RICHARD EDELSON: My involvement with extracorporeal photochemotherapy, ECP, started at the beginning, because in fact, it was an accidental, very fortuitous discovery by me and my colleagues, then at Columbia University's College of Physicians and Surgeons. I was, at that time, a young, tenured full professor with a clinical expertise and a scientific expertise in the study of the properties of the malignant cells of cutaneous T-cell lymphoma.

I took care of very seriously ill patients with that disease. And I was continuously attempting to develop selective immunotherapy for the disease and even for the individual patients, because frankly, we weren't doing that well. Patients with the advanced disease were unresponsive in any meaningful long-term way to the combination of chemotherapy. And we were therefore attempting to exploit the scientific discoveries that we and others had made about the special properties of [INAUDIBLE] themselves.

What we had done already, and it set the stage for ECP, was that we had shown that we could use an anti-T-cell antiserum-- in those days, not yet monoclonal antibodies-- to treat the malignant disease. We would use that antibody intravenously. It would attack and destroy all sensitive T cells, including the malignant T cells of advanced cutaneous T-cell lymphoma. And we reported that study initially as the first use of an antibody against the malignancy in the medical journal *Lancet.*

The problem was that there were too many of the malignant cells to completely destroy. So although we had clinical responses, they were very short-lived, and the malignant cells found ways around it. So we took a step, which is what led to ECP, which was to say, we had those antibodies, but perhaps we could increase their efficacy if what we did is decrease the total amount of malignant cells, the so-called tumor burden in the patients, and now come back with the monoclonal antibodies, which we now could also use against T cells, and clean it up. So in other words, we needed a first treatment that would massively reduce the tumor burden, so that the antibodies that we were going to use were not like dumping water from a pail in the ocean.

The treatment that we devised was the crude antecedent of ECP. We knew that the drug 8-Methoxypsoralen, abbreviated 8-Mop, is a unique, naturally occurring molecule in nature that has no activity by itself. If you take it by mouth, it's excreted from the body in entirety in 24 hours. But if it encounters long-wave, i.e., low-energy ultraviolet light such as would come through a window glass, the drug gets activated instantaneously to this potent DNA cross linking chemotherapeutic agent, only where the light and the drug come together, and only for the milliseconds that follow a light exposure.

So we hypothesized that if we could use that drug, activated by light, shined on blood from patients that had a large number of malignant cells in their blood already-- in other words, they had leukemic and tissue phase-- pass that blood through an ultraviolet exposure field inside transparent plastic tubing and return it to the patient, perhaps we could kill a large number of the malignant cells, rely on the liver or the spleen, other components of the filtering reticuloendothelial system to remove the dying cells, and then, with a smaller tumor burden left, come back with those antibodies.

So we took five of my own patients with therapeutically resistant-- chemotherapy-resistant, actually-- cutaneous T-cell lymphoma in a leukemic phase, and tried this approach. It was the first time that anybody at least has reported treating the blood with a photo-activatable drug. What happened was the extraordinary thing that we now call photopheresis, ECP, because we actually got such a good response-- a complete response, in fact, in two of those five first patients-- that we never got to use the antibody.

We just, for reasons that we can discuss, realized that we were dealing with something very special in this strange, fortunate turnaround. Indeed, by treating those first two patients two days in succession at monthly intervals, waiting to see how safe this was, and doing that through three monthly cycles, we were astonished to get complete eradication of their T-cell malignancy.

We did it despite the fact we were treating all the cells in the blood that pass through the ultraviolet light field. We did it without encountering any generalized immunosuppression in a disease that normally ultimately kills patients, not only by heavy infiltration of vital organs, but by suppression of the normal immune system, and leading to opportunistic infections of the same type that can kill AIDS patients. That didn't happen at all.

So we were struck with the fact that we had, in two or five patients, somehow induced a tremendous immune reaction by only treating an estimated 3% to 5% of the malignant cells in the body, exposing them to this photo-activated drug, 8-Mop, returning those cells immediately to the patient, and leading to the kind of an immune reaction that no one had seen in any cancer, an immune reaction in which the other 90-plus percent of the more human cells, which had not been exposed to the light-activated drug, disappeared.

We had no idea at that time how this had happened, but we knew a few things. And I knew it, especially as a cutaneous T-cell lymphoma physician confronted with the care of these patients, my own patients with this advanced disease. we had no other therapy available to us in medicine at the time that could do something like that, even though it had only happened in two out of the five patients. The other three patients had advancing disease despite what we did.

But we knew that we had done something that appeared to be, for some mechanistic reason that medicine at the time, immunobiology of the time could not explain, had induced in patients that were previously immunologically tolerant of the malignancy, allowing it to regress-- we had somehow turned on a selective-- and the keyword is selective, we'll keep coming back to that-- immune reaction. It only knocked off the malignant cells, leaving the rest of the immune system intact.

Since immunology-- and at that time, I was also at Columbia. I was the director of the immunobiology component of the Columbia Cancer Center. I knew, and my colleagues knew, that whatever the principle was that we landed on, it was something that was not known. And that's how the entire quest that we'll talk about a bit occurred, because these are extremely exciting days. It turns out that we now know that principle, and it changes and opens the entire vista. That's where it came from. And that's where the GPS started.