Oral History Dr. Gary Peck

July 6, 2021

GM: I'm Dr. Gordon Margolin, a volunteer in the Office of NIH History and the Stetten Museum, about to initiate an oral history today, July 6, 2021, with Dr. Gary Peck. Dr. Peck is a dermatologist who spent 21 years, from 1969 to 1990, at NIH at the National Cancer Institute. He was a senior investigator in the Dermatology branch during those years.

Thank you, Dr. Peck for joining us for this interview today. I am very pleased to get to know you and to learn about your major accomplishments over these multiple years, largely at NIH. Just to become familiar as we start out, I would like first to learn briefly about your early years, when and where you were born, and a little about your early life and your family background. So I'll let you tell us the story in your own words.

GPeck: I was born in Detroit in 1938 and my childhood is unique in that I had three fathers and two mothers. My own father died suddenly at age 27 in 1941 from rapidly progressive pneumonia prior to the availability of penicillin. My mother was overwhelmed by his passing and as a result my grandparents took me to live with them for the next 10 years. In effect, they became my parents for those years. Eventually my mother remarried and my stepfather became my third father. He played a major role in my life. He was an archaeologist and at the point that he came into my life I was in junior high school. I was in the practical arts program and he made me change from practical arts to college prep in the 9th grade. I did not do it willingly, but it made a major difference in my life. He steered me toward classical studies like Latin and Ancient Greek and eventually to medicine. I went through the Detroit public school system and I went to the University of Michigan, both undergrad and medical school.

GM: And what year did you graduate medical school?

GPeck: 1962, a long time ago.

GM: Yes, well, time has a way of getting away from us. When did you know that you really wanted to be a physician?

GPeck: I basically wanted to be a teacher. In high school I was the top math and science student in my class and received an $100 award from the school. In college, I focused on science classes but I also took 8 English literature and 3 anthropology classes as well. Eventually, I evolved into becoming pre-med. I had never wanted to be a full-time private practitioner because the concept of running an office was not something that I looked on favorably. I preferred to be a teacher in an academic setting. That was my goal.

GM: But you went on with training as a physician.

GPeck: That's right. After graduating from medical school in 1962, I interned in San Francisco and then did my dermatology residency at the University of Chicago from 1963 to 1966. Dermatology training was different then. At the time our main journal was called the Archives of Dermatology and Syphilology. In my resident's clinic at the University of Chicago about 20% of my patients were workups for positive serology for syphilis. I actually did spinal taps, about one a month, to rule out neurosyphilis. This is very different from the type of training you get in dermatology now. Also we had a radiation therapy machine in our dermatology clinic. I actually performed radiation therapy for patients with basal cell carcinomas in the dermatology clinic. That's no longer the case today. We were also part of the University of Chicago Hospitals Department of Internal Medicine. As a result, we had to do a complete internal medical history and physical exam for each new dermatology patient. That is also something that is not done now in dermatology residency training.

GM: You're right. The nature of medical education has changed a great deal over these years, and the why and how and so forth are up for a lot of discussion but we won't get too deep into that today. When you finished your dermatology training, how long was that training?

GPeck: It was three years. That was a customary training period. People could choose to go on to do additional training, for example in a Mohs Surgery fellowship for skin cancer, or in dermatopathology. But the majority of dermatology residents limited their training to three years.

GM: After those three years, I guess you were due for some government service and that's what you did next. You probably didn't have a choice.

GPeck: Yes, I didn't have a choice. It was the Vietnam war era and I was, shall we say, recruited to go into the Air Force for two years from '66 to' 68. I was stationed at Wright-Patterson Air Force Base outside of Dayton, Ohio. We were the main evacuation hospital for the wounded from Vietnam for the northeast sector of the United States. I treated the dermatologic conditions of the soldiers returning home from Vietnam as well as the local soldiers and their dependents. I would see six patients an hour, eight hours a day, five days a week for the two years I was in the Air Force.

GM: It's not exactly the teaching role that you anticipated or envisioned for yourself.

GPeck: It was physically exhausting. But it turns out that half of the patients that I saw had warts, and half of the wart patients had plantar warts. I didn't want to spend the rest of my life being a wart doctor and I thought being in private practice would mean exactly what I had done in the Air Force. I didn't look forward to that career. As a result, after the Air Force, I returned to the University of Michigan and did a biochemistry fellowship with Dr. Isidore Bernstein, who was a biochemist in the Department of Dermatology.

GM: What did you do during that year? Was that a research year or was that a clinical experience?

GPeck: It was research. The goal was to isolate and characterize keratohyalin granules from the epidermis of newborn rat skin. Unfortunately, we were unsuccessful, but there was the benefit of being recruited from Dr. Bernstein's laboratory to NIH as a result of my having taken the biochemistry fellowship.

