahead, instead of granite.

*What turned you on to science?*

I grew up in a scientist's family. So my interest, and later love for science were a case of "nature" and "nurture" together. My father, now 87, retired and living in Salt Lake City with my mother (and my sister's family nearby), was a physical chemist in Moscow, devising methods for production of heavy water. That work, a blend of fundamental and applied physical chemistry, was a part of Russia's atomic bomb project. He got interested in DNA in the 1950s, joining other physicists and chemists who were leaving their fields at that time for the nascent world of molecular biology.

My father, mother, I, my sister Marina (born in 1954, when I was 7), and our nanny Maria ("Marusya") lived in a single room of a communal apartment typical for its time, in a city desperately short of decent housing. The apartment was essentially a corridor with many doors, one of which led to a cramped toilet, another to a communal kitchen, and the rest to about fifteen single rooms. Each of them housed a separate family. My earliest realization, at 5 or 6, that my father received special treatment by the world came in the shape of milk bottles. The largesse of the atomic bomb project trickled down even to people twice removed from it. My father was given a "free" bottle of milk every day, on the grounds of his working with "isotopes". They were stable isotopes, but never mind. He was supposed to drink that milk on the premises, but instead brought it home, where I was told that the milk was from mad cow, a frightening but attractive description to a 5-year old, many years before "mad cow" came to signify a less benign proposition.

Friends of my parents often visited them. Becoming a teenager (by that time, the family moved to a small apartment on the outskirts of Moscow), I began to see scientists among my parents' guests as separate, more interesting people. A din of conversations about physics, chemistry and biology surrounded me at dinner parties, with serious talk dwarfed by jokes, laughter, and political commentaries that would have been unthinkable in Stalin's time. The regime didn't lose its fangs but the willingness to use them had diminished, and people were emboldened a bit. By 16, I wanted to do all of science, mathematics included, dreamt of becoming a writer too, and felt, without evidence, that all of this was possible. That mania grandiosa eventually subsided, perhaps not entirely. To the world outside I was a typical "academichesky malchick", a Russian idiom for "professor's son": an alloy of cockiness, nerdiness and insecurity, the latter camouflaged by arrogance. To myself, I was the Eighth Wonder of the World, a secret knowledge to be sure, but it surfaced with regularity that must have made dealings with me a chore.

My initial interest in science soon upgraded itself to love. Memoirs by scientists, their biographies, particularly of physicists and mathematicians, became my favorite reading, and the personages themselves my closest friends, all the more so because I was ill at ease with real people. At about 17, I read Einstein's remark that one cause of his attraction to science was the desire to be shielded from everyday existence, from its unbearable cruelty and inconsolable emptiness, from the prison of one's constantly changing whims. I was astonished to see he felt that way, for I did too, but didn't discuss the subject with anyone, then.

*How strong was your father's influence (knowing that he was a substantial scientist)?*

It must have been important, in more ways than one. Here's my father's advice, given when I was 16. "So you are interested in biology. Good. But ignore biology for now, kind of. Get the best background in math, physics and chemistry that you can possibly achieve, then worry about biology. Learning biology is much easier than physics and math, so focus on them first." By then, I knew enough to immediately sense he was right.

*Was it difficult to get into that most prestigious school, Moscow State University? Was it particularly difficult for a Jew? Why did you choose the Chemistry Department, rather than Biology or Physics?*

I became a student in the Chemistry Department of Moscow University in 1964, having decided to do biology but wanting to learn physics, math and chemistry as well. There were five entrance exams, amidst heavy competition. I received an "A" in all of them (math, physics, chemistry, "literature", and history of the Communist Party), and was admitted. There were several other Jewish freshmen as well, in a class of about 300 students. I heard of course, from people whose veracity I trusted, about other outcomes and discrimination, overt or covert, against Jewish applicants at Moscow University and elsewhere, especially in math departments. My own experience was different, possibly because it was problematic not to admit a candidate who did well on exams. I didn't know much about discrimination because I was a space cadet, barely noticing dangers and obstacles in my path. "A sea doesn't rise above drunkard's knees" ("Pianomu more po koleno") is a Russian proverb that describes my emotional makeup then, and later as well. If such immaturity doesn't lead to disaster right away, it can produce an illusion of invulnerability, before a blow.

I began moonlighting in a biochemical lab during the second year at university, loving that work from the first. The subject occasionally reciprocated. At nineteen, in 1967, listening to a lecture on quantum mechanics, I was visited by the first genuinely new scientific idea I ever had. Around that time, the Lac and lambda repressors, predicted by Jacob, Monod and their colleagues in the early 1960s, were demonstrated to actually exist, by Gilbert, Müller-Hill and Ptashne. But the thought I had was different: what regulates repressors? Could it be that repressors regulated themselves, for example by inhibiting their own synthesis? I was so stunned that such a simple idea might be new, let alone correct, that I bolted from the classroom, went to the library and buried myself there, forgetting such trivia as attending lectures and laboratory courses. Skipping lectures was OK, because one could prepare for exams by reading. But playing hooky with practical courses was madness, since one had to complete them to qualify for next semester. Predictably, I came very close to expulsion from university. That would have been a disaster (of my own making), for I was, by then, of sufficient age to be immediately drafted for a 3-year stint in the Soviet Army. The main reason I wasn't expelled was my having been a straight-A student up to the moment of the repressor idea announcing itself.

I read, wrote and rewrote, preparing a theoretical paper and furnishing it with differential equations that described the behavior of circuits in which repressors regulated themselves. The paper was published in the January

1968 issue of Russian "Molecular Biology", then a new journal. Nowadays, the modeling exercises I labored over in that paper would be called "systems biology". My version of it in 1967 was too simplistic to be of any use. But the idea itself was new, and turned out to be correct for some repressors. Models of biological regulators regulating themselves began to be considered in English-language papers around 1971, naturally without reference to the 1968 publication in a relatively obscure Russian journal.

That idea, and my coming close to expulsion from university because of it, were a searing experience. I saw that I was capable of thoughts that were genuinely new, and possibly even correct. This deepened my commitment to the craft. I also saw, a bit later, that my penchant for equations should be postponed for a remote future, since biochemical systems at hand were too dimly understood to allow quantitative modeling realistic enough to be useful.

*Your first and only place of work after university was the Institute of Molecular Biology. Even the name of that Institute signified a change in Soviet life. For example, at the Fifth International Congress of Biochemistry that took place in Moscow in 1961, the term "molecular biology" was*

James Watson and Jacob (Yakov) Varshavsky at the Fifth International Congress of Biochemistry, Moscow, 1961.

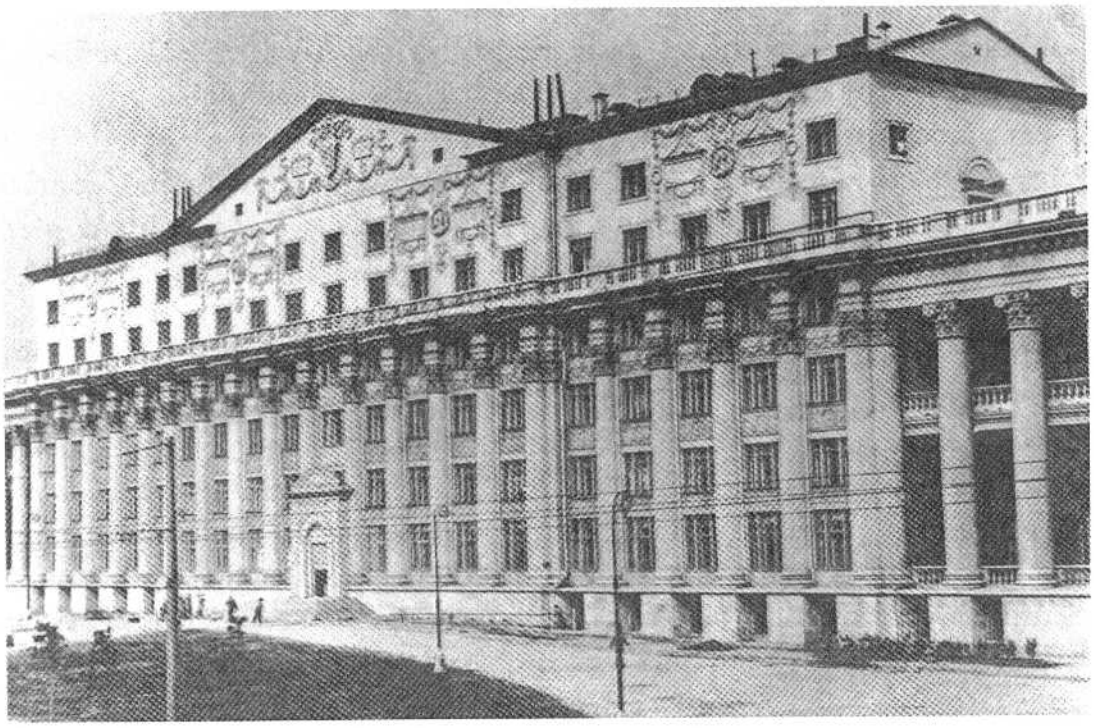
*not permitted to be used. Would you comment on the situation of molecular biology in the Soviet Union over the years?*

The shadow of Trofim Lysenko was still visible in the 1960s. He was a textbook example of a power-hungry demagogue. A wily but limited man who posed as a scientist (and probably saw himself as such) but never understood science. In the mid-1930s, Lysenko began his campaign against the community of Soviet geneticists. His power derived from his support by Stalin, to whom Lysenko promised great agricultural harvests. Stalin and Lysenko had much in common as sociopathic characters and chieftains, but differed in their demeanor, with Stalin reserved (in public) and Lysenko a histrionic bully. Stalin held the entire country in his fist, while Lysenko's fiefs were biology and agriculture. By the late 1940s, Lysenko became the tsar of whatever remained of Soviet biology. Several leading geneticists were killed or imprisoned. The lucky ones were fired, or dropped their studies early enough and turned to safer occupations. Lysenko's own brand of "Marxist" biology is not worth recounting. (There are books in English about the life and career of that Rasputin-like figure.)

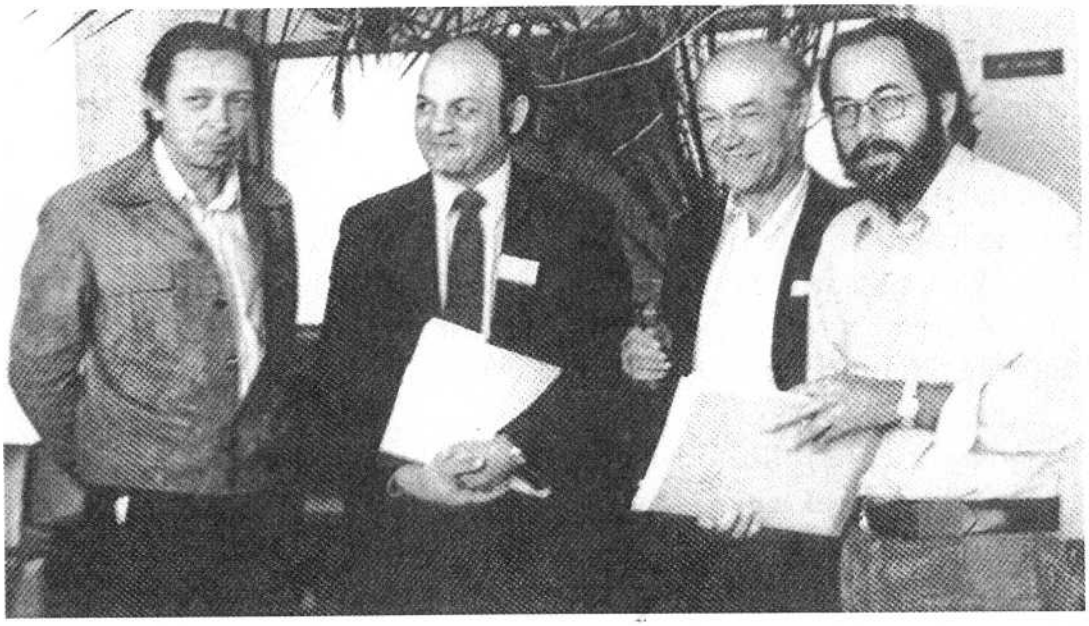
One consequence of the Lysenko's reign in Soviet biology was the near-disappearance of people who understood genetics professionally enough. Entering science in the 1960s, I could see the effect of that gap. One evening in 1968, a leading Russian biochemist was giving advice to an undergraduate: "Ah, Alex, don't waste your time on genetics. It's mostly obsolete. Beautiful in a strange way, but next to useless. They keep tormenting fruit flies, but it's us biochemists who will produce the understanding that really matters." Having spent a day reading genetic papers, I sensed he couldn't be right, that genetics was essential too. But that was just a hunch on my part, not an obvious truth it would have been in a more enlightened setting.

Khrushchev, the successor of Stalin, continued to support Lysenko, but Khrushchev ran a "milder" dictatorship, and people became less afraid. Leading Soviet physicists, whose cachet with apparatchiks derived from physics' importance in military technology, helped Vladimir Engelhardt, a distinguished Russian biochemist, to organize a new research institute in 1959. Its baroque name was the "Institute of Radiation and Physico-Chemical Biology", since "Molecular Biology" was still verboten. The place was renamed the Institute of Molecular Biology (IMB) around 1970.

