

Ralph S. Freedman, M.D., Ph.D.

Interview #10

Interview Navigation Materials

This binder package contains:

Interview profile edited to new format

Original Interview Profile

Table of Contents

Original Segment Summaries

Ralph S. Freedman, M.D., Ph.D.

Interview #10

Interview Profile

Interview Information:

Two interview sessions: 4 February 2012, March 1, 2012
Total approximate duration: 4 hours 25 minutes
Interviewer: Tacey A. Rosolowski, Ph.D.

For a CV, biosketch, and other support materials, contact:

Javier Garza, Archivist, Research Medical Library
jjgarza@mdanderson.org; 713.792.2285

About the Interview Subject:

Ralph S. Freedman, M.D., Ph.D. (b. 1941, Capetown, South Africa) joined the Department of Gynecologic Oncology as a Fellow in 1976 and was hired the following year as an Assistant Professor ('87 Full Professor). He has a joint appointment in the Division of Surgery. Dr. Freedman specializes in immunological approaches to ovarian and cervical cancer. Later in his career he became involved with policy-making. He served on the National Cancer Advisory Board and worked for many years on the MD Anderson Cancer Center's Institutional Review Board. When he retired in 2007, he was Director of the Laboratory of Immunology and Molecular Biology in the Department of Gynecologic Oncology. Since retirement, he has served on the Oncologic Drug Advisory Board.

Major Topics Covered:

Personal and educational background; experiences in native South Africa

MD Anderson history and culture in the seventies and since

Research: immune mechanisms and gynecologic cancers; vaccines, T-cells, monoclonal human antibodies, inflammatory system, eosinoids and inflammatory responses to tumors.

Department of Gynecologic Oncology: building immunology research

Institutional Review Board at MD Anderson

Lyndon Baines Johnson Hospital and indigent care

The National Cancer Panel, the Drug Advisory Board

Institutional change and growth

**University of Texas MD Anderson Cancer Center
Making Cancer History Voices® Oral History Project**

Research Medical Library: Historical Resources Center

ORIGINAL Interview Profile: Dr. Ralph S. Freedman, M.D., Ph.D.
Submitted by: Tacey A. Rosolowski, Ph.D.
Date revised: 6 June 2014

Dr. Ralph S. Freedman, M.D., Ph.D. (b. 1941, Capetown, South Africa) speaks about his career in this interview of 4 hours 25 minutes conducted over two sessions in spring of 2012. Tacey A. Rosolowski, Ph.D., interviews Dr. Freedman at his home in Houston, Texas.

Dr. Freedman is a gynecologic oncologist who joined the faculty of MD Anderson in 1976. When he retired in 2007, he was Director of the Laboratory of Immunology and Molecular Biology in the Department of Gynecologic Oncology. He was also a Professor in that Department and continues to hold a position as a Clinical Professor in the Division of Surgery (the same department). Dr. Freedman specializes in immunological approaches to ovarian and cervical cancers; later in his career he became involved with policy-making related to cancer, serving on the National Cancer Advisory Board and working for many years on the MD Anderson Cancer Center's Institutional Review Board. Since retirement, he has served on the Oncologic Drug Advisory Board. Among his awards are MD Anderson's Distinguished Service Award ('07) and Educator of the Month ('03). Since retirement, has been teaching residents in gynecologic oncology at the Lyndon Baynes Johnson County Hospital in Houston.

Dr. Freedman earned his MBCh (Bachelor of Medicine and Bachelor of Surgery; Latin *Medicinæ Baccalaureus et Baccalaureus Chirurgiæ*) in 1965 at the University of the Witwatersrand, Johannesburg, South Africa. He did Internships at Johannesburg General Hospital, Baragwanath Hospital, and the Johannesburg Group of Teaching Hospitals, the latter residency ('68-'71) for Obstetrics and Gynecology. Dr. Freedman was on the faculty of the University of Witwatersrand before earning his Ph.D. in Medicine in 1975 at the same institution, after which he came (in 1976) to MD Anderson as a Fellow in the Department of Gynecology. He was hired as an Assistant Professor in Gynecologic Oncology the next year ('81 tenure; '87 Full Professor).

In this interview, Dr. Freedman discusses his research and his administrative roles at MD Anderson and also covers his advisory and oversight roles on the National Cancer Panel, MD Anderson's Institutional Review Board, and the Drug Advisory Board. Dr. Freedman is a very candid and thorough interview subject who sketches details of experimental and biological processes very clearly. His interest in history shows in his ability to provide relevant context for his discussions of research, various departments, and his own decision making as a researcher. It is no surprise that he served for so long on the Institutional Review Board and takes part in national advisory boards that safeguard public safety and health: Dr. Freedman is clearly interested in the ethical dimensions of medicine, as he demonstrates in a fascinating discussion of how he distributed tissue samples to other researchers when he closed down his own laboratory.

Ralph S. Freedman, M.D., Ph.D.

Interview #10

Table of Contents

Session One: 4 February 2012

Interview Identifier

Chapter 00A

An Early Desire to Enter Medicine and a Growing Interest in Oncology

Chapter 01 / A: Professional Path

Discovering and Rich and International Community at MD Anderson in the Seventies

Chapter 02 / A: Joining MD Anderson/Coming to Texas

Research into Treatment for Gynecologic Cancers

Chapter 03 / A: The Researcher

Interview Session Two: March 1, 2012

Interview Identifier

Chapter 00B

Setting Up Testing Laboratories and Clinics and Building Research

Chapter 04 / B: Building the Institution

Building A Departmental Focus on Immunological Approaches to Gynecologic Cancers

Chapter 05 / : Building the Institution

Two Decades Overseeing Human-Subject Research

Chapter 06 / B: Building the Institution

Service On the National Cancer Advisory Board and Other National Bodies

Chapter 07 / A: Professional Service beyond MD Anderson

Working with LBJ Hospital and Indigent Care

Segment 08 / A: Post-Retirement Activities

MD Anderson Growth and Changes to Institutional Culture

Segment 09 / B: Institutional Change

Ralph S. Freedman, M.D., Ph.D.

Interview #10

Chapter Summaries

Session One: 4 February 2012

Chapter 00A
Interview Identifier

Chapter 01
An Early Desire to Enter Medicine and a Growing Interest in Oncology
A: Professional Path

Story Codes
A: Personal Background
A: Inspirations to Practice Science/Medicine
A: Influences from People and Life Experiences
C: Experiences of Injustice, Bias
C: Formative Experiences
A: The Researcher
A: Professional Path
A: Joining MD Anderson

In this chapter, Dr. Freedman talks about his family life and education in South Africa, noting that his family physician inspired him to enter medicine. He explains the differences of the South-African, British-based educational system and then, during the next twenty-five minutes he turns to his growing interest in endocrinology (Ph.D. on breast feeding habits on maternal disease of the endometrium) and cancer. He explains that he applied for an Eli Lilly fellowship (instead of going to England, as was more usual for South African residents and post-doctoral fellows) because “the future was more in the States than in Britain.” Dr. Freedman explains that he came to the U.S. to work with Dr. Joseph Sinkovics in 1976. He talks about how South Africa’s apartheid system affected his medical training: his exposure to the variety of uterine diseases among Black South African women led him to do a Ph.D. and to collaborate with virologists on a variety of studies of uterine cancer. Immunology, virology, endocrinology, and his interest in cancer coalesced at exactly the right time to create a new research path leading to MD Anderson, working with on cervical cancer cell lines, a precursor to his work on vaccines and cytokines and immunotherapy.