GM: I understand that. Now let me interrupt and ask you the question, what do you mean when you say keratohyalin granules? What is that?

GPeck: The epidermis is composed of several layers of cells—the basal layers, the spinous layers, the granular layers, then the stratum corneum. The granular layer is so named because of the presence of the cytoplasmic keratohyalin granules. We wanted to analyze them chemically and try and determine their function, but my efforts were not successful.

GM: Well, you came to NIH with the idea of continuing that particular study?

GPeck: But there was somebody already there who was working on the exact same project. Interestingly, instead of newborn rat epidermis which has only a two- or three-layer thickness of the granular layer, he found that fetal calf hooves have instead an 80 cell thick layer of stratum granulosum. Since the granules were far more abundant, he was able to extract them and isolate them and begin to characterize them. He was dedicated to continuing his research and I had to find a new project to study at NIH.

GM: But that's what got you into NIH, I gather.

GPeck: Right. Well, then, just the fact that I was research oriented, and the Dermatology Branch also needed a clinician who was research oriented to join their staff at NIH.

GM: You were working at the Clinical Center at that time?

GPeck: Yes, Building 10, Clinical Center, 12th floor.

GM: Seeing patients obviously?

GPeck: Yes, research patients

GM: Then, as you told me before, you had to go looking for another topic to do research on. You spent

time doing that. Tell us that story.

GPeck: Fortunately, my chief who recruited me, Dr. Marvin Lutzner, gave me six months library time in order to read everything I could and come up with a topic for my research at NIH. I happened to come across an article written by Dame Honor Fell from the Strangeways Research Laboratory in Cambridge, England, in which she took explants of embryonic chicken leg skin and put them in organ culture *in vitro* and added vitamin A to the medium. What was fascinating to me, frankly it's still fascinating, is that she found that the normal pathway of differentiation of the epidermis of the skin to produce keratin was suppressed, and instead of keratin being produced, mucin was produced. It was a fascinating discovery that a simple 300 molecular weight molecule could interfere with the differentiation pathway of the skin to change it from keratin-producing to mucin-producing. It seemed like an ideal project to investigate the mechanism of this process.

GM: I gather she was working with embryonic chicken skin of about 13 weeks gestation.

GPeck: Yes, that's right. So I did the same project but instead of vitamin A I used retinoic acid.

GM: Let me ask you, when you compare the two skins—the chicken skin and the human skin—are they very similar?

GPeck: Yes, in the sense that they both produce keratin. But adult human skin is not capable of undergoing mucous metaplasia and in order to culture it, you have to use embryonic skin that is not already committed to keratin formation. There might be a stage in human development where, if you had an early aborted fetus, that you might try it but it's not something that's readily available to study. We can't say whether this process would occur in human embryonic tissue.

GM: You didn't actually take embryonic human skin and try to duplicate her work.

GPeck: Not human skin. No, I did chicken skin.

GM: So you also did chicken skin. What promoted or what caused her to work on chicken skin with vitamin A? What was the tie-in there?

GPeck: Good question. I can't recall the initial thinking that led her to choose that. It's possible there might have been a previous article that I was unaware of. That same transformation has been seen in other tissues though. There was a doctor at the University of Guelph in Ontario who plucked the vibrissae from mice and was able to transform the hair root cells from keratin- producing to mucin-producing by exposing them to vitamin A in organ culture. Also, at NYU, Dr.Larry Prutkin was able to treat carcinogen-induced keratoacanthomas on rabbit ears with retinoic acid and induced mucin formation in those tumors. So there are other tissues where this process can happen. It hasn't been a very popular subject compared with other areas of research so I can't give you a list of other tissues at this point. But to me it's still fascinating.

GM: It's fascinating to me, too. What is the difference between vitamin A and retinoic acid?

GPeck: Well, vitamin A is also known as retinol; it's an alcohol. It has a hydroxyl group on the 15th carbon in the side chain. Whereas, in retinoic acid there is an acid moiety, namely -COOH.

GM: You had the insight to take retinoic acid which was similar to vitamin A and apply it to human beings. That seems to have been a huge jump in opportunity or thought process. How did you do that, using retinoic acid?

GPeck: Commercially, Retin-A cream is an acne medicine that contains retinoic acid, but it has been used not only in acne, but in a variety of other diseases as well. It is more potent than vitamin A. Oral vitamin A had been used since 1940 for treatment of a whole host of diseases, as has retinoic acid cream. I chose to use retinoic acid in my study.

GM: I understand you found an available retinoic acid already partially studied at Hoffmann-Laroche.