*Can you describe your early experiences of working in a lab, at the university and later at IMB?*



The Institute of Molecular Biology (IMB) at 32 Vavilov Street in Moscow, where Alexander Varshavsky worked in 1970–1977.



From left, Georgii Georgiev, the head of Alexander Varshavsky's lab at IMB; Alexander Rich, visiting from Massachusetts Institute of Technology; Jacob (Yakov) Varshavsky, head of another lab at IMB; and David Baltimore, also visiting from MIT, Moscow 1975.

At Moscow University, both I and people around me knew that "real" molecular biology was being done largely in the West. The latter could have been just as easily on the Moon, for it was impossible to visit either. Russian laboratories were strapped for everything — hard currency (rubles were worthless outside Russia), clean reagents, equipment, and contacts with Western scientists. Promotions and funding were based on merit once in a blue moon, while capacity for intrigue and membership in the Communist Party rode far in front. I sensed the provinciality of my scientific milieu. It depressed me for sure, but I was spared, for a while, the full comprehension of a gulf in quality (notable exceptions notwithstanding) between Eastern and Western molecular biology. One reason for slow awakening was the sheer appetite for work: even washing dishes in the lab was not a chore to shirk from if it could accelerate an upcoming experiment. Another reason was my love of physics and math, where Russian scientists were anything but provincial. Leading mathematicians in Russia were second to none, and theoretical physics was world-class as well: Lev Landau (before his dreadful car accident in 1961), Vladimir Fok, Yakov Zel'dovich, Igor Tamm, their former students, and other terrific scientists. But I wasn't a mathematician or theoretical physicist, and the bleak reality of my circumstances began asserting itself soon after graduation from university. I got a job at the Institute of Molecular Biology, a flagship place for doing such biology in Russia. The laboratory I worked in was led by Georgii Georgiev, one of the best scientists at the institute. We studied chromosomes and RNA. Things were looking up, but there also was, in the midst of excitement, an undercurrent of second-ratedness in my larger surroundings. My fear was that I would cease being aware of that, and become one of many who gave up or never aspired in the first place. What sustained me was youth, love of science, and ambition, a heady mix. It kept me working and hoping, against all evidence, that things might improve. The time was mid-1970s, a couple of years away from a chance to escape it all.

"Doing science is like driving a car at night. You can only see as far as your headlights, but you can make the whole trip that way." Long before I encountered this metaphor, by E. L. Doctorow (his actual remark was about writing a novel), I sensed the attraction of scientists' racket: an air of open-ended adventure, a contest of sorts, with the landscape rough, unpredictable, with other cars racing toward Holy Grails out there, and occasionally colliding with yours, by accident or not quite. A rambunctious life to be sure, but quiet

on the outside, with maelstroms and lava flows hidden from casual view. A set of qualities for such a life must contain a genuine interest, beyond mere curiosity, in understanding the world's design, but an ambition too, even with thinkers whose visage suggests otherwise. Photos of old Einstein, a serene photogenic sage, free of strife, do not recall the assertive and ambitious young man in Switzerland, on the cusp of initial success, and his later, often overt, competition with rivals, a great German mathematician David Hilbert amongst them. Hilbert produced (and correctly interpreted) the equations of general relativity simultaneously with Einstein, a fact unmentioned in popular accounts of the subject but known to those who are interested in physics' history. *What Mad Pursuit* is the title, from a poem by Keats that Francis Crick chose for his autobiography. And mad it is, propelled not only by desire for knowledge but also, in no small measure, by desire to impress and awe — oneself, others, posterity. That's where one's genetic makeup comes in particularly strongly, I think: a predilection for life of a certain shape and texture.

My mother tells me that her ancestry is traceable to the chief rabbi of Prague in the early 17th century. Had I been born a few centuries earlier in the Jewish ghetto of Prague, I might have ended up a religious scholar, splitting hairs with fellas at a yeshiva about the subtleties of the Talmud and Kabala. It's nice to hope that I would have discerned, unaided, the incorrectness of religious outlook, recognizing its vacuity in the midst of semi-medieval Prague. Wrong hope, most likely, for it is difficult, nowadays, to appreciate the acuteness of insight, in addition to independence of spirit, that would be necessary for such a discovery before the rise of modern science. But some, quite rare, people in both antiquity and Middle Ages must have glimpsed this insight. That the names of early doubters are largely unknown to us is no accident. From times immemorial to roughly the 1700s in Europe, one could safely declare a disbelief in deities and their deeds only in total solitude. Even centuries later, the nonbeliever's view of extant religions is a majority opinion only among scientists, not in the public at large. But the long-term trend, on the scale of centuries, although a turbulent one, with transient local reverses, is clearly toward secular, science-informed outlook. A stance in which things and phenomena we don't have good explanations for are called mysteries or puzzles, without attempts to camouflage the insufficient understanding by theology and fairy tales.

*How, when, and why did you decide to emigrate? How much do you feel Jewish, and how much of your environment considered you Jewish, in the Soviet Union and in America?*

By the 1970s, the idea of emigration was in the air, especially amongst Russian Jews, whose treatment by the regime was strikingly inconsistent. It was more difficult, though not impossible, for a Jew to become a student at a good college, more difficult to get a good job, to be promoted, and certain professions, particularly those linked to politics and power, were nearly closed to them. But, somehow, the very same Jews were allowed to apply for emigration to Israel and often actually left the country, a privilege denied to other ethnic groups, Russians included. Besides the usual human inertia and fear of the unknown, a major reason that the entire Jewish population of the Soviet Union, about 3 million, didn't simply pack up and leave (a lot of them did) was straightforward: the possibility of being refused permission and the resulting legal limbo, including the loss of one's job, harassment or worse. The main causes of this policy by the Soviet state — discrimination and preferential treatment at the same time — are well understood: several centuries of anti-Semitism in Russia, agreed with and abetted by the authorities, but also their desire to curry favor with the West, in return for economic subsidies, direct or indirect.

I am non-religious, and know neither Hebrew nor Yiddish, if one doesn't count a smattering of Yiddish words, many of them a part of English slang. Reading about the history of Jews, I saw it as a singular one, but my connection to it was untinged by patriotic zeal. My appearance then did not identify me as a Jew right away. And so I was, from time to time, an uneasy listener to people who complained to me about "those Jews", or even vented their hatred of them. Fascinating experiences, for it was clear, especially in "hatred" cases, that one dealt with a person whose inner turmoil or rage, compounded by lack of introspection, has found a traditional, centuries-old outlet. This is not a treatise on the Russian brand of anti-Semitism, a beast very much alive. The example above is just an illustration of the unease that accompanied the lives of Russian Jews even in relatively benign times.

The idea of attempting to leave the country occurred to me rather late, a couple of years after graduation from Moscow University. I was engrossed in loving my profession and trying to succeed in it, kind of forgetting that a better way would be to change the place of one's pursuits. My marriage

history didn't help either. It became even more checkered later on, until I got lucky, in 1990, after many years and less than happy marriages. My first wife was my girlfriend at high school. I was 19 when we got married. Our daughter Victoria was born two years later, in 1968. By 1970, we were divorced. It would be flattery to call my first marriage a caricature of the real thing. Both of us were immature, and selfish in ways that children, not adults, tend to be.

I received my Ph.D. in 1973, and continued to work at the Institute of Molecular Biology, where Georgiev, the lab's head, allowed me to supervise a graduate student and an occasional undergraduate. He was supportive in other ways as well. My subject was the structure and organization of chromosomes, then a mystery. This problem is huge, multifaceted, and remains a partially explored territory. In the early 1970s even "elementary" questions, about the path of DNA at the first level of its folding in chromosomes, and about the role that histones (DNA-associated structural proteins) play in this folding, were unanswered. Our work in those years contributed, in a minor way, to the problem's eventual solution by Roger Kornberg, who worked in England then.

My papers were published not only in Russian journals but in Western ones as well. I began to receive invitations to give talks abroad, but my attempts to receive permission to travel to Western countries were a waste of time. I was allowed, though, to visit other barracks of the "socialist camp". One of them was Bulgaria, the other German Democratic Republic (GDR). Three decades of rule by communists damaged but didn't destroy German industriousness. The GDR was unfree and much less prosperous than its Western counterpart, but its standard of living was still higher than Russia's. I could glimpse West Berlin across the Wall, but that was all I could do, being too macroscopic for teleportation.

Then a stroke of luck, at first unrecognized. In 1976, I received a letter from England, an invitation by Aaron Klug, an outstanding structural biologist, to give a talk at a symposium in London he was organizing. Knowing that permission to travel would be refused, I was about to write a polite declination, then decided otherwise and requested an appointment with the Institute's director Vladimir Alexandrovich Engelhardt, a man in his eighties then, a member of the Soviet Academy and one of most highly positioned scientists in Russian biology. I didn't hope for much, and was unprepared for what I heard.

*How did you manage to leave Russia?*

Vladimir Engelhardt, the founder and first director of the Institute of Molecular Biology (IMB) of the then Soviet Academy of Sciences, in the 1960s.

Engelhardt, the founder and director of the IMB, knew me from the time of my joining Georgiev's lab in 1970, in part because my father headed another lab at the same institute. Georgiev spoke highly to Engelhardt about my work, or work habits (I spent days and nights in the lab), and he became interested. A relationship developed, utterly unequal but a real one. Engelhardt occasionally called me to his office and asked about ongoing work. I learned not to bore him with actual studies, for which his attention span was no longer equipped, and confined myself to just-so stories about chromosomes and stuff.

This time, I told Engelhardt about receiving an invitation from Aaron Klug to attend a symposium in London and give a talk there. He didn't let me finish. "I know Klug. Fine scientist, he. Hmm, and I haven't been to England for some time ... Are you the only one he invited from here?" I replied that I had no way of knowing for sure, but presumed that Klug invited just me. "Very well, then," said the old man and became as animated as I ever saw him to be. "Why don't we travel to London together, you and I?" "Vladimir Aleksandrovich, I would be delighted to, but do you think this idea is realistic?" "But of course," was the reply. "Let's begin by sending a cable to Klug, and inquire whether he can send a formal invitation to me as well. Once we receive that invitation, I'll see what can be done. Please wait." I did, expecting refusal. A few months later, in February 1977, I boarded the Soviet IL-62 for a flight from Moscow to London. I was in coach and Engelhardt way upfront, in first class.

I'll never know how he managed to obtain permission, from the directorate of KGB that handled such matters, for me to travel with him. My case was an open-and-shut one. A Jew, for starters. Divorced, i.e., morally unstable: if he left his marriage, he can leave the motherland too. Well known to the said directorate as someone who tells anti-Soviet jokes at Institute's parties. Besides, I didn't have hostages. In the former Soviet Union, and in places like North Korea today, a person trusted enough to travel abroad was expected to leave behind someone he would have difficulty parting with for good. Children, in a stable family, were best hostages. A wife or husband was a so-so hostage, but better than nothing. Parents were no hostages at all. By the lights of KGB, I shouldn't have been allowed to come close to that IL-62, let alone fly in it. It must have been Engelhardt himself, his limited but tangible influence that made the difference. Being the director of a major institute, he served apparatchiks above him. Apropos, Engelhardt was of German, not Jewish, descent, a plus in his dealings with those characters. He kept the furnace of loyalty hot and burning for years, and in return received occasional favors, such as taking his word that a nerd who didn't deserve to travel abroad and was a defection risk to boot, should be allowed to come with him.

A week-long jaunt to England was over fast, a bewildering experience. I flew back to Moscow with Engelhardt, feeling miserable and believing, on good grounds, that I'd lost my first and last chance of escape. The trip itself soon became a distant recollection, a collage of images. My talk at a symposium in London. Meeting scientists whose work I admired from afar. Traveling from London to Cambridge, where colleagues received me most kindly, and were generous with gifts of reagents and gadgets for benchwork. Walking in downtown London at night, marveling at the shop windows and profusion of lights in the streets. But never telling a policeman that I wished to ask for political asylum.

*Why did you decide not to stay in England? What happened next?*

Without telling a soul, I planned to defect in London, and was sure I would do so right after arrival. Then something happened to my resolve. The sight of an old man who was kind to me and seemed to trust me; his fragility; and my concern that he might just die from stress and disappointment if I defected were the main reason, an attack of altruism if you will. There was also a smidgeon of fright, a reluctance to cut the knot so abruptly and irrevocably. In 1977, the Soviet Union appeared to

me, and to everyone I knew, as a Thousand Year Reich. Leaving it would guarantee my never seeing family and friends again, a price I thought was acceptable, then discovered it wasn't.

Returning to Moscow, I regaled acquaintances with tales of a life they never saw, but felt sad, and was sure I missed the only chance of escape. Then, a few weeks later, an utterly unexpected phone call: "Alexander Yakovlevich? Vladimir Leonidovich is my name. I'm a colonel at Komitet Gosudarstvennoi Bezopasnosty." (Hence the acronym KGB.) "How was your trip to London? Good impressions? Lots of science, I gather." He continued before I managed to reply. "My colleague and I would like to meet with you next week, if you don't have objections." I didn't. A few days later, I was going up in the elevator of the hotel Moskva, near Red Square, having been instructed to knock at the door of a room on the seventh floor. Two men stood up to greet me, one of them in his forties ("Vladimir Leonidovich"; he never told me his last name), and a younger one, who introduced himself as "senior lieutenant". Both wore civilian clothes.