Chapter 02
Discovering and Rich and International Community at MD Anderson in the Seventies
A: Joining MD Anderson/Coming to Texas

Story Codes

- A: Joining MD Anderson/Coming to Texas
- B: MD Anderson Culture
- B: MD Anderson History

Dr. Freedman begins this segment with a fuller discussion of how he came to MD Anderson. He also comments on his family's adjustment to life in the United States and the social life of MD Anderson in the mid-Seventies, with its international faculty.

Segment 03

Research into Treatment for Gynecologic Cancers

- A: The Researcher

Story Codes

- A: The Researcher
- A: Overview
- A: Definitions, Explanations, Translations
- D: Understanding Cancer, the History of Science, Cancer Research
- D: The History of Health Care, Patient Care
- D: On the Nature of Institutions
- C: Evolution of Career
- C: Professional Practice
- C: The Professional at Work
- C: Collaborations
- C: Discovery and Success

In this segment, Dr. Freedman discusses his "travels in the lab," first explaining how his Fellowship work on cell lines transitioned to the development of vaccines for gynecologic cancers. He talks about the prevalence of these cancers, explaining the special challenge of ovarian cancer. He explains the logic behind the vaccine strategies tested (e.g. intra-peritoneal injection) and the immune mechanisms stimulated, and also notes the clinical challenges faced, which led to work on an approach using T-cells. He then details his work with T-cells, describing some of the equipment used, the procedures attempted, and his evaluation of those procedures, concluding that his work added "building blocks" to the understanding of the immune system, as well as the creation of a mono-clonal human antibody. Dr. Freedman then goes on to talk about the relationship between the immune system and the inflammatory system and his work with eosinoids and inflammatory responses to tumors. It may be possible, he explains, that if the inflammatory response can be stopped, a tumor will stop growing. He notes that his research has given him new respect for how difficult it is to treat cancer, pointing out that mortality rates for cancer has not changed substantially over the past years. He discusses the difference between private practice and academic medicine then describes what it was like to establish his own laboratory after working collaboratively in others' labs. He offers his views on translational research. Dr. Freedman then talks about how he dismantled his lab and projects when he decided to retire.

Interview Session 2: March 1, 2012

Segment 00B
Interview Identifier

Segment 04
Setting Up Testing Laboratories and Clinics and Building Research
B: Building the Institution

Story Codes
A: The Administrator
A: The Researcher
A: The Clinician
A: Definitions, Explanations, Translations
B: MD Anderson History
B: MD Anderson and Government
B: MD Anderson Snapshot
B: Devices, Drugs, Procedures
A: Overview

In this segment, Dr. Freedman explains how he came to assume the positions of Director and Chief of Immunology and Molecular Biology Research ('88-'07). This narrative brings together various details: treatment of rare gynecological cancers, billing practices, regulation of laboratory testing, and research.

Segment 05
Building A Departmental Focus on Immunological Approaches to Gynecologic Cancers
B: Building the Institution

Story Codes
A: The Administrator
A: The Researcher
A: Definitions, Explanations, Translations
B: MD Anderson History

Dr. Freedman begins this segment by sketching the hopes he had as Director and Chief: to understand the biology of the diseases from an immunological perspective and try to identify new strategies to treat ovarian and uterine cancer, with their (continued) dismal outcomes (in comparison to advances made with cervical and endometrial cancer). He notes that the main contribution IMBR made to ovarian cancer was to demonstrate that T-cells can be activated in the patient, a fact indicating that a vaccine approach might potentially be used. He goes into detail about the biological mechanisms of the tumors and of the patient's immunological system. He notes that it is important for researchers to determine adequate ways to measure clinical benefit of treatments.

Segment 06
Two Decades Overseeing Human-Subject Research
B: Building the Institution

Story Codes

B: Building/Transforming the Institution
B: MD Anderson History
B: MD Anderson Snapshot
B: MD Anderson and Government
D: Understanding Cancer, the History of Science, Cancer Research
D: The History of Health Care, Patient Care
C: Leadership
D: Ethics
C: Professional Practice
C: The Professional at Work

In this segment, Dr. Freedman discusses his more than twenty years of experience overseeing human subject research on the Institutional Review Board (IRB). He sketches the history of human subject guidelines and clarifies IRB procedures, potential conflicts of interest (between IRB members and the institution), and the kinds of research protocols of concern to the IRB, whose primary function is the protection of human subjects. He then discusses his belief that regulation is very necessary, but that it has currently gone too far. He points out that different protocols represent different levels of risk, some of which may not require IRB regulation, such as experiments in which the main risk is to patient privacy. Dr. Freedman offers rich detail about the challenges to researchers and describes systems that might satisfy the public's need for privacy and information security while easing the burden on researchers who want to move ahead quickly with their work. "We needed these systems yesterday," Dr. Freedman asserts. He gives examples of how his understanding of the need for regulation and its potential complexity evolved as his experience as a researcher grew, then expands his focus again and discusses how regulation can influence how a researcher focuses his or her career.

Segment 07

Service On the National Cancer Advisory Board and Other National Bodies

A: Professional Service beyond MD Anderson

Story Codes

A: Contributions
B: Beyond the Institution
D: Understanding Cancer, the History of Science, Cancer Research
D: The History of Health Care, Patient Care
D: Business of Research
D: Fiscal Realities in Healthcare
B: MD Anderson and Government
C: Professional Practice
C: The Professional at Work
C: Critical Perspectives
C: Faith, Values, Beliefs
D: Ethics
A: Post Retirement Activities

In this segment, Dr. Freedman discusses his role as a presidential appointee to National Cancer Advisory Board (President Bill Clinton, '00 – '06). He begins with a brief sketch of the birth of the NCAB (and the National Cancer Institute) in the National Cancer Act, then covers NCAB review processes and grant procedures and compares the different styles of the Directors of the

National Cancer Institute, who work with the NCAB. He shares his view that all the institutes need to reconsider the kinds of clinical research they are supporting. This discussion leads naturally to his post-retirement role on the Oncologic Drug Advisory Board (since '09), "one of the most productive Boards at the FDA," in Dr. Freedman's words. He notes that he had to divest himself of certain stocks and remove himself from committees to satisfy the Board's conflict of guidelines. He also talks about the Board's procedures for questioning drug companies, offering several examples (including a drug company's challenge to a rejection). He concludes that "They [the FDA] do a terrific job of protecting the public."