GPeck: Well, there came a point when Dr. Frank Yoder, one of our dermatology clinical associates, who had been working in an immunology laboratory, decided that he wanted to do a clinical research study instead, and he came to me and asked if he could work with me. I said yes, but that it would have to involve vitamin A derivatives. There was an article from Germany in which they had used all trans retinoic acid, which was the same molecule as in Retin-A cream, but they gave it by mouth for treatment of patients with genetic skin diseases in the category of disorders of keratinization and had some benefit. But there were toxicities. It was a drug from Hoffmann-La Roche in Basel, Switzerland. I called Hoffmann-La Roche in Nutley, New Jersey, and I asked for the use of the same all trans retinoic acid that had been used in Germany. They said they didn't have it, but they did have 13-cis retinoic acid available on their shelves, which had been intended for cancer prevention studies in populations at very high risk of developing cancers such as in smokers, uranium miners, and so on. This was largely the work of Dr. Michael Sporn, also at NIH, who had studied the effects of retinoids on hamster tracheas in organ culture. And because of his findings, he was a proponent of using 13 cis-retinoic acid as an agent for cancer prevention studies. As a result, Hoffmann-La Roche, did keep the drug on the shelf for future research. However, there was some hesitancy in the oncology community in using 13 cis-retinoic acid as a chemopreventive agent. In the first place the concept of chemoprevention was new. It was assumed

that in patients at high risk of forming cancer, lifetime usage of a chemopreventive agent might be necessary. As a result, it was thought that any effective chemopreventive agent must also be free of toxicity, acute and chronic, since the patients would be essentially healthy and disease-free at the time that treatment was initiated. In 1975, there were no published articles describing therapeutic results of 13-cis retinoic acid. Efficacy, toxicity and dosage were not known at that time.

Hoffmann-La Roche in Basel, Switzerland tested 13 cis-retinoic acid using an assay system for preventing skin cancers in carcinogen-induced mouse papillomas as a model system. They found that etretinate, which was a second-generation retinoid, was better than 13 cis-retinoic acid and, later on, it was found to be better in the treatment of psoriasis. So they had abandoned 13-cis retinoic acid in favor of etretinate. It was only Dr. Sporn's work in cancer prevention and his communications with Hoffmann-La Roche in Nutley, New Jersey that kept 13 cis retinoic acid available. Luckily, I was able to write an NIH-approved clinical protocol and send it to Hoffmann-La Roche and they also approved it. Hoffmann-La Roche then sent me the medication and I began testing it in the spring of 1976. After my initial study was published in Lancet in 1976, a bladder cancer prevention trial using 13 cis retinoic acid was initiated. Unfortunately, it was terminated early due to mucocutaneous toxicities, such as chapped lips.

GM: Of course, it was oral. You also told me that Hoffmann-Laroche had other, what we call isomers, similar drugs, on their shelf.

GPeck: The category of vitamin A and its derivatives are called retinoids and I was told that they had 5,000 of them that had been manufactured, chemically synthesized, but not yet tested. Only 13-cis retinoic acid was available to me at the time.

GM: So that wasn't much of a choice. That's all you had an opportunity to use.

GPeck: Yeah, it's take it or leave it. I took it.

GM: You really fell into that in a way that was kind of miraculous to me.

GPeck: Yes, at that point there had been no experience of using it in man. Based on the experience in dermatology of using oral vitamin A in high doses since 1940 and the recent German study of using oral retinoic acid, I felt comfortable in testing oral 13-cis retinoic acid in patients.

GM: So your studies went straight to clinical. You didn't have any good scientific backup on it, I'd gather, sort of a trial and error opportunity.

GPeck: Well, we had assumed that we would at least see the benefits that we had seen with vitamin A and with oral all trans retinoic acid, so we expected to see some response. We didn't know how much of

a response it would be, and we didn't know what the side effects would be, but we did know the side effects of vitamin A and we did know the side effects of oral vitamin A acid or retinoic acid.

GM: So you applied it to what kinds of diseases dermatologically?

GPeck: We made a list of every disease that had been treated either by oral vitamin A or by topical retinoic acid, or oral retinoic acid also, and these ranged from acne to skin cancer to cutaneous disorders of keratinization which are diseases in the general category of papulosquamous diseases like psoriasis and ichthyosis. There are many genetic severe dermatologic diseases that unfortunately in 1976 had no effective treatment at all, including, for example, Darier's disease, also known as keratosis follicularis. We tried treating these categories of patients since there were several patients with this type of disease at NIH already.

GM: These are all epidermal diseases that you're talking about primarily?

GPeck: Yes. Primarily.

GM: Because 13 cis-retinoic acid seems to work on the epidermis?