Our conversation, details of which I remembered for years but never wrote down, was lurching from one irrelevant subject to another. I played along, knowing they didn't invite me to hear interminable tales, interrupted by insincere laughter, of their catching a huge pike or carp in the Oka river. Roughly a year later, when a guy from the CIA came to Cambridge, Massachusetts to debrief me at MIT, and heard that the room in question was at the Moskva hotel, he shook his head and said, "Yah, Yah. Seventh floor, a room with an oil painting of a woman on the wall near window, right?" "Absolutely right," I replied, dumbfounded by the CIA's colossal erudition.

Meanwhile, in that very room my camaraderie with the KGB grew in leaps and bounds. They finally got tired of describing fishing trips, and Vladimir Leonidovich suggested, insinuatingly, "I betcha you would like to travel abroad often, wouldn't you?" "Sure, who wouldn't," I replied, playing a level-headed fella, honest to a fault. "I enjoyed the visit to London, and my work at the Institute benefited from that trip." After another digression and burst of camaraderie, a proposition was advanced, simple and clear. "Look, Alexander Yakovlevich. We hear good things about you as a scientist. But not so good things about jokes at parties, ga-ga-ga!!!" Having recovered from mirth, he continued. (The meeting was long and not worth recounting in detail. I learned more about pikes and carps than I ever cared to know.)

"The Soviet Union and the entire socialist camp are surrounded by enemies. Counter-intelligence officers must know what the other side is up to. Genetic engineering — you know about that stuff, do you?" I nodded. "It may soon become an instrument in the hands of American military." To say "military", he used a quintessentially Soviet-Russian word, "voienschina": something to despise, but also to fear. "We should be on the lookout for these bastards' plans, to pre-empt them, and if necessary to develop countermeasures."

Countermeasures, my foot. From their remarks about molecular biology, in between guffaws and small talk, I knew that my counter-intelligence chums had a rather vague idea of what DNA was, but they bravely pretended otherwise. Their orders from above were probably clear: to find out what that new imperialist trick — genetic engineering — was. Not that anyone cared, with carps, vodka and fishing gear looming larger in their minds than adenine or cytosine, but reports had to be produced, "*competent scientists*" consulted, gathered intelligence properly recorded. The rusty machine creaked on, and invited me into its craw. It didn't occur to me then, but became clear later, that Paul Berg, David Baltimore and their colleagues who organized the 1975 Asilomar Conference, where concerns about possible dangers of genetic engineering were discussed in a public setting, have discombobulated not only the more impressionable amongst U.S. public officials, but apparently scared the KGB too! Thus, remarkably, my collaboration with the KGB that made the escape possible was helped by events far away, when the Asilomar conferees decided to discuss their pros and contras in public, with reverberations that reached Vladimir Leonidovich, the man without a last name.

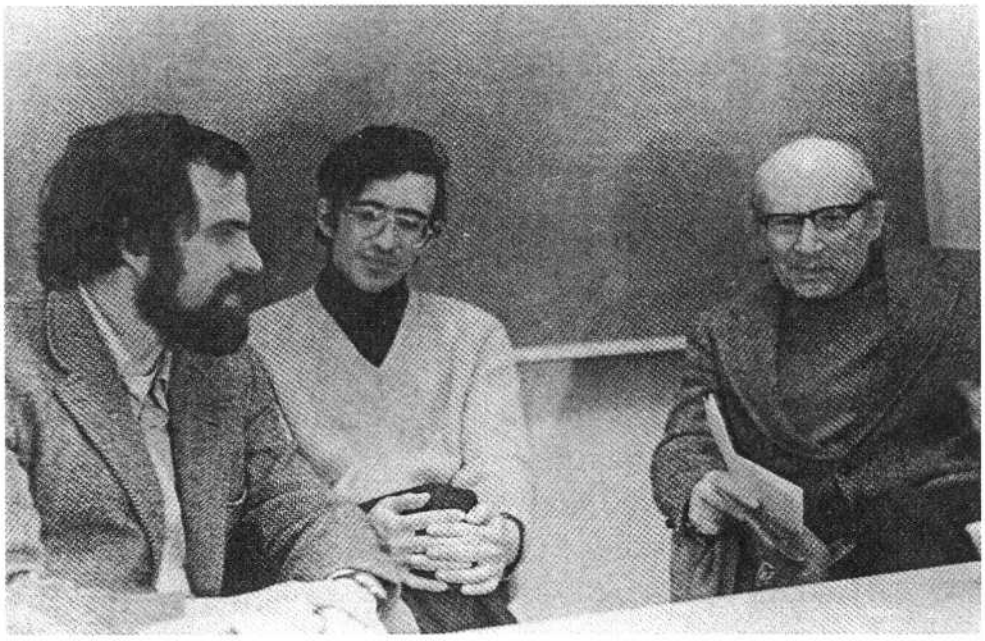
Everything went swell that day. I told them, with a straight face, that my foremost duty as a Soviet citizen was to assist the counter-intelligence branch of "organs" (Russian slang for the KGB) in its valiant efforts. To do the job, one would have to travel to the West, naturally. That was fine, I was told, just fine, and we parted. This time, my good behavior on a trip would be vouched for by KGB apparatchiks I didn't care about, the mother of all understatements.

It so happened that before the visit to the Moskva hotel I received an invitation to give a talk at the international symposium on chromosomes in Helsinki, Finland. A few months rolled by. Near the end of August 1977, the senior lieutenant, in a gesture of seeing an agent off to a mission, gave me a lift to the railway station. The destination was Finland, a Western

country but not a good place to defect in, I was told by an acquaintance. The gist of his warning was that the Finnish authorities were appeaseniks of the Russian bear at their border, and would eventually return a defector, after giving him another chance to escape, this time from a Finnish police precinct. Nowadays, throngs of people from Russia and other, now independent, states that comprised the former Soviet Union are attempting to resettle themselves in the U.S. and Europe. Unlike me in 1977, these people have no problem leaving their countries. Their difficulty is to be allowed to enter their destinations, in a world where a defector from Russia is an extinct species. Not so in 1977, when the West would welcome a person who managed to flee a Communist dictatorship. Such people were rare birds, and didn't overwhelm the generosity of the receiving country.

Whether or not the warning about Finland was actually correct I don't know to this day, but my taking that advice seriously made it necessary to cross, somehow, from Finland to Sweden, without a visa to the latter. But I didn't worry too much about it, because I counted on meeting a friend in Helsinki.

*Who was that friend, and how did you escape? There are stories about your emigration, but there are also puzzles about it. How could you*



From left to right: Robert Hoffman, Leonid Margolis, and Israel Gelfand, Moscow, 1977.

*turn up in Germany, for example, when you had been let out to attend a meeting in Finland? Did you have the necessary visas?*

A year before my trip to Finland, Robert Hoffman, a young American scientist, came to the IMB for a sojourn of several months, and began working there, sharing his time between IMB and a lab at Moscow University. He was the first American I met for more than a few minutes, a remarkable apparition. Gregarious, friendly, free, cracking jokes, learning new language and taking delight in four-letter words that Russian is justly famous for, Bob Hoffman was a breath of fresh air. It became obvious right away that Bob wasn't exactly a fan of the American political system. He described to me, a denizen of full-employment country, the problem of unemployment in the U.S. and other such nightmares. Sensing that he is far more intelligent than his naiveté (about to be cured) suggested, I pulled no punches in telling Bob what I thought about the worker's paradise he decided to explore. Just two weeks of Bob's exposure to realities of Soviet life produced a complete transformation. I was working at the bench when Bob burst into the room and shouted, mercifully in English: "Alik!" ("Alex" is "Alik" in Russian.) "Do you know you're living in a fascist country?!" Making sure we were alone in the room, I replied that I did, that now he knew it too, and if our neighbors on the floor didn't know it already they would have learned it this very instant.

It didn't take long for Bob and me to become close friends. We walked the streets around the IMB, discussing everything we could think of. I came to trust Bob unconditionally, and confided with him about the approach by the KGB, the impending trip to Helsinki, and my decision to escape from there to Sweden. Bob wholeheartedly approved, and suggested, with warmth and generosity of spirit — his particularly endearing trait — that he, too, would fly to Helsinki, but from Boston, to which he was about to return, being on leave from a lab at the Massachusetts General Hospital. Our idea was that Bob would meet me in Helsinki and help with the escape. The two conspirators promised each other to keep mum about their plans. I knew the dates of the symposium, and we decided, a la le Carré, that Bob would wait for me at the Helsinki's railway station every hour on the hour for three days in the row, and that I would try to find him there if I went to Finland, permission being in the hands of my KGB handlers and still uncertain at the time. Two friends in Moscow, Misha Evgenev and Lucya Ulitskaya, then husband and wife, also knew of my plans. Misha was a geneticist at an institute close to IMB. Lucya

Varshavsky with Michael Evgenev, a geneticist and close friend back in Russia, Moscow, 1977.

shepherded two little children then. She is a well known writer today, an outstanding one, actually. I trusted Misha and Lucya entirely, and left with them a few documents, such as my Ph.D. diploma, that I didn't dare to travel with, lest my suitcase be searched.

Bob Hoffman and I met again in Helsinki, exactly as we had planned. My talk at the symposium was scheduled for the first morning. In the afternoon of that day, there was a reception for participants, at a hall right across from the railway station. Just minutes after discussing science with Francis Crick and his colleague Ruth Kavenoff, I went to the railway station. Bob Hoffman, having crossed the ocean to meet me, was there all right, sitting on a bench. He was conspicuous not only because of his height. The collar of his raincoat was straight up despite good weather, courtesy of spy thrillers. We embraced, Bob looked around, checking for agents with machine guns (none showed up, having more interesting things to do), and we proceeded to concoct the escape plan. A large ferry crossed the Baltic sea between Helsinki and Stockholm every day. It turned out that Bob had flown from Boston to Stockholm, then took the ferry to Helsinki, and noticed that most passengers were not asked to show their passports, a blessed Scandinavian attitude. He would buy two tickets to the ferry from Helsinki to Stockholm, departing next morning, and we would travel together, on the assumption that a ticket checker would let me in without a visa.

The actual escape was nothing to write home about. A guard at the ferry, bored and indifferent, glanced at the ticket and waved me through.

Bob and I went to a cubicle in the ship's belly, stayed there and emerged when the ferry arrived at Stockholm. At Bob's suggestion, we took a taxi and drove straight to the U.S. embassy. Its security officer was courteous but not exactly thrilled by our feat. He needed a Russian defector like a hole in the head. "I'll ship you to our Consulate in Frankfurt, Germany," he said. "It's a big place, you know. There must be folks there who would assist you with getting a visa to the U.S." Hours later, we were in Frankfurt. The Consul was too busy to receive me. A Consulate's apparatchik, talking dishearteningly like apparatchiks I knew in the other life, explained that he could do nothing about the visa, but could send me to Rome, Italy, where lucky Jews who left the Soviet Union legally were cooling their heels, waiting (sometimes for months) for a visa to the U.S. Having escaped, I longed to begin scientific work as soon as possible, so Bob and I decided that I would stay for a few days in Frankfurt, trying to get an audience with the Consul. The next day, we had another idea. I called David Baltimore at MIT in Cambridge, Massachusetts. The call stemmed from a shaky hope that Baltimore might remember me from a few encounters at the USA–USSR symposium in Kiev, Ukraine two years before. David was well known, already then, for his co-discovery of reverse transcriptase, a contribution for which he received the 1975 Nobel Prize in Physiology or Medicine.

David remembered me, was friendly and gracious (in stark contrast to the gentleman at the Consulate), and suggested that I remain in Frankfurt for a few days, while he tried to find out whether anything constructive could be done about the visa. In the meantime, Bob Hoffman had to go back to his job in Boston. He gave me money and left. I stayed at a seedy (as I realized only later) hotel in the Frankfurt's red-light district, a memorable experience for a runaway from a country with puritanical sexual mores. An audience with the Consul didn't seem to be in the cards, but my mood couldn't be deflated by such a trifle. There was a Burger King nearby. I went there for breakfast, lunch and dinner (often followed by a second, late dinner), thinking that cheeseburgers and French fries belonged in the antechamber of Paradise, perhaps at the Place itself. One morning, a black limo made its way to the hotel along a narrow street. The Consulate's apparatchik emerged from it, and half an hour later I was in the presence of the Consul. He smiled at me most benignly, and announced that he had in his hands an airline ticket. First class, nonstop, all expenses paid, from Frankfurt to New York, and my U.S. visa too. The next time I flew first class was 15 years later. I wasn't told the cause of such a startling reversal

of fortune, and didn't inquire, having assumed (correctly, as it turned out) that our phone call to David Baltimore was involved. Years afterward, I learned that David called the MIT office of Frank Press, a distinguished geophysicist who was, at the time, the science advisor to Jimmy Carter and had an office at the White House. My visa may have been cabled from an office traceable to that House. (I don't actually know.) That would account for the Consulate going overboard in sending me across the ocean immediately and in style, instead of in coach. Having arrived at New York's JFK, I flew to Boston. Bob Hoffman met me at the airport, and in no time at all I saw my first American apartment — Bob's — in Cambridge, near Harvard University. A nice place, with an unoccupied sofa that became my bed.