Segment 08

Working with LBJ Hospital and Indigent Care

A: Post-Retirement Activities

Story Codes

A: Post Retirement Activities

A: Professional Values, Ethics, Purpose

B: Beyond the Institution

D: The History of Health Care, Patient Care

D: Business of Research

D: Fiscal Realities in Healthcare

In this segment, Dr. Freedman talks about the Lyndon Baines Johnson Hospital in Houston, a public county hospital that has many MD Anderson faculty who work part or full time. Dr. Freedman has worked with the gynecological oncology resident training program since his retirement: a choice he made to continue seeing patients, which he felt he could not do at MD Anderson under conditions where patients required continuous monitoring. He notes the economic burden that indigent patients represented for MD Anderson in the past; he has also had an opportunity to note how many more women physicians are in the field.

Segment 09

MD Anderson Growth and Changes to Institutional Culture

B: Institutional Change

Story Codes

C: Critical Perspectives

B: MD Anderson History

B: MD Anderson Snapshot

B: Growth and/or Change

B: MD Anderson Culture

B: Multi-disciplinary Approaches

C: Understanding the Institution

C: The Institution and Finances

A: Career and Accomplishments

A: Post Retirement Activities

In this segment, Dr. Freedman shares his observations about the growth of MD Anderson since he came to the institution in 1975. He notes its particular strength in clinical research and multi-disciplinary approaches (gynecologic oncology being one of the first Departments to put together multi-disciplinary fields). He hopes that MD Anderson will continue to always do the

right thing for patients, “since we are there for them, not for ourselves.” In the final minutes of the interview, he talks about going to Galveston, Texas, to fish and enjoy the water, as he did when he was young, in Capetown, South Africa. Since retiring, he has been able to indulge his love of history and travel, talking about his trip to Russia. “It’s a good thing to leave some time,” he says, to have a chance to do other things besides work.

Ralph Freedman, MD

Interview Session 1—February 24, 2012

About transcription and the transcript

This interview had been transcribed according to oral history best practices to preserve the conversational quality of spoken language (rather than editing it to written standards).

The interview subject has been given the opportunity to review the transcript and make changes: any substantial departures from the audio file are indicated with brackets [].

In addition, the Archives may have redacted portions of the transcript and audio file in compliance with HIPAA and/or interview subject requests.

The views expressed in this interview are solely the perspective of the interview subject. They are not to be interpreted as the official view of any other individual or of The University of Texas MD Anderson Cancer Center.

Chapter 0

Interview Identifier

Tacey Ann Rosolowski, PhD

0:00:04.2

I'm Tacey Ann Rosolowski interviewing Dr. Ralph Freedman for the "Making Cancer History Voices" Oral History Project run by the Historical Resources Center at MD Anderson Cancer Center in Houston, Texas. Ralph Freedman is a gynecologic oncologist who joined the faculty of MD Anderson in 1976. When he retired in 2007, he was director of the Laboratory of Immunology and Molecular Biology in the Department of Gynecologic Oncology. Do I have that correct?

Ralph Freedman, MD

0:00:33.6

Yes.

Tacey Ann Rosolowski, PhD

0:00:34.5

He was also a professor in that department. He continues to hold a position as a clinical professor in the Division of Surgery in the Department of Gynecologic Oncology.



Interview Session: 01
Interview Date: February 24, 2012

Ralph Freedman, MD
0:00:44.4
That's correct.

Interview Session: 01
Interview Date: February 24, 2012

Tacey Ann Rosolowski, PhD

0:00:45.1

This interview is taking place at Ralph Freedman's home in Houston. This is our first interview session. Today is February 24, 2012, and the time is about thirteen minutes after 1:00. Thank you, Ralph Freedman, for taking the time for this oral history project.

Ralph Freedman, MD

0:01:08.6

It's a pleasure.

Interview Session: 01
Interview Date: February 24, 2012

Chapter 1

A: Professional Path

0:01:08.7 to 0:35:46.8+

An Early Desire to Enter Medicine and a Growing Interest in Oncology

Story Codes

A: Personal Background

A: Inspirations to Practice Science/Medicine

A: Influences from People and Life Experiences

C: Experiences of Injustice, Bias

C: Formative Experiences

A: The Researcher

A: Professional Path

A: Joining MD Anderson

Tacey Ann Rosolowski, PhD

0:01:08.7

And I wanted to start with just some general, personal background—where you were born and when and where you grew up.

Ralph Freedman, MD

0:01:17.2

I was born in Capetown in 1941, and my mother was from Capetown. She was a daughter of people who emigrated from Russia—Lithuania—and my father was from Natal, which was the opposite side of the country. He had gone down to work in the Cape and was introduced to her, and they got married in Capetown. So the first 6 years of my life were spent in Capetown, South Africa, and then we moved to Durban, Natal, which was the place where my father was born.

Tacey Ann Rosolowski, PhD

0:02:00.6

And I'm missing the name of that town. Durban?

Ralph Freedman, MD

0:02:02.7

Durban—D-U-R-B-A-N. It's named after Sir Benjamin d'Urban. Of course there was a very fascinating history. I don't want to get too much about the—you had the Dutch who were interested in the Cape. They first came there, and then the British followed when they swept the Dutch off the seas, and the British settled in Natal, which is on the eastern seaboard. So a lot of Natal is very British oriented; whereas, the Cape had a mixture but had a lot of Dutch background. So I went to school. I went to—I had started, of course, early school in Capetown, but then I continued at school in Durban and went to Durban High Preparatory School and then

Commented [T1]:

In this segment, Dr. Freedman talks about his family life and education in South Africa, noting that his family physician inspired him to enter medicine. He explains the differences of the South-African, British-based educational system and then, during the next twenty-five minutes he turns to his growing interest in endocrinology (Ph.D. on breast feeding habits on maternal disease of the endometrium) and cancer. He explains that he applied for an Eli Lilly fellowship (instead of going to England, as was more usual for South African residents and post-doctoral fellows) because "the future was more in the States than in Britain." Dr. Freedman explains that he came to the U.S. to work with Dr. Joseph Sinkovics in 1976. He talks about how South Africa's apartheid system affected his medical training: his exposure to the variety of uterine diseases among Black South African women led him to do a Ph.D. and to collaborate with virologists on a variety of studies of uterine cancer. Immunology, virology, endocrinology, and his interest in cancer coalesced at exactly the right time to create a new research path leading to MD Anderson, working with on cervical cancer cell lines, a precursor to his work on vaccines and cytokines and immunotherapy.