GPeck: But also with acne on the sebaceous glands as well.

GM: Okay. Are sebaceous glands in the dermis?

GPeck: They're attached to hair follicles and so they're below the level of the epidermis.

GM: How did you start doing these studies? You found very difficult patients and tried it on them or how did you choose the cases?

GPeck: I chose to begin treating those diseases that had been treated in dermatology by vitamin A or topical vitamin A retinoic acid. My very first patient had a condition called pityriasis rubra pilaris which dermatologists referred to as PRP. She had been treated with extremely high doses of vitamin A without response and also with methotrexate without response. And then within a month of using 13 cis retinoic acid she had a beautiful response and was almost clear. The downside was that in her case, it was a chronic, childhood-onset condition and when we stopped the treatment, the disease relapsed. It would require almost continuous lifetime exposure to the drug if we were to keep her skin disease free. But with long-term therapy you run into the potential for chronic toxicity.

In addition to pityriasis rubra pilaris, we treated patients with a variety of ichthyoses, such as lamellar

ichthyosis, which was the most common one we treated, and epidermolytic hyperkeratosis, and several others. There are a variety of diseases in the ichthyosis family and we treated as many as we could. Fortunately, most, if not all of the ichthyoses that we treated, responded very nicely. We also performed skin cancer prevention studies in patients with nevoid basal cell carcinoma syndrome and xeroderma pigmentosum, as well as studying cystic and conglobate acne, the scarring forms of the disease.

GM: This obviously became popular for acne, a high incidence disease. Tell us about some of the opportunities you had to try it out.

GPeck: We recruited patients from the whole country for all of the different diseases that we studied. Some of our Darier's disease patients came from Idaho, Missouri, North Dakota, and Ohio. And our acne patients came from Massachusetts, New Orleans, and a variety of other states, as well as locally from Washington. These were often extremely severe patients who had been on treatment with antibiotics for 10 or 20 years or even longer. One patient had been treated at Massachusetts General Hospital by the professor and chairman of dermatology for about 12 years, but she still had quite severe, treatment-resistant, scarring cystic acne at the time I saw her. She cleared completely with 13 cis-retinoic acid, or isotretinoin as it later came to be known. In the '70s the drug was still called 13 cis-retinoic acid, which is the chemical name, and the generic name, isotretinoin, was coined in 1980. Then when the drug came onto the market, the name Accutane was the trade name.

GM: How extensive was this particular patient's disease that the doctor had been treating for 12 years?

GPeck: All of our patients had severe, scarring cystic acne. Cystic acne lesions are like small abscesses. In some patients cystic acne was limited to the face, but quite severely. In other patients it covered the chest and the back, as well as the face, and was very debilitating and had both physical and psychological consequences.

GM: You had some patients that changed their whole outlook on life from having been treated. Tell us about those.

GPeck: Often patients were withdrawn and depressed and anxious and sometimes hostile, like they had a chip on their shoulder, because they felt that they were rejected. In fact, many were socially excluded. There was one fellow who had his acne on the chest and back and the lesions would bleed, and pus would drain, and they were painful. And if his parents tried to hug him, he would withdraw because the hugging was very painful. So these patients would literally push people away. Parents and friends wouldn't understand at first that the reason they were being pushed away is that it was painful to the patient to be hugged.

Many patients who had acne of the trunk with lesions that were bleeding would not wear white shirts, for example, because the blood would be very obvious. They would wear dark shirts and they would always take a change of clothing or a change of shirt to work with them in case the lesions started to bleed. They would change the shirt and put on a fresh one.

Many patients walking down the street would have their head down staring at the sidewalk so they would not make eye contact with passersby who might be appalled by the acne on their face. They didn't want to see how people reacted to them. They often would not go window shopping because they didn't want to see their face reflected in the window; they would often walk on the shady side of the street as opposed to the sunny side because they're more likely to see the reflection in the window on the sunny side.

One patient who worked at a TV studio was always in the background and never got on air until the acne cleared up and then she was given air time to tell the stories that she was working on. Many people started dating after their acne was improving and several of my patients became engaged at the end of their Accutane treatment period when their skin was clear.

One of my patients married the woman he was dating toward the end of his Accutane treatment period and he had four children. As soon as the first child developed his first pimple, he brought the patient to me in my part-time private office and insisted on having his child treated with Accutane because he wanted to prevent the child from going through what he had suffered during his adolescence. I eventually treated all of his children. It was not an unusual thing. There are several families where I've treated all their children.

GM: Is acne considered a hereditary disease?

GPeck: Severe acne can be.

GM: So you've got to see whole families.