Our first priority was to send a couple of cables to Moscow's IMB. The joy of having escaped was weighted with concern about repercussions for my parents and sister in Moscow, and for Georgiev and Engelhardt as well. My cables, written together with Bob, were designed to convey an image of space cadet who didn't comprehend the irreversibility and hurtful seriousness of what he has done, and even "*hoped to return one day*". It didn't matter whether or not the self-portrait, in those cables, of a bumbling knucklehead was believed by the apparatchiks in charge of punishing people who remained behind. The incipient tiredness of the Soviet regime was reflected in its (relatively) laid-back attitude to transgressions perceived as unthreatening. The "evidence", in the form of cables, that I was a loony would give officials a formal pretext to be restrained in their penalties, if they preferred so. I was denounced, in due course, at the IMB's public meeting. Engelhardt remained the director. Georgiev received a formal reprimand. My father was at first expelled from membership in the Communist Party, but was reinstated later. That reinstatement saved his job as professor at the IMB. Everything went just about as well as it could, but only on the surface. Feelings were another matter. My mother and father were flabbergasted by my escape. It took years, and efforts on both sides, to overcome a divide that these events engendered. (My parents left Russia in 1991, long after me.)

*You were hired by MIT soon after coming to Cambridge/Boston. How did it happen? How did you manage at the beginning?*

Right after my arrival in Cambridge, in September 1977, the laboratory of Bob Hoffman at the Massachusetts General Hospital, across the river

in Boston, became my second home. Bob and the lab's head Richard Erbe gave me a bench, and my work in the U.S. began, a dream realized. I was struck by the luxury of having disposable supplies, things like capillaries (precursors of tips in modern pipettes), clean napkins, little gadgets of all kinds, chemical reagents that were neither dirty nor difficult to obtain. In Moscow, I would have washed those capillaries with loving care, reusing them until the end of time.

A few days later Bob and I paid a visit to nearby MIT. We wished to thank David Baltimore for his help with the visa to the U.S. I also hoped to meet with Alex Rich, another outstanding MIT scientist who traveled to Russia and visited the IMB. David wasn't at MIT on that day, but Alex Rich was. He made a suggestion I didn't expect. "You traveled to Helsinki to attend a symposium," he said. "Ergo, you must have slides of your talk. Why don't you give us a seminar about your work in Moscow?" A few days later I gave that talk, and was told it went well. The results I described, while not particularly exciting, were genuinely new and spanned a broad range, from the organization of nucleosomes to the folding of SV40 viral minichromosomes. Unbeknownst to me, MIT's Biology Department was initiating a search for a junior faculty member in the area of chromosome structure. Although my field of work was appropriate for the planned appointment, the idea of offering that job to me must have been a difficult proposition, for I had fallen into Cambridge from the Moon just days before, utterly outside of a formal search.

A few days after the MIT seminar, I received a call from Cyrus Levinthal, of the Columbia University in New York. He asked how I was, and offered me a job of assistant professor at Columbia. (I don't know how that decision was made in New York.) As if the offer from Levinthal were not enough, I learned from Gene Brown, the genial chairman of MIT's Biology Department, that Francis Crick, whom I had met for less than an hour in Helsinki (he attended my talk there as well), has called Brown and inquired whether he could be of help in finding a job for me in the U.S. or U.K. A few days later, Gene Brown offered me the assistant professor's position at MIT, less than two months after my leaving Moscow. I said, "*I accept*" before Gene finished describing the offer.

A large room with seven lab benches and a small adjoining office was cleaned up and ready for me in no time at all. I moved there, and began working in my own lab, alone and happy, going to nearby laboratories when I needed equipment. Most "heavy" equipment at Moscow's IMB

was imported from the West, so I knew how to use the instruments. Gene Brown signed my requisitions for consumable supplies, and told me that I would be able to buy equipment and hire personnel in a year or so, once I receive my first grant, which I was supposed to write and submit to the NIH as soon as possible. Since I didn't know about "start-up" funds for equipment and personnel that a newly hired faculty member was supposed to be given, I didn't request such funds, and received none. Learning of that omission several months later, I felt no less grateful to Brown and his colleagues, for I knew that hiring me must have been a gamble on the Department's part.

Colleagues at MIT, particularly Alex Rich, David Baltimore and Howard Green, were the source of help and moral support from the beginning. I can't thank them enough. Roger Kornberg, the discoverer of nucleosomes, who was then at the Harvard Medical School (I met him on the 1977 trip to London), contacted me soon after my arrival to Cambridge and was of tremendous, warm-hearted support. Robert Horvitz, a geneticist who studied nematode biology, began his work as an assistant professor at MIT almost simultaneously with me. His laboratory was across the corridor from my lab. Bob helped me with advice in more ways than one. His science went from strength to strength right away, and was a great example for me.

Bruce Alberts, whom I first met in the Soviet Union in 1975, was a professor at Princeton in the 1970s, before his move to the University of California at San Francisco. Bruce and I met again soon after my coming to the U.S. We have kept in touch ever since. My friendship with Bruce, his attitude to life and work had effects on me that I have difficulty putting into words. Looking at the Bruce's oeuvre, his discoveries in the lab and his involvement with the scientific community, I saw that one could be a first-rate scientist without being inward-bound. But my deck of genes wasn't Bruce's, and there was nothing I could do about it.

In the excitement of the initial months at MIT, I managed to forget that Bob Hoffman may need some privacy, as he eventually told me, in a most tactful way, seeing that I didn't grasp, as yet, the advantage of living in my own apartment, rather than his. He also explained the benefits of sleeping on a real sheet, with a real blanket, as distinguished from rags on Bob's sofa. Having heard this, I encountered yet another miracle in my new country, for it took me an hour, from start to finish, to rent a place in Cambridge. My apartment was a walk-up one-bedroom joint, in a creaky two-story house that was so infested with cockroaches (as I found later) that getting rid of them

in my cubicles didn't make sense: the fallen were swiftly replaced by cousins from adjoining flats. I was taken aback, a little, by those cockroaches, as they were absent in my parents' Moscow apartment. But the nuisances of everyday life barely registered. Work was all I cared about, with the intensity even greater than in Moscow, where I managed to get married, divorced, went to parties and found other ways to waste my time. None of that in Cambridge, Massachusetts. The monk was determined, and more single-minded than Savonarola ever was.

I must have nursed a childish pride in my work ethics, as the following episode illustrates. One evening, soon after joining MIT, I was in the midst of an experiment that was to last through the night. Near the elevator, I ran into Boris Magasanik, a great yeast geneticist who worked late that day and was going home. Hearing that I was going to work in the lab all night, Boris inquired how often I did that. "As often as possible, twice a week," answered the happy simpleton. Boris' reply was terse: "That's dull." Having learned, later, of Magasanik's wide-ranging interests, I saw his reply, its lack of tact notwithstanding, as a disappointment in the narrowness of my mind. The immediate result of that encounter was my becoming a bit more worldly in what I said to colleagues. But not worldly enough. A day later, I told Gene Brown that I didn't wish to teach students. Having convinced myself that I was in a breathtakingly free country, where one can finally say what one thinks, I carried the license far and wide. Gene listened to my pronouncement, muttered something under his breath, then collected himself and told me, in an even voice, that things were very simple: if I refuse to teach, I will be fired. That information put a stop to refusals, but it took some time before the illusion of "totally free country" dissipated closer to reality's level. One day, in my first year at MIT, I had a conversation with Graham Walker, a fellow assistant professor and a nice man. Gram told me, in his gentle way, that he heard of my mutiny against teaching duties. "We were hired to teach as well, you know," he said. "And there's another thing to consider: tenure. Teaching figures significantly in tenure decisions. Way down the road, but still ..." I appreciated Gram's advice, and am grateful to the MIT folks for their correct perception of my post-escape self as being "drunk on freedom", as a colleague put it.

The dislike of teaching was not about teaching itself, for I understood its importance. I begrudged the time. No science could be done while delivering a lecture, and no learning either, with my exiting the classroom

having the same knowledge I had possessed before entering. Worse than that, I grew excited, despite myself, while actually teaching. So the dervish was tired after a lecture, and had to catch his breath before returning to work, yet another delay. Later, having read about the life of Ludwig Wittgenstein, a semi-nutty philosopher (more than semi, actually), I felt great respect for, indeed identification with, the man's intensity. My respect did not extend to philosophy, the subject of Wittgenstein's labors. But the intensity, the utter immersion in one's work, to nearly the complete exclusion of everything else, was a quality for which Wittgenstein was a paragon. I approved of his way of living a life with all my heart, and had a private name for his and my phenotype: the Wittgenstein Syndrome. It can be illustrated by a passage in Bertrand Russell's memoir. Russell was a tutor, of sorts, to young Wittgenstein, a scion of wealthy Jewish family in Austria who renounced his inheritance, left Vienna and came to study with Russell in Cambridge, England. The story is about Russell, in the company of lady friends and Wittgenstein in tow, going to Cambridge river to watch a boat race. After a while, Russell saw an agitated Wittgenstein going back and forth on the embankment and muttering to himself. "What's up, Ludwig," called Russell. The man-child he addressed swung around and near-whispered, the indignation too great for a normal voice: "How can you, Bert, waste time on this meaningless, mind-numbing exercise, when the work remains undone?!" And he strode away. "Good for you, Ludwig," I thought, happy for Wittgenstein and for myself too, as I shared the attitude wholeheartedly.

*How well did you adapt yourself to your new life, to the transition that was so abrupt? Were you well prepared for this job? Did you have to catch up? How did you readjust yourself from the Soviet system of science to the American one, with its competition for grants, etc.?*

My first year at MIT, when I worked alone, could buy supplies anytime, and had access to equipment I needed, was happiness itself. I usually walked from my apartment to MIT in late morning, having returned home the night before as late as I could. I often sang aloud on the way to MIT, beginning another day of work I loved, with no bosses in sight and no shortages of equipment or reagents. I knew the experiments to do, or thought I knew, and didn't worry a single bit about grants, tenure and things of that sort. The reason was simple. Having escaped from a constricting professional life in Russia, I sensed my total commitment to the craft, which I did

not perceive as a profession at all, but rather as the only thing I would ever wish to do, the only thing worth spending life on. Such a feeling, impossible to acquire at will, renders one much less vulnerable to usual career concerns. I knew there would always be a bench for me to work at. If I were good at what I did, a lab and co-workers would be there too. I resided, at last, in a place where excuses didn't apply: I could no longer blame anything or anyone but myself for professional failures, if such were to occur. My attempting to move to the West was propelled, in part, by desire to find such a place, and I did. That alone kept my spirits up.

The actress Barbara Hershey played in Martin Scorcese's movies, and said this a few years ago to Mark Singer, who was writing a piece about Scorcese: "... Who knows what talent is? ... I don't think talent is as rare as the need to express it or the strength to handle the rejection. I don't think Marty can help it; there is nothing else he can do with his life." Irrespective of what I think about Scorcese's films, Hershey's description of the phenotype is dead-on, including resilience in a world where failure is right around the corner. The accompanying cost — an obsessive, often narrow personality — is endemic amongst denizens of science and other competition-heavy fields. Marvin Minsky's remark sums up the downside: "If there's something you like very much, you should regard this not as you feeling good but as a kind of brain cancer, because it means that some small part of your mind has figured out how to turn off the other things."

I sensed, dimly at first, that I will eventually come to see the rest of life, its everyday's array, including entertainment, travel and even human relations, as too predictable, let alone disappointing, and would begin to distance myself, graciously if I could. This outlook was incipient then, for I was still too young for it, and was curious about the world I fell into. But my later selves kept gravitating to that premonition, with two exceptions. One was literature, both fiction and nonfiction. Finding and reading good books (and occasional schlock) gave me pleasure, laughter, understanding, and kept alive the suppressed desire to be a writer. I also had a pipe dream: meeting a woman who would become a wife as a soulmate, a person whose closeness would fulfill one's entire need for human contact. A hermitage of two, with total absence of inattention and selfishness that are the stuff of life and that I knew many marriages to suffer from. Improbably, that hope came true with my fourth marriage, to Vera, whom I met in the 1980s in

Vera and Alexander Varshavsky in 2001.

New York. She was a physician, and loved her profession even more than I did mine, if that was possible. Her patients were lucky people. We got married in 1990. Our closeness, trust and mutual dependence did not arrive in one day, and are a major blessing, for both of us.

The year 1978, my first year away from Russia, had a quality that never recurred, in part because I worked alone. Being perpetually short of time, I ate in a hurry, mostly at self-service MIT joints or at McDonalds and Burger Kings. Fast food was tasty enough. That regimen went on for a year, until late fall of 1978, when I fell ill, most likely from avitaminosis and other nutritional misbalances. My "diet" of cheeseburgers and French fries ignored fruits and vegetables. Save for a bout of infectious mononucleosis at 16, I was never seriously ill before, and was baffled by rapidly worsening health: aches in the joints, wracking cough, difficulty sleeping, and frequent colds. I was rescued by a kind woman named Elena Erez, also an émigré from Russia. She saw the cause of my condition better than I, guided me to healthier food, and cooked for both of us. At the beginning of 1979, she moved to my Cambridge apartment.