Interview Session: 01
Interview Date: February 24, 2012

Durban High School, which is the same school my father went to. It was an all-boys school. From there I went to the University of Witwatersrand to study medicine. I'm not quite sure what year that was, but eventually it was a six-year training period, and I graduated from there. And then I—

Tacey Ann Rosolowski, PhD

0:03:35.3

Can I interrupt you just for a second to ask you about your undergraduate degree? What was the name of the degree?

Ralph Freedman, MD

0:03:45.6

Okay so the—it follows the British system in which essentially we do an MBChB degree, so it's not like the system that's done here, where people will go and do an Arts degree or a Science degree and then go and do an MD. It's all integrated. So your first year basically is chemistry and physics, and it is part of the medical curriculum.

Tacey Ann Rosolowski, PhD

0:04:18.2

So what does MBChB stand for?

Ralph Freedman, MD

0:04:20.5

Bachelor of Medicine and Bachelor of Surgery.

Tacey Ann Rosolowski, PhD

0:04:22.9

Oh, I see.

Ralph Freedman, MD

0:04:23.6

It's Latin letters. MB is Bachelor—I used to remember the Latin terms. But basically it means Bachelor of Medicine, Bachelor of Surgery, and it's a six-year course.

Tacey Ann Rosolowski, PhD

0:04:39.5

And you got that degree in 1965?

Ralph Freedman, MD

0:04:41.8

In '65 yes.

Interview Session: 01
Interview Date: February 24, 2012

Tacey Ann Rosolowski, PhD

0:04:43.3

Okay. I just wanted to check because that system sounds—you know—I was struck when I saw that particular series of letters, and I thought, Okay, this is a different system.

Ralph Freedman, MD

0:04:52.6

It's an all-or-nothing system. In other words, if you drop out after the first year and you decide to go to architecture or something else, there is no credit. You're out, and you start again.

Tacey Ann Rosolowski, PhD

0:05:03.6

When did you decide you wanted to go into medicine?

Ralph Freedman, MD

0:05:06.9

I wanted to do medicine probably—I started thinking about it, I guess, in my high school year, probably a year or two before I finished.

Tacey Ann Rosolowski, PhD

0:05:17.9

What was it that inspired you?

Ralph Freedman, MD

0:05:19.5

Interestingly, I was—Our family practitioner, I still remember his name—Dr. Hudson Bennett—was the—I was quite inspired by him and by his approach toward us. I was a child, of course, when I went through that with him. The only bad experience I had with him was really when he wanted to give me some injections for catarrh. I ran around the place, and they tried to coax me back in by giving me ice cream.

Tacey Ann Rosolowski, PhD

0:05:59.7

What is catarrh?

Ralph Freedman, MD

0:06:01.8

Catarrh is colds.

Interview Session: 01
Interview Date: February 24, 2012

Tacey Ann Rosolowski, PhD

0:06:03.4
Oh, I see.

Ralph Freedman, MD

0:06:04.1
Flu—type of flu. They used to use catarrh injections, and each shot increased in volume and discomfort so—I did remember him for that as well. But he actually wrote the letter of recommendation—one of the letters of recommendation—for me to the med school.

Tacey Ann Rosolowski, PhD

0:06:22.2
And I'm curious; what about his approach did you warm to?

Ralph Freedman, MD

0:06:26.7
I think he was just very— These are the old-style physicians; they used to do house calls. And when they visited with you they were very—they were almost part of the family, basically. Well, enough that my parents could interact with him, and also when it came to asking for a reference for me to— It's like your lawyer, your accountant, and your doctor sort of completing the circle of people that are important in a family situation. And so I certainly remember that period growing up and eventually went to medical school in Johannesburg. My parents, of course, lived in Durban, and so I was away from the family for some years. Then toward the end of that— well, let's see—I got married. I got married, for the first time, to a musician. That was my first year out of medical school, and it didn't work out. So we split. Then a few years later—two or two years later—I met Jennifer, who herself had been married, and she'd lost her husband under tragic circumstances. He actually had a heart attack in front of her, and that had been about two years or three years before. And we happened to meet because her brother and I went to the same gymnasium. We'd seen each other for some years before that, and then he introduced me to Jennifer. Jennifer had a son that we adopted, of course, when I got married. And then I have a daughter as well, Laura. So, Paul is my son—he's now forty-two—and Laura is thirty-eight. So that's how things were at that point. Meantime, at the point that I married Jennifer, I had finished the equivalent of a residency. They call it a registrarship. Again, it follows the British system. And I was already on staff at the University of Witwatersrand in a teaching capacity. I had broad interests in endocrinology and in cancer care, and I guess you're coming to the point of how I got here?

Tacey Ann Rosolowski, PhD

0:09:27.6
Well, there were a few questions I wanted to ask you about a little bit earlier periods.

Interview Session: 01
Interview Date: February 24, 2012

Ralph Freedman, MD

0:09:32.0
Okay.

Tacey Ann Rosolowski, PhD

0:09:32.7
I wanted to ask you if there was anyone else in your family who was involved in the sciences.

Ralph Freedman, MD

0:09:37.7
No. No, not—I don't believe anyone else that I can think of.

Tacey Ann Rosolowski, PhD

0:09:48.3
What did your parents do? Do they do?

Ralph Freedman, MD

0:09:51.6
My mother's side—she did not have a college education and my father—this was during the war periods—he actually worked for the South African Railways, and he worked as a water treatment officer. He went to college for the first two years, and the family was quite poor, so he couldn't continue his college degree. He was interested in law, and he'd actually—I think he'd done a couple of years of law, and the family tried to raise—they were quite a big family—they tried to raise some money for him to continue, but they were not able to do so. So he did not complete his college education even though he really wanted to do so, and I think that was one of the incentives—a lot of parents of the generation—our generation—and they did for the kids what they couldn't do for themselves. And so, that was— And then unfortunately he met his death here by a terrible accident. This was just after I graduated and before I did the specialty in obstetrics and gynecology. He fell down an elevator shaft. He got stuck between floors, and he knew how to open the outside door and tried to get out and slipped between the floors. My mother was a widow at quite an early age. My sister, whom I haven't mentioned—she's a physical therapist in Johannesburg—and my mother moved out to Johannesburg. She stayed with her for a number of years. She's still alive today. She was widowed— He was only fifty-one at that point.

Tacey Ann Rosolowski, PhD

0:12:00.1
That's very young.

Interview Session: 01
Interview Date: February 24, 2012

Ralph Freedman, MD

0:12:02.0

So that's sort of a background that we had.

Tacey Ann Rosolowski, PhD

0:12:07.2

Your mother and father's names?

Ralph Freedman, MD

0:12:10.3

My mother is Hilda, and my father was Barry.

Tacey Ann Rosolowski, PhD

0:12:16.1

And your sister's name?