GPeck: Another patient I would like to mention is a teenage girl who had the worst acne I have ever seen in a woman. Not only was her face and the V of her chest involved with severe nodulocystic acne, but her entire back from the neck to the waist was covered with these red, painful, and bleeding lesions. Her routine each morning was to cover each of these lesions with a band-aid. There were at least 100 of these lesions and it took her at least one hour to do so. Once the acne was gone, she was freed from this routine and was able to move on with her life.

Aside from acne, I want to mention a patient with severe Darier's disease covering most of his body. His disease was also secondarily infected with bacteria producing a strong odor. As a result, he stayed indoors at home for two years before coming to see me at NIH. He actually had made suicidal gestures four times by putting a rifle in his mouth but was unable to pull the trigger. With isotretinoin treatment his disease responded beautifully within one month. His goals in life were to get married, have a child, and become a long-distance truck driver. With isotretinoin treatment he was able to accomplish all 3 of these goals.

GM: That's interesting. What age group did you see the most?

GPeck: Most of my patients were referred as being untreatable and they had been through, let's say, a decade of treatment by other doctors. So rather than teenagers I most commonly saw patients in their 20s and 30s. The oldest acne patient included in my study was in his 40s.

GM: Does acne tend to go away as people age?

GPeck: Mild acne does. These patients with severe nodulocystic acne would have it for 10, 20,30 years.

GM: I had no idea that acne could be so severe that it caused such a psychological downside as you describe in these patients. That's a fascinating side effect.

GPeck: The patients with more severe acne also had anemia of chronic disease. Fortunately, the anemia of chronic disease disappeared just by treating the acne.

GM: That's interesting. How did the drug finally get the name Accutane? Where did that come from?

GPeck: I was told that the drug company had the name on file. They had a copyright on the name for another product that they had abandoned. Since they already had the name available, it was simply attached to this product. Jokingly one of my colleagues suggested to them the name "Peckutane" but La Roche did what you just did—they also just laughed.

GM: That's too bad because you would have gotten more recognition on it, but that's the way life goes.

GPeck: So it goes.

GM: Besides acne, have you used the drug in a lot of different diseases in the same way?

GPeck: Since it was initially intended to be a cancer prevention drug, we used it in patients who would get multiple cancers per year. The two main groups that we treated were patients with the nevoid basal cell carcinoma syndrome and those with xeroderma pigmentosum . We also treated patients who had other causes for their skin cancers, such as arsenic exposure or radiation therapy for acne when they were teenagers as well as sunlight induced multiple skin cancers. I had a World War II veteran who had spent four years in the Pacific without a shirt and he had multiple skin cancers. We treated all these types of patients. Initially we wanted to see whether the drug could cure any of the cancers and we gave a dose to them that was about eight times higher than our acne dose. We pushed the dose as far as it would be tolerated. We found that we only accomplished about a 10% cure rate of existing tumors, and most of the tumors that responded were smaller ones—like three, four, or five millimeters—whereas although the larger tumors reacted, they became inflamed, but they didn't disappear completely. However, we noted that new tumors stopped coming. So we changed our focus from chemotherapy of

the tumors to prevention of new ones. We found that with lower doses, in the range of the acne treatment range in terms of dosage, we could reduce the incidence of new tumor formation of basal cell carcinomas both in nevoid basal cell carcinoma syndrome and also in xeroderma pigmentosum and the other etiologies of cancer as well. By the way, my main colleagues in the xeroderma pigmentosum cancer prevention study, published as a lead article in the NEJM, were Drs. John DiGiovanna and Kenneth Kraemer who remain active researchers at NIH today.

GM: This is still being used these days for these purposes?

GPeck: It's used more in medical oncology now. I did a literature search in Pub Med, the National Library of Medicine's search engine, under the term "retinoids and cancer" and found over 17,000 references for all types of cancers, including lung cancer, lung cancer prevention, treatment of leukemias, but also other tumors such as breast, ovary, prostate, bladder, and brain. Usually in dermatology the systemic therapies that we use have been used first in other specialties. Then we bring them into dermatology. For example, methotrexate, which is a chemotherapy drug, has been used by dermatologists for over 50 years to treat psoriasis. But the retinoids, such as isotretinoin, were first used in dermatology and then spread to general use in other fields, particularly in oncology.

GM: I think you said this was the first systemic drug that was used in dermatology ever?

GPeck: No. What I am saying is that this might be the first time that a drug was entered into clinical medicine coming from dermatology, and then into other specialties. As best as I can recall, it's always been the reverse: other specialties discover a drug first and then dermatology starts uses it later.

GM: Then you were a real true pioneer.

GPeck: Well. I do feel satisfaction when I learn about the expanded uses of systemic retinoids in other fields of medicine.