I soon recovered, and resumed the usual hard work at MIT. Elena and I were discovering, gradually, that ours wasn't a durable union when she started to feel unwell, near the end of 1979. After several months of uncertainty, an aggressive cancer, leiomyosarcoma, was found. At the time of diagnosis we were unmarried, but got married soon afterwards. Elena

was educated (though not medically) and intelligent, but a diagnosis of cancer often diminishes one's rationality, especially if remedies are meager or nonexistent. I tried to hide the truth from Elena, describing spontaneous remissions and other optimistic stuff. But knowing, or at least suspecting, that hers was metastatic cancer with a poor prognosis, she wanted to try her luck with "healers" in the Philippines, who claimed to cure cancer and most other diseases by "operations" done with bare hands, without knives, as booklets that Elena received had described. The healers were also priests, or claimed to be such, and had their base of operations in Baguio, a city not far from Manila, the capital of Philippines.

We went there in early 1982, and stayed at a Baguio hotel owned by the racket that the "priests" ran. I expected charlatanism, but was still unprepared for its brazenness, and for the willingness of patients to be duped by low-grade magician's tricks. The patients were ill adults, like Elena, or parents with sick children, paying for every "operation", of which there were going to be "many". Unable to offer Elena a cure from her illness, I felt obliged to keep my view of the place to myself. Elena enjoyed living at a tropical resort and seemed not to notice that healers were mountebanks. After two weeks in Baguio, I had to go back to MIT, while Elena stayed at the hotel, where she preferred to be, saying that "treatments" were helping her. Three months later, I flew to Philippines again, and brought Elena home. She knew that her condition was getting worse. My mantra about spontaneous remissions, while politely listened to, was probably no longer believed. A course of utterly useless chemotherapy at the Boston's Beth Israel Hospital ensued, recommended to Elena by oncologists who (I bet) knew as well as I did that their witch's brew wasn't any better than "operations" in Philippines. Elena died in October 1982.

I kept working throughout that time, to the extent I could. By then, I had a functioning laboratory. Back in 1978, I had learned how to apply for grants. It wasn't difficult, just time-consuming. The competition for grants, while considerable, wasn't as depressingly cutthroat as it is today. By 1982, I had received two NIH grants, one for studies of eukaryotic chromosomes, the other for work with circular SV40 viral "minichromosomes", which served as a model of vastly larger (and linear) chromosomes of mammalian cells.

*How did you manage at the beginning? What studies did you do during your first years at MIT? How successful was your project, or perhaps projects?*

In the first year, from late 1977 to summer of 1978, I worked alone and continued studies that began back in Moscow. I used the SV40 minichromosomes isolated from virus-infected mammalian cells as models of cellular chromosomes, and tried to address the problem of nucleosome arrangement. Were nucleosomes distributed in a pattern that was specific vis-á-vis DNA sequence? Or was the arrangement quasi-random, in addition to being dynamic? (Nucleosomes are repeating superhelical turns of DNA wrapped around the oligomeric structural proteins called histones, with the adjacent nucleosomes connected by DNA segments called linkers.) To reduce potential nucleosome "sliding" (nothing was known about it at the time), I "fixed" isolated minichromosomes with the crosslinker formaldehyde, then treated them with restriction endonucleases, which cut SV40 DNA either once or at multiple specific sites. At first I learned little, but later saw that one site in the minichromosome was much more susceptible to cleavage than any other site. Remarkably, that single restriction site resided in the most "interesting" region of SV40, its origin of replication, an area of ~ 400 base pairs (bp) that also housed transcriptional promoters. Soon thereafter, an analogous experiment with the multiply cutting endonuclease *HaeIII* hit the jackpot: the above ~ 400 bp region could be "excised" from formaldehyde-fixed minichromosomes as a single fragment of histone-free DNA, in contrast to the rest of the minichromosome, which was still an intramolecular aggregate, held together by formaldehyde-produced DNA-histone and histone-histone crosslinks.

This and related advances yielded two insights: that the control region of SV40 minichromosomes was strikingly more exposed to endonuclease attack, and also that nucleosomes were either absent from that region or were in a configuration noncanonical enough to preclude histone-DNA crosslinks. These discoveries have become a major part of the modern understanding of chromosome organization, because later work, by us and many other labs, has shown that the exposed (nuclease-hypersensitive) regions, which allow access to DNA in the otherwise tightly coiled chromosomal fibers, are the universal feature of chromosomes at replication origins, transcriptional promoters, and other functionally important sites. The use of formaldehyde in that 1978–1979 work, which stemmed from my Moscow studies with Georgii Georgiev and Yuri Ilyin, was the precursor of later formaldehyde-based studies in my lab that led to the invention in 1988, by Mark Solomon, Pamela Larsen and myself, of a method for detection of the *in vivo* locations of specific chromosome-associated proteins. This

technique,[1] called the chromatin immunoprecipitation (CHIP) assay, has become a key method for mapping and dissecting the interactions of chromosomal proteins with DNA *in vivo*. Various incarnations of the CHIP assay,[1] including its most recent, genome-scale applications, are revealing the dynamic organization of multiprotein structures that assemble on transcriptional promoters, replication origins, and other functionally active sites in chromosomes.

In late spring of 1978, when I was completing the work that revealed nuclease-hypersensitive regions in chromosomes, two MIT graduate students, Olof Sundin and Michael Bohn, had joined the lab and the project. We published the first results in *Nucleic Acid Research* in 1978 and a more detailed account in 1979 in *Cell*, then a 5-year old publication founded and edited by Benjamin Lewin that had already become a leading journal in molecular biology and related fields. Two other groups, Carl Wu and Sarah Elgin at Harvard, and Walter Scott at the University of Florida, independently discovered nuclease-hypersensitive regions in chromosomes, using a different approach that involved nonspecific nucleases such as DNase I.

Bohn soon left MIT for a medical school, while Sundin and I continued working with SV40 minichromosomes. One day in late 1978, I was reading a paper on SV40, and noticed a faint "ladder" of bands of electrophoretically fractionated SV40 DNA. The paper's authors didn't comment on the "ladder". I got a wrong idea, at first, of what those bands might be, but even that idea was exciting enough to suggest to Sundin that we should try to establish whether the "ladder" was for real, and if it was, to figure out its nature and significance. Neither of us suspected that we were beginning a 3-year study that would lead, in 1980–1981, to a fundamental discovery: the first and universal pathway of chromosome segregation at the level of DNA.[2,3]

Briefly: when a circular chromosome such as SV40 begins its replication, two replication forks run from the origin of replication in opposite directions, meeting halfway around the circle and leaving behind two daughter minichromosomes. Analogous processes take place during replication of larger and linear chromosomes containing multiple origins of replication, except that a replication fork meets a fork running "toward" it from the adjacent origin. (In a mechanistically distinct but topologically equivalent model, it is the chromosomal fiber that moves, with replication forks being spatially fixed in the nucleus.) These pictures of chromosome replication had a problem that wasn't even recognized as such at the time:

how do the two converging replication forks (large nucleoprotein structures containing polymerases, helicases and other proteins) replicate the last several hundreds of nucleotide pairs that the forks themselves occupy? We discovered, in part through the invention of high-resolution, two-dimensional electrophoretic techniques for analyzing DNA replication intermediates (these methods are still employed in the field), that before the replicated daughter chromosomes segregated to yield individual circles, they went through a remarkable "topological" dance of being, at first, wound around each other as *multiply intertwined catenated DNA*,[2,3] a new form of DNA at the time, since only singly intertwined catenated DNA circles were detected before 1980.

We had shown that the transition from two circles of daughter chromosomes that are still linked through a remaining (short) DNA duplex to two separate circles proceeds through a set of intermediate structures, dimeric multicatenanes in which the two daughter circles intertwine around each more than 30 times. *In vivo*, under normal conditions, these essential intermediates are rapidly processed, one intertwining at a time, through the action of enzyme called topoisomerase II (topo II). We also found that while decatenation was going on, other enzymes, including DNA ligases, were filling in and sealing the initially gapped or nicked daughter DNA duplexes into uninterrupted (covalently closed) circular DNA. *In vivo*, the two processes could be shown to take place at the same time, so that a population of late replication intermediates was a dynamic "matrix" of many structures (distinguishable by our electrophoretic methods), with different (nicked or closed) states of individual circles and different levels of catenations (intertwinings) in the topologically linked replicated chromosomes. All of these structures, previously unseen and not even suspected to exist, rapidly converged *in vivo* to the final state: two covalently closed, separate chromosome circles, or two separate linear chromosomes, as shown later by other groups. Many subsequent studies have demonstrated that the chromosome segregation pathway we discovered in 1980–1981 with the SV40 minichromosomes[2,3] was both essential and universal, operating in all organisms, from eukaryotes to prokaryotes.

At the time of our work on the multicatenane-mediated chromosome segregation, topo II enzymes were a novelty, having been discovered, in the form of DNA "gyrase", by the Martin Gellert's laboratory in late 1970s, and characterized by his and other labs, notably by those of James Wang, Bruce Alberts and Nicholas Cozzarelli. One aspect of our insight was that

topo II was now expected to be essential for decatenating *multiply intertwined* daughter chromosomal fibers that formed at the final stages of chromosome replication and functioned as key replication intermediates.[2,3] That topo II was indeed essential for segregating chromosomes through the decatenation pathway was shown around 1985 by Connie Holm and David Botstein, then at MIT, by Rolf Sternglanz and co-workers at the University of New York at Stony Brook, and by Mitsuhiro Yanagida at the Kyoto University, Japan.

The segregation of chromosomes at mitosis involves two fundamental processes, acting together: one is the *decatenation of multiply intertwined daughter chromatids*, including those at the centromere of a mitotic chromosome.[2,3] The other is the *physical separation of sister chromatids*, pulled to the opposite poles by the spindle's microtubules. A critical part of the second segregation pathway was identified many years later, in 1999, by the laboratory of Kim Nasmyth, through the finding that a specific protease, termed separase, cleaved a subunit of oligomeric protein called cohesin (its molecules hold the sister chromatids together), thereby allowing the separation of sister chromatids,[4] *provided that their multiple DNA catenations had been resolved by the first segregation pathway*, discovered by us 25 years ago.[2,3]

Having been gradually swamped by ubiquitin studies in the lab (they began in 1978), I did not continue chromosome segregation work after 1983, and did not expect to return to that field, which grew from our elucidation of the first chromosome segregation pathway[2,3] into a major arena that encompasses both the mechanics of segregation and its regulation. But fate held a surprise. In 1999, Hai Rao (a postdoctoral fellow) and I saw, in a paper by the Nasmyth lab, that a fragment of separase-cleaved cohesin subunit bore N-terminal arginine, which our previous work had shown to be a degradation signal in short-lived proteins, recognized by the ubiquitin-dependent N-end rule pathway. Hai and I wished to determine whether that fragment of cohesin was in fact short-lived *in vivo*, and if so whether its degradation was functionally important. In 2000–2001, our collaboration with Frank Uhlmann (then a postdoc in the Nasmyth lab) and Kim Nasmyth demonstrated that the N-end rule pathway indeed targeted the cohesin's fragment for degradation.[5] Crucially, this degradation was shown to be *essential* for the proper functioning of cohesin machinery and high-fidelity chromosome segregation.[5] Other investigators, particularly Douglas Koshland, had previously found that "upstream" events, including the activation of separase, are also regulated by the ubiquitin system.

Thus, my laboratory's studies of chromosome segregation ended up to underlie the understanding of this fundamental process at three levels: through the discovery, in 1980–1981, of the first (DNA-based) chromosome segregation pathway, which involves the *decatenation of multiply intertwined daughter chromosomes*[2,3]; through the discovery, in 1984–1988, of *the essential role of ubiquitin conjugation in the cell cycle*[5,6,14] (see below); and through the discovery, in 2001, that high-fidelity chromosome segregation requires the *destruction, by the N-end rule pathway, of separase-produced cohesin's fragment.*[5]

Other non-ubiquitin work of the early years included my finding, in 1981, that growth factors, such as hormones or tumor promoters, can strongly increase the *frequency* of gene amplification in mammalian cells under conditions of cytotoxic stress. (The lab was small then, and I could still work at the bench.) The phenomenon of gene amplification was discovered in 1978, by Frederic Alt and Robert Schimke. What I found was that this process could be greatly accelerated under certain conditions, including those mentioned above. Analogous gene amplification events contribute to rapid evolution of cancer cells in a tumor, and to the emergence of drug-resistant cells during anti-cancer therapy. Thea Tlsty and Robert Schimke independently discovered, also in 1981, the same phenomenon of induced (accelerated) gene amplification.

In 1984, Francois Strauss (then a postdoc in the lab) and I demonstrated that the previously-developed (by Donald Crothers and Arnold Revzin) gel shift assay, which until then was used for studies of purified DNA-binding proteins such as Lac repressor, could be employed to detect specific DNA-binding proteins in the presence of other DNA-binding proteins, including nonspecifically binding ones. That 1984 work[4] converted the gel shift assay into an exceptionally powerful method for detecting specific DNA-binding proteins in crude extracts. Since then, this method has become a major tool in studies of gene expression.

Ubiquitin, a small protein universal amongst eukaryotes, entered my life in 1977. Ubiquitin studies in the lab initially competed with other projects, some of which are described above. The situation changed abruptly in 1980–1981, when I saw that there might be a genetic route to discovering the *biological significance and specific functions* of the ubiquitin-dependent proteolysis. This proteolysis had just been demonstrated by Avram Hershko's laboratory in Israel, in experiments with cell-free systems and isolated enzymes.[6,7] My laboratory's ubiquitin and non-ubiquitin studies continued

in parallel for several years afterwards, with ubiquitin gradually taking over the entire lab.