Ralph Freedman, MD

0:12:19.0

Phyllis. We were sort of named after uncles all around, family members from either side. I had an uncle who was killed in Tobruk, and his name was Phillip. So Phillip became Phyllis. There were other Phillips in the family. And Ralph, my first name—my grandfather on my mother's side was a Ralph. Well, sorry, his son was a Ralph and one of my father's brothers was also Ralph. My middle name, Stuart, is named after my grandfather on my father's side. He was actually from Scotland. My father's family—my father's mother and father—the father was from Scotland, and the mother was from Sunderland, which is just to the south.

Tacey Ann Rosolowski, PhD

0:13:31.8

Returning to your work in graduate and postgraduate education, when did you decide to specialize in gynecology? And then when did that take the turn into cancer?

Interview Session: 01
Interview Date: February 24, 2012

Ralph Freedman, MD

0:13:46.0

That's a very interesting question because I've thought about that a number of times, and when I was working on the staff at the General Hospital, we didn't have the subspecialties that you have today here. So we did basically everything. We did OB—and my main emphasis shifted from OB to gynecology. I was involved with the care of a lot of cancer patients, and I still recall the first patient that I gave chemotherapy to. It was a drug called Alkeran, which is not used much anymore. It's an oral chemotherapy agent, and this patient went into total remission, and I was just flabbergasted about this. Of course, it's just lack of experience to know that you could get this type of response if you treated enough patients, but I was very fortunate. And then I happened to read a book by a physician called Joseph Sinkovics, and he was at MD Anderson at the time. He was actually in the Department of Internal Medicine. I think it was under Howell. Anyway, he was a brilliant man. He'd come from Hungary. I guess he was one of the people that emigrated about '57 with the Russians moving in there. He actually left his family behind, and he came over to the States, and he was absolutely brilliant. Anyway, I read this book about tumor immunology and all the genomes. I said, "You know, that's such an interesting area. I'd like to get involved." I started to follow the area more. Then came a point at which I had to decide. I did my PhD while I was working, actually, and the PhD was in relation to the breastfeeding habits of women and the relationship of absence of breastfeeding to maternal diseases, particularly with regard to the endometrium. So I came to a point where I was thinking of doing something postdoctoral, and I applied for and I got a fellowship called Eli Lilly International Fellowship to go to the United States, to come to work in Dr. Felix Rutledge's department, and at the same time to work with Dr. Joseph Sinkovics in Immunology. It's interesting because I—probably I was the first to go to the United States from our institution. Most of the people, the residents or registrars, when they wanted to do postoperative work they went to the Nuffield school in Oxford because that was the sister school. They were very experienced in obstetrics, and Sir John Stalworthy was the head of the department and was also quite interested in cancer. But I decided that I thought the future was more in the States than in Britain, and so I decided to try for the— If I hadn't got the fellowship, I wouldn't have been able to go, and I probably would have ended up going to England, if anywhere. But I was fortunate enough to get that fellowship and so I ended up coming here.

Tacey Ann Rosolowski, PhD

0:17:33.7

Could I ask you just a couple of questions, if I'm not derailing you from your—?

Ralph Freedman, MD

0:17:39.5

No, that's fine.

Interview Session: 01
Interview Date: February 24, 2012

Tacey Ann Rosolowski, PhD

0:17:40.9

I wanted to ask you why you chose to do the PhD after you'd received your MD.

Ralph Freedman, MD

0:17:46.9

I guess I'd always had a sort of enquiring mind. I was working in—I was actually working in—there were different hospitals. Now you might recall that South Africa was under the apartheid system until nineteen—what was it?—1980s or late 1980s, and so it only came down after I had emigrated to the US. And I spent a lot of time at the black hospital because there was strict separation of races in South Africa—the blacks were treated in the black hospital at Baragwanath, which is opposite Soweto. And the coloreds, which were basically of mixed blood, and Asians were treated at another hospital. And then the whites were treated in Johannesburg General Hospital. But when we did our rotations, they made sure they'd be rotated through all these different centers, and actually some of the best training that we had was out at the hospital opposite Soweto, which is actually one of the largest hospitals in the southern hemisphere.

Tacey Ann Rosolowski, PhD

0:19:05.3

Why was the training there so good?

Interview Session: 01
Interview Date: February 24, 2012

Ralph Freedman, MD

0:19:07.3

Well there was a lot of— Because you saw a lot of things, and you had a large population— tremendous population—from Soweto. There were probably a million people living there. In addition, there would be people coming in from the countryside with all kinds of problems— obstetrical problems, gynecological problems, advanced cancer—and one of the things that we noted there was that uterine cancer—cancer of the body of the uterus—was very rare in the black African in South Africa. There was actually a pathologist from the US, Dr. Ackerman, who came to visit one time—we used to get quite a few people who came to visit from Britain and even from the US. Of course, we could always show the fascinating cases that—something they'd never seen before. We got into a discussion about why cancer of the uterus was so rare in the African and yet the cervix was fairly high. Now we knew that cervix was much more common than in the western countries, and that was because people didn't get pap smears and diagnoses were made late. But there was still this big difference. An epidemiologist by the name of Oettle had done field studies and had remarked on the fact that cancer of the body of the uterus versus the neck of the uterus is very uncommon. So I gave it some thought, and then I landed a— this is one of the steps that took me into the PhD because I was encouraged to look at this in more detail. The more I look at it I thought, "You know, it's amazing what's happened here."

Breastfeeding had been very common up until probably the '30s and the '40s, and there was quite a bit of literature on this from the States showing that it was declining. And why it was declining was for two main reasons. One of them was that women wanted to go to work and they needed to spend more time at work. Of course, you don't have all the mechanisms for them to breastfeed at work like they do today. Even the companies make arrangements for them to do whatever they need to do. But the other thing was the availability of infant formula. With the availability of infant formula, we saw quite detrimental effects. For example, the African who often had a level of nutrition which was kind of borderline, and the children that were born and raised often were raised under very difficult circumstances—things that you probably see on the movies—from time to time they show the situation in Africa. Well, it was like that in southern Africa as well, and this is before AIDS. Of course, they did have TB and malaria and things like that, but they also had malnutrition, and one of the problems that the women ran into is they shifted to infant formula and then they stopped feeding the babies on their breast. Well, of course, the babies then developed enteritis and diarrhea, and many of them died. On the other hand, if they would have kept breastfeeding they would have had more chance to get to a stage of maturity that the child's immune system would be stronger and they— So that was one aspect, but the other, from the maternal point of view, was also interesting—that we suspected that what was happening is that the physiology of a woman is designed to support pregnancy and to support a period of lactation afterward. But if they stop prematurely, they would develop menstrual irregularities, and some of these irregularities would predispose to excessive estrogen stimulation of the lining of the uterine. We speculated that if you did that, then this could predispose, over a long period of time, to cancer.