GM: As quite an accomplishment in the whole field. Tell us about the dosage limitations that you had initially.

GPeck: In 1975 there had been no clinical studies so we didn't know what an effective and safe dose would be. We didn't know if the doses we were choosing were too high or too low. We decided to start with a dose that we thought was a low one and then increased the dose, depending on the response in our first studies. It was like a dose-finding study as well as an efficacy study combination. Eventually in acne we settled on a dosage of anywhere from a half milligram per kilo per day, up to two milligrams per kilo per day. The average man is 80 kilograms so the dose range would be anywhere from 40 milligrams to 160 milligrams a day for acne. Patients with some of the cutaneous disorders of keratinization required higher doses, such as two or three and sometimes even four milligrams per kilo per day. It's

much higher than what we'd use in acne patients.

GM: But you also had a limitation of timing, four months, or something like that. You were limited.

GPeck: The investigators' drug brochure that we were given was from 1972 and the only human beings who had been tested with the drug were normal volunteers. There was animal testing also. The longest that animals had been given the drug was four months. We were told by Hoffmann-La Roche that our studies could only last four months because there had been no prior human or animal data giving the drug for more than four months. We were told by Roche that the FDA would not allow us to treat longer, so we had to stop treatment at 4 months according to our protocol. We designed the clinical trial so that there would be a four-month treatment period followed by a two-month break from treatment. This break was intended to allow the acute toxicities to resolve completely and perhaps to reduce the likelihood of chronic toxicity developing. This was our justification for the four-month schedule.

GM: Did you treat a lot of patients multiple times?

GPeck: The patients with disorders of keratinization we treated indefinitely, but we always had to give them a break between treatment courses. At one point in my studies we extended the treatment period from four months to six months. Even then, we still gave them a 2-month treatment-free period at the end of the course of treatment. Our goal was to try to prevent or minimize chronic toxicity, if possible.

GM: Does that limitation apply even today to the use of Accutane?

GPeck: It's mainly used for acne, and patients with acne, generally, are not being given chronic therapy. They're usually given one or two courses of treatment. Acne is really the only disease where the patients are actually cured or enjoy very long-term remissions after you stop the treatment. All the other diseases relapse except for a disease called adult onset pityriasis rubra pilaris. For those patients, once it clears up, they often do not relapse. So other than those two conditions the diseases that we've treated all relapse upon discontinuation.

GM: Is the drug authorized by the FDA for treatment of more than acne?

GPeck: No, I wish it were. The only chronic toxicity that I know of is called diffuse idiopathic skeletal hyperostosis, except in this case it's not idiopathic because we know that the drug causes it. It causes deposits of calcium in tendons and ligaments and particularly the anterior spinal ligament which often leads to a bony bridge between vertebrae and reduces the patient's flexibility, and that is a major problem. That is a definite limitation. It depends on the dosage, but I would say if a patient received two milligrams per kilo per day or higher for at least two years that there would be radiologic changes visible.

GM: At the end of two years you could see the changes?

GPeck: Yes, at these high doses.

GM: The high dose?

GPeck: Yes, two milligrams per kilo is a high dose.

GM: What other adverse effects had been noted or considered?

GPeck: The serious side effects that have generated lawsuits include cases of depression, teratogenicity, and inflammatory bowel disease. Also pancreatitis in patients who have prolonged massive elevations of triglycerides. There have been numerous lawsuits regarding Accutane-induced birth defects, and there have been a few lawsuits regarding patients who committed suicide while on treatment with the implication that the depression was induced by the drug.

GM: Have those diseases been proved to be related to the drug? Have those conditions been proved to be related to the drug or they just happen to occur despite use of the drug?

GPeck: Yes, there is no question about teratogenicity. One has to assume that all retinoids are teratogenic. Regarding depression, if a dermatologist has not had a patient with depression from Accutane, they don't believe that it happens. I've had 10 patients over my career starting back in '76. My first patient was the daughter of a prominent surgeon in Washington who came into my office and challenged me, saying, "What are you doing to my daughter? She used to be very positive and outgoing and now she's withdrawn and it's due to the medicine you're giving her." That's the first case that I had personally and what I found is that when I stopped the drug the depression went away within two to seven days in these ten patients. It was the rapid response of return to normal that was also additional proof to me that this was drug related. I mean, only one of my patients had had depression before. These were people who were not known for previous psychiatric history. I think maybe only one of them was a teenager and all the rest were in their 20s or 30s, so it was not like it was a teenage depression due to severe acne.