*Was there any difficulty with receiving tenure at MIT?*

I was granted tenure in 1982, largely on the basis of our non-ubiquitin contributions, some of which are described above. By that time, the lab was still small (if I recall correctly, 4 or 5 people), but reasonably well established. The work that led, by 1984, to the first biological breakthrough in the understanding of the ubiquitin system began in 1981, by me and Daniel Finley, then a graduate student. (Other ubiquitin research by the lab started in 1978, but until 1981 it did not involve proteolysis.) Having been interested in chromosome studies, I had difficulty leaving them, but saw that the lab would have to do it if I was committed to follow my hunch in 1980 that the ubiquitin system (then an interesting *in vitro* finding, undefined biologically) was likely to be both complex and uncommonly multifunctional.

*How and why did you begin the ubiquitin work? What was key insight or insights? How did it develop in your lab?*

There were few similarities between my Moscow milieu and the astonishing new life. The libraries were one of them. They were just as quiet and pleasant in Cambridge as in Moscow, and a library at MIT soon became my second home. Reading there in late 1977, I came across a curious paper, of the same year, by Ira Godknopf and Harris Busch. They found a DNA-associated protein that had one C-terminus but two N-termini, an unprecedented structure. The short arm of that Y-shaped protein was joined, through its C-terminus, to an internal lysine of histone H2A. The short arm was soon identified, by Margaret Dayhoff, as ubiquitin (Ub), a universally present protein of unknown function that was described (as a free protein) by Gideon Goldstein and colleagues in 1975.

I got interested in that first ubiquitin conjugate, Ub-H2A. Back in Russia, I had begun to develop a method for high-resolution analysis of nucleosomes, based on electrophoresis of DNA-protein complexes in a low-ionic-strength polyacrylamide gel, a forerunner of the gel shift assay (see above). At MIT, my first postdoc Louis Levinger and I developed this method further in 1978–1982, by adding the second-dimension electrophoresis of either DNA or proteins, and mapping the spots of fractionated

DNA by southern hybridization. We located Ub-H2A in a subset of the nucleosomes, succeeded in separating these nucleosomes from those lacking Ub-H2A, and showed that ubiquitin-containing nucleosomes were enriched on transcribed genes and absent from transcriptionally inactive regions such as centromeric heterochromatin.

In the meantime, Avram Hershko, his graduate student Aaron Ciechanover and their colleagues in the Hershko laboratory at the Technion (Israel) were studying ATP-dependent protein degradation in extracts from rabbit reticulocytes. In 1978–1980, they found that a small protein, termed APF1 (ATP-dependent proteolytic factor 1), was covalently conjugated to proteins before their degradation in the extract. In 1980, they suggested that a protein-linked APF1 served as a signal for a downstream protease, and began dissecting the enzymology of APF1 conjugation. In 1981–1985, through the elegant use of biochemical fractionations and enzymology, Hershko and co-workers identified a set of three enzymes involved, termed E1 (ubiquitin-activating enzyme), E2 (ubiquitin carrier protein or ubiquitin-conjugating enzyme) and E3 (an accessory component that appeared to confer specificity on E2). Although our studies of ubiquitin in chromosomes began in 1978, I didn't know about the 1978 APF1 paper by Hershko and co-workers, since the identity of APF1 and ubiquitin was unknown, at the time, to them as well. The disposition changed in 1980, when APF1 and ubiquitin were shown to be the same protein, by Keith Wilkinson, Michael Urban and Arthur Haas, who worked in the lab of Irwin Rose, a collaborator of Hershko during his sojourns at Philadelphia's Fox Chase Cancer Center.

When I read the 1980 papers by Hershko *et al.* and Wilkinson *et al.* that described, respectively, the APF1 conjugation and the identity of APF1 and ubiquitin, two previously independent realms, protein degradation and chromatin-associated ubiquitin, came together for me, suggesting a regulatory system of great complexity and broad, still to be discovered biological functions. I decided to find genetic approaches to the entire problem, because a system of such complexity was unlikely to be understood through biochemistry alone. In 1980, reverse genetic techniques were about to become feasible with the yeast *Saccharomyces cerevisiae*, but were still a decade away in mammalian genetics. I kept reading, as widely as I could. Near the end of 1980, I came across a paper by M. Yamada and colleagues that described a conditionally lethal, temperature-sensitive mouse cell line called ts85. The researchers showed that a specific nuclear protein disappeared at elevated

temperatures from ts85 cells, and suggested that this protein may be Ub-H2A. Glancing at their data, I had to calm down to continue reading, being virtually certain that the protein was Ub-H2A: in the preceding two years we had learned much about electrophoretic properties of this ubiquitin conjugate. On the hunch that mouse ts85 cells might be a mutant in a component of the ubiquitin system, I wrote to Yamada, and received from him, in 1981, both ts85 and the parental ("wild-type") cell line.

Daniel Finley, then a graduate student, joined my lab at that time, to study regulation of gene expression. He didn't need much convincing to switch to ts85 cells. A few months into the project, Finley and I made the critical observation that ubiquitin conjugation in an extract from ts85 cells was temperature-sensitive, in contrast to an extract from parental cells. While this was going on, I met Ciechanover, who came from the Hershko laboratory in Israel for a postdoctoral stint in the MIT lab of Harvey Lodish, and was studying growth factor receptors. Presuming that Ciechanover was still interested in ubiquitin (very few people were), I told him about our results with ts85 cells, and invited him to join, part-time, with Finley and me to complete the ts85 study. Ciechanover did, the work continued, and in 1984 we submitted two papers that described, primarily, the following discoveries: (i) mouse ts85 cells have a temperature-sensitive ubiquitin-activating (E1) enzyme; and (ii) these cells, in contrast to their wild-type counterpart, stop degrading the bulk of their short-lived proteins at nonpermissive temperature.[5,6]

This was the first evidence that ubiquitin conjugation was required for protein degradation *in vivo*. (The earlier studies by Hershko and co-workers were done with cell-free systems.) The results with ts85 cells also indicated that ubiquitin conjugation was essential for cell viability, the first hint of the enormous, many-sided biological importance of the ubiquitin system. In addition, ts85 cells were preferentially arrested in the G2 phase of the cell cycle, and the synthesis of heat-stress proteins was strongly induced in these cells at the nonpermissive temperature, suggesting that ubiquitin conjugation was involved in the cell cycle progression and stress responses.[5,6] In 1983, Tim Hunt and colleagues discovered unusual proteins in sea urchin and clam embryos. These proteins, which they called cyclins, were degraded during the exit from mitosis. We suggested in 1984[5,6] that cyclins were destroyed by the ubiquitin system, a hypothesis shown to be correct in 1991, by Michael Glotzer, Andrew Murray and Marc Kirschner, and independently by Hershko and co-workers as well.

It may be helpful to place the above advance in historical context. Despite some hints to the contrary, until the 1980s and the two 1984 *Cell* papers,[5,6] the prevailing view was that intracellular protein degradation was a simple and even mundane process, serving largely to dispose of "aged" or otherwise damaged proteins. Cellular regulation was believed to be a separate affair, mediated primarily by repressors and activators of gene expression, which were assumed, often tacitly, to be long-lived. Among the reasons for this lopsided perspective was the difficulty of connecting the long-recognized proteolytic system in the lysosomes to specific pathways of intracellular regulation. Thus, most people studying gene expression in the 1960s and 1970s assumed that the regulatory circuits they cared about did not involve short-lived proteins. As we know now, just the opposite proved true, especially in eukaryotes, where most regulators of transcription are conditionally short-lived proteins whose levels in a cell are determined at least as much by the rates of their ubiquitin-dependent destruction as by the rates of their synthesis. Ironically, the first physiological (as distinguished from artificial) substrate of the ubiquitin system was a transcriptional regulator, Mat$\alpha$2, which Mark Hochstrasser (then a postdoc) and I demonstrated in 1990 to be short-lived *in vivo*, and delineated its degradation signal.[7] As mentioned above, a mitotic cyclin was the second such substrate identified, in 1991.

In addition to having been a breakthrough that indicated the importance, indeed the requirement, of the ubiquitin system for intracellular proteolysis, cell viability and cell cycle progression, the ts85 papers were also the first instance of a study that addressed the *in vivo* workings of this system. In 2004, this pair of 1984 papers[5,6] was selected for re-publication by the editors of *Cell* as being amongst the most important papers that have been published in the *Cell*'s 30-year history. In a review accompanying re-publication, Cecile Pickart, one of the early pioneers in the ubiquitin field, summed up the papers' contribution: "*The two papers ... led to a new world-view; not only was the ubiquitin/proteasome pathway a major proteolytic mechanism in the average mammalian cell, but it was also likely to regulate cell cycle progression. These conclusions are so well accepted today that it is difficult to appreciate the magnitude of their impact at the time the two papers appeared.*"[8]

Although the ts85 discoveries left little doubt, among the optimists, about the importance of the ubiquitin system in cellular physiology, it was difficult to extend these findings in the same system, owing to limitations of mammalian somatic cell genetics, which was hampered at that time by

the impossibility of altering genes at will. In addition, the advances with ts85 cells produced little more than hints about *specific* physiological functions of the ubiquitin system, and also did not address another fundamental problem: the *source of specificity* of ubiquitin conjugation, i.e., the existence and structure of degradation signals, the features of proteins that make them the targets for ubiquitylation.

Therefore in 1983, even before the completion of ts85 work, Dan Finley and I, together with other colleagues in the lab, began systematic analysis of the ubiquitin system in the genetically tractable yeast *S. cerevisiae*, a project that soon expanded to occupy the entire laboratory. Between 1983 and 1990, this work revealed the first *specific* biological functions of ubiquitin conjugation. (Our ts85 results[5,6] demonstrated the importance of the ubiquitin system in general physiological terms, such as the overall *in vivo* proteolysis and cell viability, but only hinted at more specific functions.) Briefly mentioned below are key advances of those early years that established the physiological fundamentals of the ubiquitin field.

In 1984, Engin Özkaynak, Finley and I cloned the first ubiquitin gene, and found it to encode a polyubiquitin precursor protein.[9] By 1987, we showed that this gene, UBI4, was strongly induced by a variety of stresses, and that a deletion of UBI4 resulted in stress-hypersensitive cells.[10] These genetically based results validated and deepened the earlier indirect evidence with mouse ts85 cells,[5] thereby establishing one broad and essential function of the ubiquitin system.

In 1986, Andreas Bachmair, Finley and I discovered, through the invention of the ubiquitin fusion technique, the first degradation signals (degrons) that target proteins for ubiquitin conjugation and proteolysis.[11] By revealing the *basis of specificity* of intracellular protein degradation, this critical advance has spawned the field of degradation signals, a major arena of current research. One set of degrons discovered in 1986 gives rise to the N-end rule, a relation between the *in vivo* half-life of a protein and the identity of its N-terminal residue.[11] The seemingly simple N-end rule is underlied by the remarkably complex N-end rule pathway, whose functional and mechanistic understanding has gradually become a major project in the lab. The N-end rule pathway is still a focus of our work, surprising us by what it has up its sleeve, including its functions, which continue to emerge.[12]

In 1987, Stefan Jentsch, John McGrath and I discovered that RAD6, a protein known to yeast geneticists as an essential component of DNA repair pathways, was a ubiquitin-conjugating (E2) enzyme, the first such

enzyme to mediate a specific physiological function.[13] We noticed that the sequence of RAD6 was weakly similar to that of CDC34, an essential cell cycle regulator (of unknown enzymatic activity) defined genetically by Leland Hartwell. In 1988, a collaboration between Breck Byers's and my laboratories demonstrated that CDC34 was indeed a ubiquitin-conjugating enzyme.[14] This discovery produced the first definitive evidence for a function of the ubiquitin system in cell cycle control, a role suggested but not proved by our earlier ts85 studies.

In 1989, Dan Finley, Bonnie Bartel and I discovered the functions of the other yeast ubiquitin genes, UBI1–UBI3, which were shown to encode fusions of ubiquitin to one protein of the large ribosomal subunit and one protein of the small ribosomal subunit,[15] an arrangement conserved from yeast to mammals. *In vivo* experiments with mutationally altered yeast UBI proteins indicated that the presence of ubiquitin in front of a ribosomal protein moiety, despite being transient *in vivo*, was required for the efficient biogenesis of ribosomes. Remarkably, ubiquitin acts, in these settings, not as a degradation signal but as a cotranslational chaperone. This first nonproteolytic function of ubiquitin, mediated by its fusions to ribosomal proteins,[15] appeared to be an exceptional case until years later, when Linda Hicke and Howard Riezman demonstrated that ubiquitylation of a plasma membrane-embedded receptor signals its endocytosis. Ubiquitin is now recognized to have numerous nonproteolytic functions.

In 1989, Vincent Chau and other colleagues in my laboratory discovered that ubiquitin conjugation results in a *polyubiquitin* chain of unique topology, with links between adjacent ubiquitin moieties through a specific lysine residue of ubiquitin.[16] We also showed that a substrate-linked polyubiquitin chain was essential for the substrate's degradation by the proteasome,[16] yet another beginning of what, nowadays, is a major arena of ubiquitin studies.