Interview Session: 01
Interview Date: February 24, 2012

0:24:13.6

Now the African, on the other hand, most of them did continue to breastfeed, and they breastfed for a year and sometimes two years after birth. Instead of getting abnormal menstrual patterns, they got amenorrhea—their periods went away. So it was sort of a protective effect. It seemed to have a protective effect because there were multiple pregnancies often—one, two, three, four, up to 5, and nine sometimes—so that the woman might go through life with hardly having a period at all. She was always having babies and then ending up with a lot of—we used to see—of what we called secondary amenorrhea, where a woman's period stopped at a relatively young age—thirty-five, forty. You could never find out exactly what it was. But a number of them had repeated pregnancies.

0:25:19.7

So it was this aspect, and then the other aspect that brought me closer to cancer was the fact that we were seeing a lot of cervical cancer and wondered whether—well, of course at that stage we didn't know about HPV. And I did study with the people from the Poliomyelitis Institute where we started to look at taking samples from the vaginas of women we saw at the hospital—looking for viruses that could contribute to this disease. Now, we were not looking at HPV, but we were looking at Herpes type 2 and actually published a paper on that with the virology folks, showing that there was a higher frequency of Herpes type 2 serum antibodies in this population. They also had higher exposure to all the other STDs, and it was higher than you might expect if you compare them with controls—control—a woman who had not got cancer but of a similar age. Now Kauffman—Ray Kauffman—who was head of Gynecology here at Baylor until he died—he died last year. He was, of course, very interested in the herpes question as well. I got a chance to talk to him before he died, and he remarked on the fact that he still feels, even though we know that HPV is a primary factor, that there could maybe—perhaps herpes potentially does play a role, but we just don't know. The data wasn't as strong for that as it was for HPV.

0:27:23.5

Interview Session: 01
Interview Date: February 24, 2012

So I was— You could see what was happening. I was getting more and more involved with cancer issues—cancer of the uterus, cancer of the cervix—and I was steering away from obstetrics. And another area of interest which I had was endocrinology—gynecologic endocrinology. You basically could do anything that you wanted to do because you had the resources, and there weren't any type of restrictions as long as you followed the principals correctly. But my interest was starting to veer already toward oncology, and all of this happened at just about the right time. Then I started to read about immunology of cancer, and I thought, "This is just phenomenal. The answer has to be here." Little different though—it was a long, arduous road and still, to this very day, we don't have clear answers. But it stimulated me a lot, and I—when working with Joe Sinkovics, who was a very bright. Of course he's written a lot about this stuff as well, and he was interested in vaccines using an attenuated form of Puerto Rican strain of virus to insert into tumor cell lines which we used as vaccines. So when I came to work with him—when I came to the United States, I used to spend my time between the clinical side, sitting in with the—going to rounds—on all the clinical rounds with the clinical people, but then that whole year I spent with Joe in his lab, and we were culturing cells; we were studying cell lines—cervical cancer cell lines—characterizing them, trying to find out what characteristics were on them. And then from there I got into the vaccine story and cytokines and other aspects of immunology and immunotherapy.

Tacey Ann Rosolowski, PhD

0:29:40.7

Can I ask you a couple of questions? You said that you felt, at that point in the mid '70s, that it was the United States where things were going to happen, not Britain. What was it that you were seeing? Because you were really looking at three situations—you were looking at South Africa, Britain, and the US. So how would you compare what was going on in those three nations?

Ralph Freedman, MD

0:30:03.1

Well I think the system in the US is more open. For example, the staff who work in academic institutions in Britain, and even to some degree in South Africa, you've got a distinct, very—how would you say?—the lines of succession are very well-ordered. In Britain, for example, you can go from your registrarship, and your chances of even becoming a consultant depend upon who you know and which area you're in. It's a very orchestrated—organized in such a way that it doesn't necessarily support the people who are the most competent. So people really have a difficult time in working through that system. And I think the same applies to—hi, Jennifer.

Tacey Ann Rosolowski, PhD

0:31:43.1

All right. We paused briefly.

Interview Session: 01
Interview Date: February 24, 2012

Ralph Freedman, MD

0:31:45.5

So we were talking about the differences in the systems. The British system is very conservative about many things, and I think it applies to promotion succession within the academic organization but also applies to their research. There are a tremendous amount of very excellent researchers in Britain, but I think it's also limited by funding, basically. And that was one of the things that I recognized when I came here immediately is that the funding is much more—there's more liberal access to funding than there was in other countries, but there was more money available. Basically that's it. Money was never an obstacle at that time. So that was also very impressive.

Tacey Ann Rosolowski, PhD

0:32:49.7

How did you find just the whole upheaval of moving to another country? And did you intend to stay?

Ralph Freedman, MD

0:32:58.2

Yes. That, I think, was the point. We did not intend to stay. That's another part of the story. We arrived here in '76. In 1976, about in March, there was an uprising in Soweto. The police fired on some young students who didn't want to be taught in their own language. They wanted to learn English. The apartheid cabinet's approach was basically "divide and rule," interestingly, the same policy that the British had applied in their colonies. So they wanted to have control over the thoughts and minds of these individuals. So what happened, we decided at that point— While this was going on, my chairman, Felix Rutledge, came to me one day—and this was at the beginning of the fellowship. I'd only been there about three months. He said, "Would you like to consider staying here? Give you the appointment. Start the following year." Something I hadn't considered and of course I had to come home and talk about this. My daughter was about one-and-a-half, I guess, getting on two, and my son was eight or nine, something like that. And of course we had a house overseas—all things that would have to happen—property values dropped to really low values with the political situation. I was on a J visa, and if I returned to South Africa, I would have to wait two years before I could come back into the US. So we decided. It was a joint decision with everyone, and family overseas as well, because they had to dispose of our property there. Once we decided to stay, it would mean that we couldn't leave the country until we had a Green Card. So we could stay; basically we couldn't move around. I mean, you could move around, but you couldn't leave to go outside the country. So we did decide to do that. And that's how it happened that I joined MD Anderson faculty in '77—late '76. I don't know, does that cover what you—?

Interview Session: 01
Interview Date: February 24, 2012

Tacey Ann Rosolowski, PhD

0:35:40.0

Yes. I mean, I have another question, but I'll ask that a bit later.

Ralph Freedman, MD

0:35:46.8

We realized that South Africa was in a time situation, and that things were—with apartheid wasn't—wasn't a good system. In South Africa it was a legislated system, and this country it was a social system. It was interesting; when I came, I heard about the different wards for—different facilities for blacks and whites in our hospitals, particularly in the south, and in fact Jim Olsen drew attention to that in the book. But in South Africa it wasn't social, it was political and legislated. It was a very harsh and strict system, and there was no way to escape from it, if you were on the other side. So we knew, but we didn't know how this was going to happen—how it was going to transition. And it turns out, fortunately later, that because of the leadership there—Mandela and Tutu and de Klerk, he was the Prime Minister, the last white Prime Minister—and because of the way that they—primarily Mandela's influence—that it turned out to be a peaceful transition, which was a remarkable thing in this day and time. But we didn't— We had no idea what was going to happen. And you think from a family point of view. You take the children back to that setting when things were looking so bad. So you added up all the things, and we decided to stay. That required some help from various people, and Bob Moreton, who was the—he was like the—he was one of the VPs at Anderson, and he was very helpful in getting us the letters of support and so forth that they had to get. In those days, people could petition for people that they wanted to work in their hospitals. Now it's not permitted. But they were able to do that in those days.