The relationship between retinoid usage and inflammatory bowel disease (IBD) remains controversial. I had one patient who was being treated with etretinate for his psoriasis develop IBD, but I have not seen it personally in my isotretinoin patients. Many dermatologists state that the incidence of IBD is isotretinoin treated patients is the same as in the general population. A national registry of systemic diseases or other unusual toxicities, perhaps at the FDA, could resolve this question with prospectively obtained data.

GM: Your contributions to medicine were obviously fantastic. A whole approach to dermatology treatment changed a great deal after you had your hands on it. You obviously have received a lot of awards as a result of these studies. Which ones have been particularly notable as far as you're concerned?

GPeck: The most notable one was the Discovery Award from the Dermatology Foundation. When I received the award, the man presenting the award to me announced that it was the Nobel Prize of dermatology except there's no cash involved. I was only the tenth person to get it and I had been nominated by the professor and chairman of dermatology at Massachusetts General Hospital, who was also the one who reviewed my paper describing the initial response of acne patients to this drug. He reviewed it for the New England Journal, and he said it was a medical milestone. It was published in February of 1979.

GM: How many patients had you studied by that time?

GPeck: Well, in that particular article just 14 acne patients but these were patients from all around the country that had been treated by all the available medications and were non-responsive. My second study was a double-blind study against placebo in which I had 33 acne patients. The thing is the double-blind aspect of it was pretty much voided at the first follow-up visit because everybody on the drug got side effects such as chapped lips. If the patient had chapped lips, I would know that they had taken the drug. The way we accumulated the data is we had to actually count the number of deep nodulocystic lesions that the patients had. At the end of the month after the first visit we could see that there was a marked increase in lesions in the placebo group and a marked decrease in lesions in the Accutane group from baseline. That is, in effect, when we stopped the double-blind phase of the trial because at that point both physicians and patients knew who was taking the medicine and who was on placebo. But even at that one-month time point it was clinically obvious and statistically significant that isotretinoin was superior to placebo.

GM: It's an amazing study. Tell me, how did you let dermatologists around the country know that you had a drug that they could refer patients for trial when they were failing in their offerings?

GPeck: We just called up everybody, just got on the phone and asked, “Hey, do you have a treatment-resistant cystic acne patient, or do you have a patient with Darier’s disease?” It's just a matter of recruiting. Fortunately NIH paid for our patients to fly to Bethesda and we put them up at the hotel and paid for their meals, and, if they had other medical problems, we treated them as well as their skin disease. So this was a unique thing to NIH. I don't think I could have done this study anywhere else in the world. Also, it was a boon to Hoffmann-La Roche in that there was no way that they could reimburse NIH for the study because we were the federal government. It wasn't like we were at a private university. Since we were not paid by Roche, it is clear that my studies were paid for by the American taxpayer.

GM: Basically, the fact that you were at NIH made it possible to do what you did and what you

accomplished.

GPeck: It would have been impossible for me to get a research grant to do the project that I did.

GM: That's an interesting observation obviously. Then you subsequently left NIH in 1990. Is that correct?

GPeck: 1990, yes, June 30th 1990.

GM: And what have you done since then?

GPeck: Well, initially I went to the University of Maryland Medical School in Baltimore and became a professor of Dermatology for three years there where I did teaching.

GM: You finally got to teaching, as originally desired.

GPeck: I remember in my first dermatology clinic a student came out of the room after she examined a patient and she saw me waiting at the nursing station. She said, “Have you been waiting for me long?” and I said, “All my life!”

GM: You finally got your wish fulfilled! That was good. Then how long did you stay there?

GPeck: Three years in Baltimore and then I transferred to the Washington Hospital Center in Washington, DC. It's a 900-bed hospital, the largest in Washington. Initially, I joined both dermatology and oncology. In dermatology I was the director of clinical research. Then in oncology I tried to set up a cancer prevention program. My first project was a grant application centering on young women with abnormal pap smears. My goal was to try to reverse the abnormal pap smears with retinoids. I collaborated with gynecologists and other doctors. The grant required us to find intermediate endpoints, so I recruited laboratory researchers to work on this project. We created what I considered to be a strong grant application. However, the results of the grant review became similar to a catch-22 situation because the grant was rejected due to the lack of any prior publications showing the intermediate endpoints that we had proposed actually worked. We didn't have money to do pilot research projects to show that they were effective as intermediate endpoints. This led to the rejection of our application. They reviewers liked my clinical project, but they rejected it because of what I just mentioned. I told my chief in the Washington Cancer Institute, Dr. Lawrence Lessin, that this was our best shot and I don't think that we're going to get a grant. He then told me, “I want you to switch paths. We need a melanoma center here,” and he assigned me to create a melanoma center, which I did. The rest of my career at the hospital was involved in the melanoma center that I created. I left the Department of Dermatology at that point to spend full time working on melanoma. Over the next 21 years we accumulated about 2,000 melanoma patients and we worked with surgeons, surgical