In 1990, Bonnie Bartel, Ingrid Wünning and I, through the use of genetic and biochemical approaches, cloned and characterized the first specific E3 ubiquitin ligase, UBR1, the *S. cerevisiae* E3 of the N-end rule pathway.[17] Many more E3 enzymes, whose mechanistic functions include the recognition of specific degradation signals in targeted proteins, have been identified in 1990s and later, a process of discovery that continues as I write, in part because the number of distinct E3 ubiquitin ligases in a mammal is estimated, at present, to exceed a thousand.

A key feature of the ubiquitin-dependent protein degradation is subunit selectivity, i.e., the ability of the ubiquitin system to eliminate one subunit of

an oligomeric protein or a multiprotein complex, leaving intact the rest of it and thereby making possible *protein remodeling*. This fundamental capability was discovered in 1990 by Erica Johnson, David Gonda, and myself, in the context of the N-end rule pathway.[18] Also in 1990, Mark Hochstrasser and I detected subunit selectivity in the degradation of Mat$\alpha$2 (see above), the first physiological substrate of the ubiquitin system.[7] Subunit-selective proteolysis is one of the most fundamental capabilities of the ubiquitin system, a feature both powerful and flexible, in that it enables protein degradation to be wielded as an instrument of protein remodeling for either positive or negative control. Among many examples are activation of a major transcription factor NF-$\kappa$B via degradation of its inhibitory subunit I$\kappa$B, and inactivation of cyclin-dependent kinases (which drive the cell cycle oscillator) via degradation of their regulatory cyclin subunits.

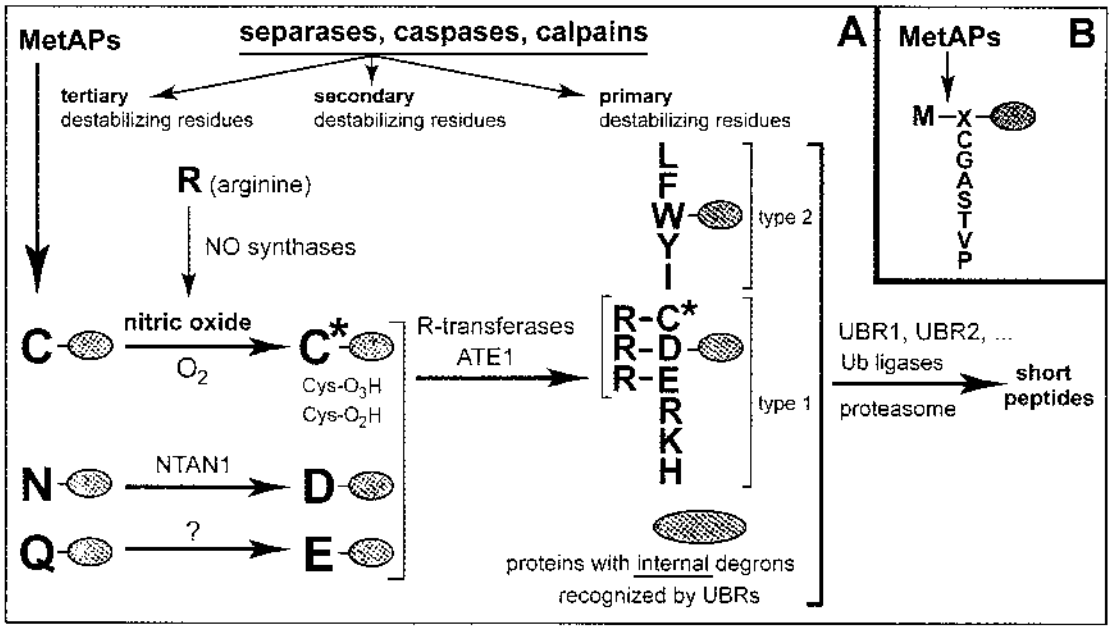
In summary, the complementary discoveries in the 1980s by Avram Hershko and co-workers, and by my laboratory, then at MIT, revealed three sets of previously unknown facts:

(1) That the ATP-dependent protein degradation involves a new protein modification, ubiquitin conjugation, which is mediated by specific enzymes, termed E1, E2 and E3.

(2) That the selectivity of ubiquitin conjugation is determined by specific degradation signals (degrons) in short-lived proteins, including the degrons that give rise to the N-end rule.[11]

(3) That ubiquitin-dependent processes play a strikingly broad, previously unsuspected part in cellular physiology, primarily by controlling the *in vivo* levels of specific proteins. Ubiquitin conjugation was demonstrated to be required for the protein degradation *in vivo*,[5,6] for cell viability, and also — more specifically — for DNA repair,[13] the cell cycle,[14] protein synthesis,[15] transcriptional regulation,[7] and stress responses.[9,10] In addition, ubiquitin-dependent proteolysis was discovered to involve a substrate-linked polyubiquitin chain of unique topology that is required for protein degradation.[16] The ubiquitin system was also discovered to possess the critically important property of subunit selectivity, i.e., the ability to destroy a specific subunit of oligomeric protein, leaving intact the rest of it and thereby making possible *protein remodeling*.[18]

The Hershko laboratory produced the first of these fundamental advances (item 1), and my laboratory produced the other two (items 2 and 3). Over



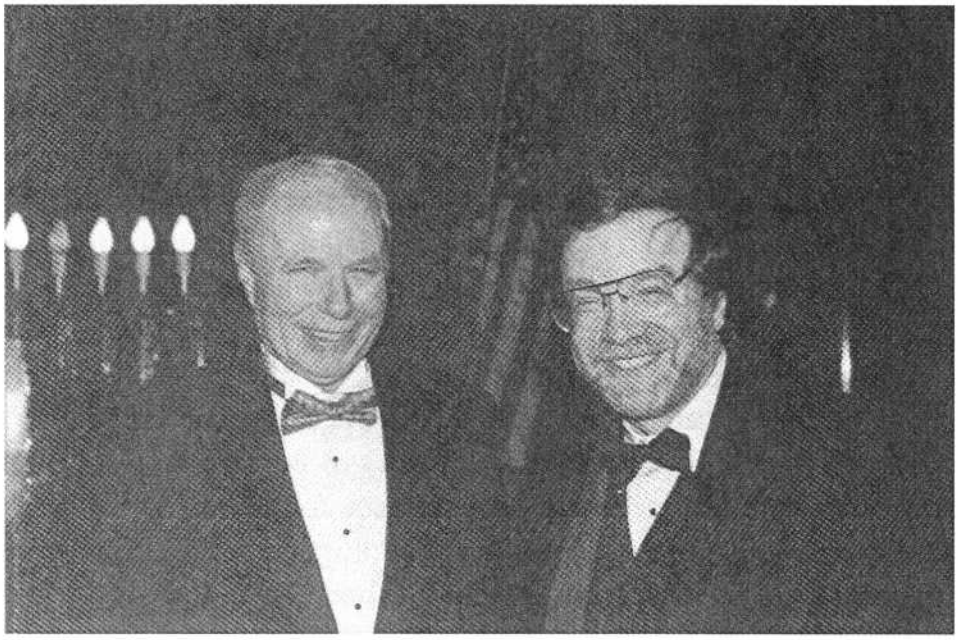

(A) The N-end rule pathway in mammals. This proteolytic pathway was the first specific pathway of the ubiquitin system to be discovered, initially in yeast.[11] It is present in all eukaryotes examined, from fungi to animals and plants. Although prokaryotes lack ubiquitin conjugation and ubiquitin itself, they, too, contain the N-end rule pathway, a ubiquitin-independent version of it.[19] Studies of this pathway, its mechanisms and functions, have gradually become a major focus of my laboratory. N-terminal residues are indicated by single-letter abbreviations for amino acids. The ovals denote the rest of a protein substrate. MetAPs, methionine aminopeptidases. The "cysteine" (Cys) sector, in the upper left corner, describes the recent discovery of a nitric oxide (NO)-mediated oxidation of N-terminal Cys, with subsequent arginylation of oxidized Cys by ATE1-encoded isoforms of Arg-tRNA-protein transferase (R-transferase).[12] This advance identified the N-end rule pathway as a new kind of NO sensor. $C^*$ denotes oxidized Cys, either Cys-sulfinic acid ($CysO_2(H)$) or Cys-sulfonic acid ($CysO_3(H)$). The type 1 and type 2 primary destabilizing N-terminal residues are recognized by multiple E3 ubiquitin ligases of the N-end rule pathway, including UBR1 and UBR2. Through their other substrate-binding sites, these E3 enzymes also recognize internal (non-N-terminal) degradation signals (degrons) in other substrates of the N-end rule pathway, denoted by a larger oval.
(B) MetAPs remove Met from the N-terminus of a polypeptide if the residue at position 2 belongs to the set of residues shown.

the last 15 years, these complementary "chemical" and "biological" discoveries in the 1980s caused the enormous expansion of the ubiquitin field, which became one of the largest arenas in biomedical science, the point of convergence of many disparate disciplines. Our biological discoveries,[5–18] together with later studies by many excellent laboratories that entered the field in

the 1990s, have yielded the modern paradigm of the central importance of regulated proteolysis for the control of the levels of specific proteins *in vivo*, as distinguished from their control by transcription and protein synthesis. In other words, these advances revealed that the *control through regulated protein degradation rivals, and often surpasses in significance, classical regulation through transcription and translation.* This radically changed understanding of the logic of biological circuits will have (in fact, is already having) a major impact on medicine, given the astounding functional range of the ubiquitin system and the multitude of ways in which ubiquitin-dependent processes can malfunction in disease or in the course of aging, from cancer and neurodegenerative syndromes to perturbations of immunity and many other illnesses, including birth defects. A number of pharmaceutical companies are developing compounds that target specific components of the ubiquitin system. The fruits of their labors have already become, or will soon become, clinically useful drugs. Efforts in this area may yield not only "conventional" inhibitors or activators of enzymes but also more sophisticated drugs that will direct the ubiquitin system to target, destroy, and thereby inhibit functionally any specific protein. I feel privileged having been able to contribute to the birth of this field, and to partake in its later development. The dynamism and surprises of this endeavor remain undiminished even today, two decades after the 1980s.

*You have received, jointly with Avram Hershko, just about every major award in biology, including the Lasker Award, which you shared with Hershko and Ciechanover. Were you surprised not to have been included in the 2004 Nobel Prize in Chemistry?*

I did not expect the Nobel Prize for ubiquitin work to be in Chemistry, rather than in Physiology/Medicine. The juries of scientific awards I received, jointly with Avram Hershko or with Hershko and Ciechanover, have done their homework, making clear the issues of credit. An easy task, given the unambiguous record of publications. In sum, the answer is yes: I couldn't help being surprised, at first, by the news in October 2004. Things became clear a bit later, when I saw the actual citation of the 2004 Nobel Prize in Chemistry: "*For the discovery of ubiquitin-mediated protein degradation.*" This citation lacks the second, biological (function-based) part, in contrast to all citations of the (earlier) joint awards to Hershko and me. In other words, the Chemistry Nobel Committee paid attention to the citation's accuracy, demarcating the Chemistry award as the one for the mechanistic



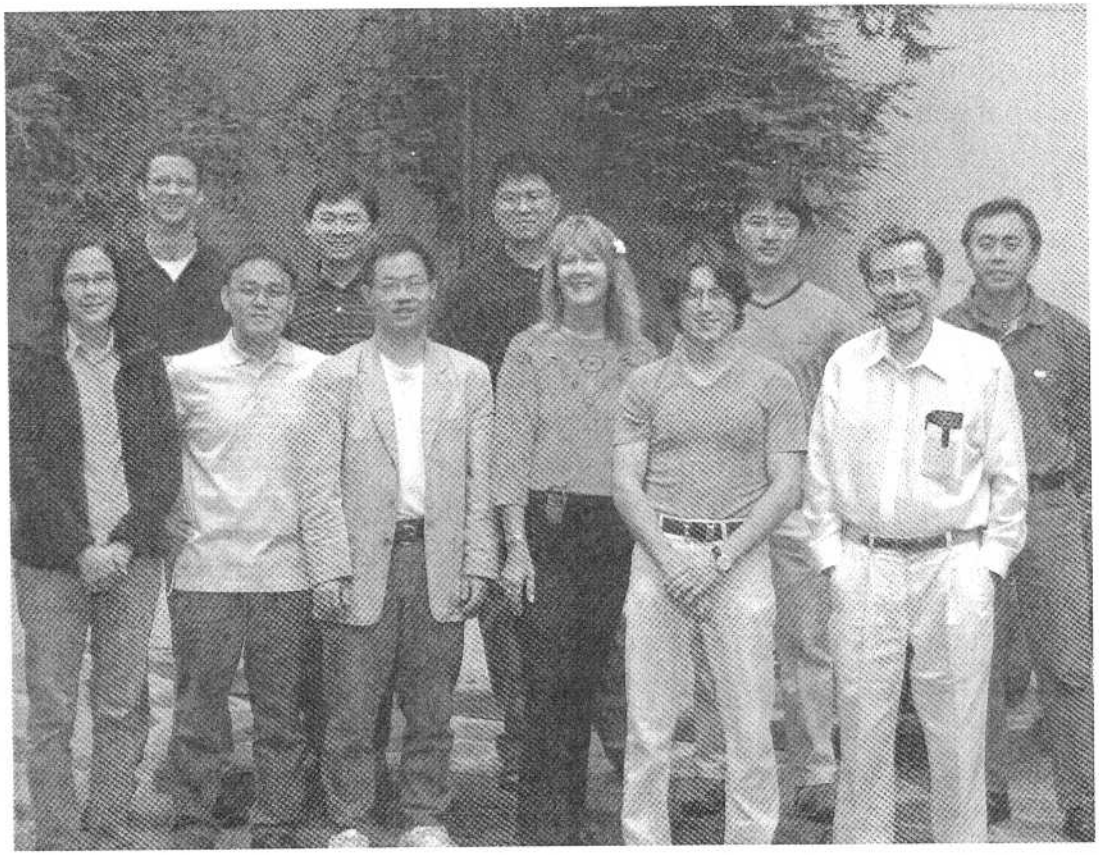
Avram Hershko and Alexander Varshavsky at the Horwitz Prize reception, Columbia University, New York, 2001.