Interview Session: 01
Interview Date: February 24, 2012

Chapter 2

0:38:14.8 to 0:41:31.6

A: Joining MD Anderson/Coming to Texas

Discovering and Rich and International Community at MD Anderson in the Seventies

Story Codes

A: Joining MD Anderson/Coming to Texas

B: MD Anderson Culture

B: MD Anderson History

Tacey Ann Rosolowski, PhD

0:38:14.8

So how did you—? When you came to MD Anderson in 1976, what did you know about its reputation and how did you find the institution when you arrived?

Ralph Freedman, MD

0:38:24.5

Well, I didn't know as much about its reputation as about individuals that worked there. I knew about Felix Rutledge, and I knew about people like Joe Sinkovics, and of course the institution was fairly young. When I joined it, it was hardly— Let's see, it's now about 60-something years old?

Tacey Ann Rosolowski, PhD

0:38:48.2

It was in its 20s then.

Ralph Freedman, MD

0:38:50.5

Yeah, it was very young. But what was interesting, when I got here I found there were many people like myself that came from all parts of the world—South America, Britain. Michael Keating was from Australia. There were several others from "Down Under," as we used to say. There were others from England, from Europe, and South America. So there was quite— I don't know the extent, but in the early stages of development of MD Anderson, there were probably quite a high proportion of individuals who were not US born.

Tacey Ann Rosolowski, PhD

0:39:39.5

A real international community.

Commented [T2]: Dr. Freedman begins this segment with a fuller discussion of how he came to MD Anderson. He also comments on his family's adjustment to life in the United States and the social life of MD Anderson in the mid-Seventies, with its international faculty.

Interview Session: 01
Interview Date: February 24, 2012

Ralph Freedman, MD

0:39:42.6

It really was. Benjamin Lichtiger is from South America. Let's see, well—pathology, I just forgot his name. Now he's the head of the transfusion service. And then the head of Pathology was from Trujillo, South America. So that's how it was.

Tacey Ann Rosolowski, PhD

0:40:13.7

What did that add to the climate—intellectual climate?

Ralph Freedman, MD

0:40:17.2

I think it added a lot. I mean it created an atmosphere of free expression, of interaction, and people learning from each other. Everybody had something to offer. In that situation, I think you have opportunities to learn. There were also potential opportunities for friction, but I think the other was predominant.

Tacey Ann Rosolowski, PhD

0:40:54.7

So in your work on the cell lines, what—? How did that evolve during the first year, and what were your findings? Were they preliminary, or were you actually coming to conclusions at that time?

Interview Session: 01
Interview Date: February 24, 2012

Ralph Freedman, MD

0:41:07.9

I don't think any of the work that I did was earth-shattering. But it was developing basic principles, characterizing cell lines. I worked with Mike Siciliano early on to—yep.

Tacey Ann Rosolowski, PhD

0:41:27.8

Here let me just pause this.

0:41:31.6 (end of audio 1)

Interview Session: 01
Interview Date: February 24, 2012

Chapter 3

0:00:20.1 to 0:27:38.9

A: The Researcher

Research into Treatment for Gynecologic Cancers

Story Codes

A: The Researcher

A: Overview

A: Definitions, Explanations, Translations

D: Understanding Cancer, the History of Science, Cancer Research

D: The History of Health Care, Patient Care

D: On the Nature of Institutions

C: Evolution of Career

C: Professional Practice

C: The Professional at Work

C: Collaborations

C: Discovery and Success

Tacey Ann Rosolowski, PhD

0:00:02.1

Okay, we're recording again after a brief break for tea. And we were talking about the research that you were doing when you were on your fellowship, and you were just kind of describing how you were transitioning from that research into the next phase.

Ralph Freedman, MD

0:00:21.7

I started to think about translating some of the knowledge that we had in clinical trials, and the first efforts were at developing vaccines for gynecologic cancers—cervix cancer and ovarian cancer—along the lines that Dr. [Joseph] Sinkovics had already done in sarcomas and melanoma. And so he did a trial in cervical cancer patients. It was a randomized trial, and the results were not spectacular. There looked like there was a little bit of a difference. Then we, at about that time—also, I think the HPV story started to come out, and it was clear that there would be efforts to produce vaccines to target the virus, and the incidence of this disease would probably go down, which is what's happening today. Not from the vaccine itself, but from the fact that pap smears are being more widely utilized. I think it is only about ten percent in this country that doesn't get pap smears. The vaccine, of course, would help to eliminate it all together. In fact, today cervical cancer is not— Let's see, you've got ovary, endometrium, and then cervix as cause of death amongst women, and cervical cancer relatively uncommon.

Commented [T3]: In this segment, Dr. Freedman discusses his “travels in the lab,” first explaining how his Fellowship work on cell lines transitioned to the development of vaccines for gynecologic cancers. He talks about the prevalence of these cancers, explaining the special challenge of ovarian cancer. He explains the logic behind the vaccine strategies tested (e.g. intra-peritoneal injection) and the immune mechanisms stimulated, and also notes the clinical challenges faced, which led to work on an approach using T-cells. He then details his work with T-cells, describing some of the equipment used, the procedures attempted, and his evaluation of those procedures, concluding that his work added “building blocks” to the understanding of the immune system, as well as the creation of a mono-clonal human antibody. Dr. Freedman then goes on to talk about the relationship between the immune system and the inflammatory system and his work with eosinoids and inflammatory responses to tumors. It may be possible, he explains, that if the inflammatory response can be stopped, a tumor will stop growing. He notes that his research has given him new respect for how difficult it is to treat cancer, pointing out that mortality rates for cancer has not changed substantially over the past years. He discusses the difference between private practice and academic medicine then describes what it was like to establish his own laboratory after working collaboratively in others' labs. He offers his views on translational research. Dr. Freedman then talks about how he dismantled his lab and projects when he decided to retire.

Interview Session: 01
Interview Date: February 24, 2012

Tacey Ann Rosolowski, PhD

0:01:54.7

The cervical cancer?

Ralph Freedman, MD

0:01:55.7

Cervical cancer. Also as compared to what we saw in South Africa, where eighty percent of the women were with advanced disease, and it was the most common cause of death from malignancy in black Africans. Here it has become the opposite, where eighty percent are in early stages and only a relatively small percentage now of the patients we see at LBJ—we are at work at the moment. And you see people who are coming from over the border or who basically haven't had any preventative care.

Tacey Ann Rosolowski, PhD

0:02:32.6

Just for the record—I'm sorry—you mentioned LBJ, and could you give the full name of that institution?