oncologists, plastic surgeons, radiation therapists, radiologists, nuclear medicine for doing sentinel node biopsies, and pathologists. It was a multi-specialty team approach and it I enjoyed creating it and being part of a multiple specialties team. In addition, we also had about 3,000 patients with multiple moles, or nevi, with an average of 100 per patient. I had patients with as many as 1,300 nevi, who were at high risk for developing melanoma. I found that 40% of my patients with 200 or more moles would eventually get a melanoma. As a result of this experience, I became an expert in melanoma diagnosis and differential diagnosis between benign and malignant lesions of the skin.

GM: Currently there's been a great effort to move research from the bench to the clinic as quickly as possible. You sort of jumped the bench and ended up straight in the clinic for most of your work, you were way ahead of the curve, the potential curve, of getting scientific findings applied to the care of patients. I think that was very remarkable.

GPeck: My work on the embryonic chicken skin, although it involved the transformation of the keratin-producing cells to mucus-producing cells, was not really cancer-focused, it led me to become expert or knowledgeable in all of vitamin A literature including the work that Dr. Sporn was doing in cancer prevention. It may not have been my personal bench work that was done, but I'd say it was Dr. Sporn's bench work that allowed me to go forward and into cancer.

GM: Cancer moved into the clinic very quickly in terms of your activities. I thought that was particularly notable in your life story and accomplishments.

GPeck: I'm primarily a clinician but I enjoyed the research I did at NIH. I enjoyed learning how to do electron microscopy, both transmission and scanning electron microscopy. My mentors in electron microscopy were Drs. Peter Elias and Bruce Wetzel. I enjoyed the tissue culture work as well.

GM: Before we end, do you have any other comments that you'd like to add to this presentation?

GPeck: Well, I want to mention how my interest in dermatology developed. We haven't covered that, but it began when I was in medical school. Dr Isidore Bernstein was my biochemistry professor who supervised me in the freshman student laboratory. He invited me, at the end of the school year, to work in his laboratory for the summer. Instead of being in the department of biochemistry, his laboratory was in the department of dermatology. During that experience I got to meet the faculty of dermatology. I met all the dermatology residents and I got to know them personally and socialize with them in the laboratory and have a cup of lousy coffee with them. During my second year of medical school, anytime that I had a free moment I would head up to the laboratory and have some coffee and just talk with the people in the lab and discuss what research they were working on. I still remember the very first project that I did. I couldn't believe that I was finding something new and that my results were original findings. I discussed the results with Dr. Bernstein and he wanted me to write up the paper. First of all, I was shy at that time and I thought that writing a paper was like creating an advertisement . I didn't want to write something that would call attention to myself. Also, I didn't believe him that my findings were really new. I thought that whatever I did must be known somewhere else in the medical literature. It took a while for him to convince me that I had discovered something new. When it finally sunk in, it was an

overwhelming feeling. I had the joy of realizing that I, as a 20-year-old, had found something that nobody else in the world knew, however trivial it was. It became a major turning point in my life where finding new research data was addictive. From then on, I wanted to continue to explore more research.

The following summer I worked in cardiac pharmacology in a research project on atrial fibrillation and in my senior year, when I had a break in my schedule, I came back to the laboratory with Dr. Bernstein and did another research project in experimental chemical carcinogenesis with Dr. Philip Anderson, an instructor in the Department of Dermatology and later the Department Chairman at the University of Missouri in Columbia. I came back to Dr. Bernstein's lab one more time after my 2 year stint in the Air Force to study keratohyalin granules.

GM: Interesting. I found your whole story terribly intriguing, the way it developed, the way it happened, especially considering your background and all the difficulties deciding on Medicine. I was pleased with your persistence in your research all the way by starting with embryonic chicken skin and finally to humans and the development of these epidermal treatment accomplishments and your work with Hoffmann-La Roche. I am amazed how all of these events come together and make such a nice story. Not only that you've contributed so much to dermatology, you've treated people with disfiguring and troublesome acne and other diseases, and you've created a whole new attention to dermatology with the use of systemic drugs that are designed for dermatology. Besides that, you've been recognized nationally and internationally for your accomplishments. I'm so pleased to have had the opportunity to talk to you and to get to know you. I find it extremely exciting and I'm so pleased that we've done this recording on you on Zoom today. We'll have all this up on our website at the History department for other people to see. I think this has really been a very worthwhile endeavor and I'm so glad to be able to feature you in it. So thank you so much for your time and your effort and all that goes into it to recall and retell this wonderful saga.

Thank you so much.