("chemical") contribution. In doing so, the Chemistry Committee separated the initial mechanistic discovery by Hershko, his student Ciechanover and his collaborator Rose from the function-based discoveries in the 1980s by my laboratory, and by other groups afterwards. I presume that the careful wording of citation by the Chemistry Committee was intended to avoid interference with a recognition, at a later time, of the complementary biological (physiological) discoveries. I cannot be sure of this interpretation. It seems reasonable. A nonpolitical, courteous letter about the subject above, entitled "Varshavsky's Contributions" and signed by numerous colleagues in the ubiquitin field, including most of its leaders, was published in *Science* in November 2004 (*306*, 1290–1293, 2004). One should like, if one can, to behold prizes through the armor of irony and common sense. But the irony, too, has limits. I was touched by the *Science* letter.

*You had a meteoric rise at MIT. Why did you leave it? Looking back, was it worth it to leave MIT for Caltech? How do you compare the two places?*

My "career" at MIT was a standard one. Transitions, at a usual pace, from assistant to associate to full professor. I was happy at MIT, worked there

for 15 years and liked living in Cambridge/Boston. There are several U.S. universities whose overall quality is comparable to that of MIT (Caltech is one such place), but none of them is "better" than MIT, certainly not in biology. The decision to move to Caltech was prompted by an unexpected event. A letter arrived in 1990 from a colleague there, describing a new "endowed chair", a fancy version of full professor position. The colleague wrote that I could be considered for that position, alongside other candidates, if I was interested. I received, occasionally, such suggestions before, but not from universities as distinguished as Caltech. I showed the invitation to my wife Vera, knowing that she loved Southern California. We visited Caltech in February 1991. The charms of Pasadena's subtropical climate, the scientific quality of Caltech, a warm reception by colleagues there, and the (later) offer of position were compelling to both of us. The lab moved to Caltech in 1992, thirteen years ago. I'll always miss MIT. The colleagues



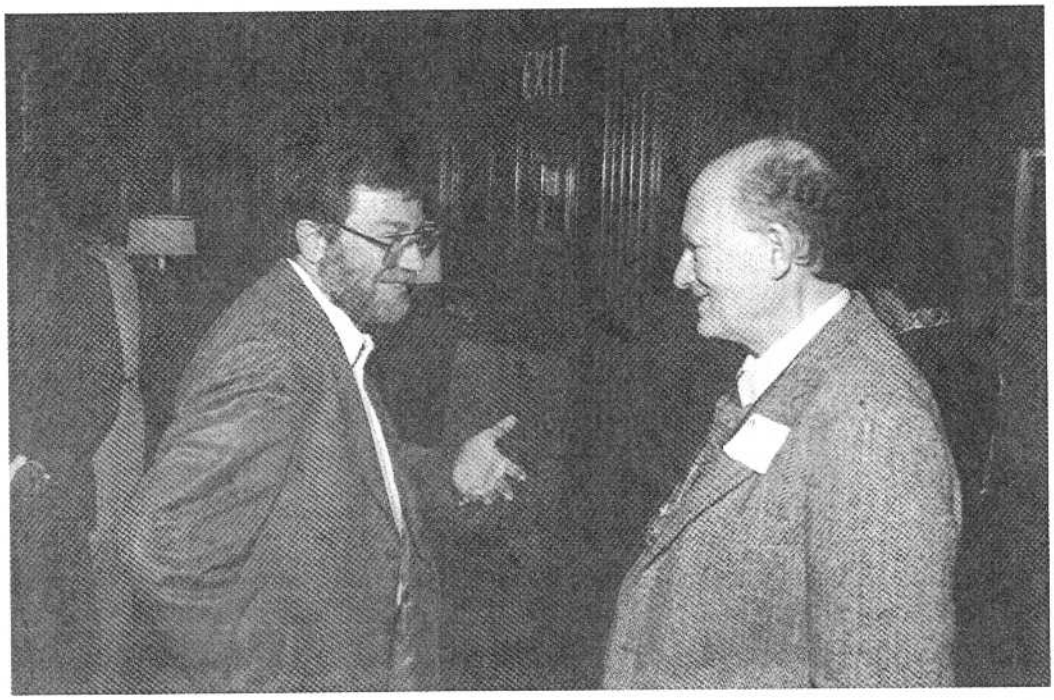
Varshavsky's laboratory at Caltech in 2004. Back row, from left, Christopher Brower, Jack Xu, Jianmin Zhou, Cory Hu, Jun Sheng; front row, from left, Emmanuelle Graciet, Cheol-Sang Hwang, Zanxian Xia, Janet Dyste, Konstantin Piatkov, and Alexander Varshavsky.

there were supportive and kind. Having begun to work at Caltech, I could see firsthand that it's a great place, unsurprisingly so, for it's akin to MIT in all respects but size (Caltech is smaller). Vera and I live in La Canada, a hamlet on a mountainside, close to Pasadena. Vera's grown-up son Roman, who became my son too, lives nearby. Bob Hoffman, my and Vera's dear friend and my comrade in the 1977 escape, lives in San Diego, California. He is professor at the University of California at San Diego, and heads a biomedical company as well.

*What are your current ambitions? What drives you nowadays when you get up in the morning and start a day in the lab? You have had a tremendous career and you are far from retirement, so how do you chart your next years?*

Percy Bridgman, a great experimental physicist, worked at Harvard in the first half of the 20th century, achieving previously impossible static pressures and using them to study materials under such conditions. To him belongs a definition of scientific method that I find delightful: "*The scientific method is doing your damnedest, no holds barred.*" Since the time I realized that nothing in life would ever interest me more than science, more than doing it, a description like Bridgman's would convey just about everything there is in my connection to the craft. I worked in several scientific fields, and continue to be interested not only in ubiquitin and proteolysis but in god knows what as well. I read widely, for it's a pleasure, and also because new ideas or directions for the lab's ongoing work might pop up in fields utterly away from it. I don't anticipate leaving the N-end rule pathway, a lovely, many-sided creature. Its new functions, some of them of medical relevance, are emerging left and right, yielding surprises[12] even two decades after the pathway's discovery.[11] There may be other adventures too. I have ideas for some, but the brevity of a day, let alone of life, puts a lid on one's flirtation with playing Leonardo in the 21st century. Even Leonardo wasn't all that good at being the Leonardo of our admiring, reality-distorting perception of him.

Seymour Benzer, a geneticist at Caltech and one of greatest biologists ever, is now 84. He runs a lab and does first-rate science. I hope to follow his example if I can, and if longevity cooperates. Never retiring, unless I'm asked to, or become unfit to continue. Playing this exacting, unpredictable, and deeply meaningful game to a hilt.



Alexander Varshavsky and Seymour Benzer at Caltech, 2004.

*Any thoughts about science in general?*

"He digs deep, but not where it's buried," averred the poet Anna Akhmatova, in a conversation cited by her biographer. She was speaking, naturally, of another poet. (Compared to writers, scientists positively love each other.) Akhmatova's unkind aphorism captures the predicament of anyone who aspires to innovation, be it a momentous way of stringing words together or major discoveries in science. There is a distinction, here, between a poet and scientist. A poet may despair of finding a way to connect an insight and its form of expression. He may never find that form, or he may find it the next minute. If he does, the result, a verse, is truly his own. While poetry is occasionally about content, it is primarily an alloy of content and form, and the form is poet-specific. (Hence the Robert Frost's definition of poetry as the part that "is lost in translation".) So the poet is, in a way, safe from being scooped. Other dangers, aplenty. But not that one. By contrast, in science a truth is a stickler for accuracy but cares little about the form. One must arrive at a truth first and mark the arrival by a published paper. The form, that unique identifier of individual, barely counts in science, and certainly does not in a long run. Hence the extreme competitiveness of scientists throughout the ages. Their genuine curiosity about the world

is warped and smothered by the haste to acquire narrow expertise and tools, lest that buried fruit is unearthed by another digger who is simply lucky, or better prepared, or (most often) both. The only thing I dislike about working in my beloved profession is my inability to enjoy a study by learning at a leisurely, pleasant pace, as broadly and gradually as I care, instead of being focused and intense. There must be scientists of sunny, relaxed, unhurried dispositions, but I never met such people amongst the peers whose discoveries are both first-rate and more numerous than one. Perhaps they are tranquil when they retire or become administrators. But they are not mellow in their prime.

## References


1. Solomon, M. J.; Larsen, P. L.; Varshavsky, A. "Mapping protein-DNA interactions *in vivo* with formaldehyde", *Cell* **1988**, *53*, 937–947.
2. Sundin, O.; Varshavsky, A. "Terminal stages of SV40 DNA replication proceed via multiply intertwined catenated dimers", *Cell* **1980**, *21*, 103–114.
3. Sundin, O.; Varshavsky, A. "Arrest of segregation leads to accumulation of highly intertwined catenated dimers: dissection of the final stages of SV40 DNA replication", *Cell* **1981**, *25*, 659–669.
4. Strauss, F.; Varshavsky, A. "A protein binds to a satellite DNA repeat at three sites which would be brought into proximity by DNA folding in the nucleosome", *Cell* **1984**, *37*, 889–901.
5. Finley, D.; Ciechanover, A.; Varshavsky, A. "Thermolability of ubiquitin-activating enzyme from the mammalian cell cycle mutant ts85" *Cell* **1984**, *37*, 43–55.
6. Ciechanover, A.; Finley, D.; Varshavsky, A. "Ubiquitin dependence of selective protein degradation demonstrated in the mammalian cell cycle mutant ts85" *Cell* **1984**, *37*, 57–66.
7. Hochstrasser, M.; Varshavsky, A. "*In vivo* degradation of a transcriptional regulator: the yeast $\alpha$2 repressor", *Cell* **1990**, *61*, 697–708.
8. Pickart, C. M. "Back to the future with ubiquitin", *Cell* **2004**, *116*, 181–190.
9. Özkaynak, E.; Finley, D.; Varshavsky, A. "The yeast ubiquitin gene: head-to-tail repeats encoding a polyubiquitin precursor protein", *Nature* **1984**, *312*, 663–666.
10. Finley, D.; Özkaynak, E.; Varshavsky, A. "The yeast polyubiquitin gene is essential for resistance to high temperatures, starvation, and other stresses", *Cell* **1987**, *48*, 1035–1046.
11. Bachmair, A.; Finley, D.; Varshavsky, A. "*In vivo* half-life of a protein is a function of its N-terminal residue", *Science* **1986**, *234*, 179–186.
12. Hu, R.G.; Sheng, J.; Qi, X.; Xu, Z.; Takahashi, T. T.; Varshavsky, A. "The N-end rule pathway as a nitric oxide sensor controlling the levels of multiple regulators", *Nature* **2005**, *437*, 981–986.

13. Jentsch, S.; McGrath, J. P.; Varshavsky, A. "The yeast DNA repair gene RAD6 encodes a ubiquitin-conjugating enzyme", *Nature* **1987**, *329*, 131–134.
14. Goebl, M. G.; Yochem, J.; Jentsch, S.; McGrath, J. P.; Varshavsky, A.; Byers, B. "The yeast cell cycle gene *CDC34* encodes a ubiquitin-conjugating enzyme", *Science* **1988**, *241*, 1331–1335.
15. Finley, D.; Bartel, B.; Varshavsky, A. "The tails of ubiquitin precursors are ribosomal proteins whose fusion to ubiquitin facilitates ribosome biogenesis", *Nature* **1989**, *338*, 394–401.
16. Chau, V.; Tobias, J. W.; Bachmair, A.; Mariott, D.; Ecker, D.; Gonda, D. K.; Varshavsky, A. "A multiubiquitin chain is confined to specific lysine in a targeted short-lived protein", *Science* **1989**, *243*, 1576–1583.
17. Bartel, B.; Wünning, I.; Varshavsky, A. "The recognition component of the N-end rule pathway", *EMBO J.* **1990**, *9*, 3179–3189.
18. Johnson, E. S.; Gonda, D. K.; Varshavsky, A. "Cis-trans recognition and subunit-specific degradation of short-lived proteins", *Nature* **1990**, *346*, 287–291.
19. Tobias, J. W.; Shrader, T. E.; Rocap, G.; Varshavsky, A. "The N-end rule in bacteria", *Science* **1991**, *254*, 1374–1377.

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# Contents

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