Ralph Freedman, MD

0:02:36.8

Lyndon Baines Johnson.

Tacey Ann Rosolowski, PhD

0:02:39.0

And it's the public hospital here—

Ralph Freedman, MD

0:02:40.4

Yes. It's one of the two county hospitals—Lyndon Baines Johnson and then Ben Taub.

Tacey Ann Rosolowski, PhD

0:02:47.7 Okay.

Interview Session: 01
Interview Date: February 24, 2012

Ralph Freedman, MD

0:02:51.2

So I work there once a week, on Tuesday. I help Dr. [Lois] Ramondetta with her clinic. She does a clinic on Wednesday, I do the clinic on Tuesday, and we'll get to that at some point. So then the next— So the real challenge for us was then, and still is, ovarian cancer. ***Tacey Ann Rosolowski, PhD***

0:03:16.1

I'm sorry. Why is ovarian cancer such a challenge? I had read that—that it's just the biggest challenge for—

Ralph Freedman, MD

0:03:23.7

Well, there's not tests for early diagnosis, unlike the Pap smear, which is early—can pick up early changes on the cervix. There is no early test. The CA-125 is not recommended or approved for early diagnosis, and apart from annual examination, that is all they have today. And the majority of patients are picked up when they have advanced disease, when the mortality is highest. So only about twenty-five percent of patients will survive five years when they have this advanced stage. So that is, and still is, the challenge. And we were thinking of immunological approaches, and I started off developing a—using the vaccine approach because we knew there were immune cells in the peritoneal cavity but they were not doing anything. And basically with, I would say, primitive knowledge that we had at the time, which would have been in the early '80s, we developed a strategy for intraperitoneal injection of vaccines. There was already intraperitoneal chemotherapy. So we thought, “Why can't the intraperitoneal route be used to administer vaccines?”

Tacey Ann Rosolowski, PhD

0:04:49.5

Could you describe what the purpose is of the intraperitoneal intervention?

Interview Session: 01
Interview Date: February 24, 2012

Ralph Freedman, MD

0:04:55.8

So the approach was, and there was some evidence that if you—and this is from Sinkovics' work that these cells—these cultured cells—if they were infected with a Puerto Rican strain of the virus, which was an attenuated virus so it didn't cause harm, and then you put this new viral antigen onto these cultured cells and then you produced extracts of the cells—so you killed the cell, so of course it can't grow, and you kill the virus as well by using UV light and the methods to destroy virus. If you use extracts of these cells, you can actually stimulate components of the immune system. And during that period, I actually collaborated with Dr. Eva Lotzova, who was—she was originally from Czech—it wasn't Czech Republic in those days, but from Czechoslovakia. And she was a noted immunologist in so-called "natural immunity"—basically, natural killer cells. And we saw, in a number of these patients who were receiving these vaccines, that it was stimulating their natural killer cell function. So we thought this was fantastic because the natural killer cells—if they can kill cells without recognizing particular antigens on cells—they have such a broad ability to kill tumor cells. Somehow they recognize that the cells are malignant. It is not a specific interaction like you have between the T-cell and the tumor. In other words, the T cell recognizes the tumor cell through its T-cell receptor recognizing an antigen that is presented in the context of the histocompatibility complex. It is a very defined, highly developed mechanism of immunity which you basically only get in mammals. Whereas more primitive species, like earthworms, they only have the NK system. The NK system was always there in the humans. It was a question of whether you could stimulate them, and we saw that this vaccine could do it. So we did treat a number of patients with intraperitoneal vaccines, and we learned a lot about the immune system.

Then they decided not to stay with that system—and a number of reasons for this. And some people seem to think, "Well, you should have stayed with it." But one of the problems was the fact that it's very difficult to quantify what you've got in the vaccine when you're that type of approach. We couldn't use the patient's own tumor because it was very—we tried, but it was very difficult to grow them to a point that you could infect them with virus. So we had to use cell lines which had no relationship to the individual. So they were histocompatibility mismatched, and also they were extracts. So when you look at all the requirements today that the FDA would require for producing a biological product that would go into humans, it was going to be an impossible kind of task.

0:08:33.0

Interview Session: 01
Interview Date: February 24, 2012

So about that time I had a post-doc in my lab, Dr. Constantin Ionnides who later on became an assistant professor in our department, and he worked with me on getting more information about the immune system. His mentor was Dr. Chris Platsoucas who used to be the deputy chairman of Dr. [Margaret] Kripke. You remember when Dr. Kripke was head of immuno—she was head of Immunology, and Chris [Platsoucas], whom I'm still friendly with to this day, was her deputy chairman. Well he was—he was—brilliant fellow—he came from Greece originally. Got his PhD at MIT, and he was an expert in cellular immunology and also molecular immunology. So he was able to sequence T-cell receptors, and he had a tremendous understanding of the mechanism of T-cell immunity. We decided at that time to try to see if we couldn't understand better and work out an approach for using the T cell, because the T cell is a very specific mechanism, and also there's more of them than there are NK cells. And also, the thought was those T cells could actually migrate and target specifically tumor cells.

Also at that time, Steve Rosenberg, who's at the NCI, was working on adoptive therapy. There were some immune therapy approaches that were available. There was interferon with Dr. Jordan Gutterman. He was working with and under—with Hirsch—Dr. Hirsch. That was the clinical department of immunology. There was a political issue because Sinkovics did not get on with [Evan] Hirsch. I liked both of these people, as it happened, but it wasn't easy when you're a fellow, by the way, to go and cross over, especially if your bosses didn't communicate or if your boss didn't communicate with somebody else. That would be a hostile move to go and do that kind of thing. But that's sort of going backward a little bit. But working with Chris was easy because he was in another department. Sinkovics was already gone by that stage. On the vaccines I'd worked with, Jim Bowen who was—he was Tomasovic's predecessor. But before that, he was the acting—I guess the acting chair of Virology. We had a Department of Virology. Ralph Arlinghaus is still in that department. I guess they may be a section now. I don't quite know whether it is a separate department anymore or not. Jim Bowen and I had a good working relationship, and he was the one that helped me develop the viral oncolysates or the vaccines for administration to patients.

0:12:02.8

Interview Session: 01
Interview Date: February 24, 2012

But at that time, too, he was— There were changes taking place in his section, and I guess he had been tapped in order to become the Vice President for Academic Affairs, which would mean he would have a limited role. But fortuitously, at that time, I met up with Platsoucas who was a basic scientist and, as I said, had a very fundamental understanding of the immune system. Jim was a virologist, so that was important for the development of the viral vaccines, but Chris Platsoucas was an immunologist—cellular immunologist and molecular immunologist. So we decided to go after the T cell, and along the lines that Rosenberg had developed but this time for ovarian cancer and to try to expand T cells that were sort of—that were activated and to put them back into a patient. And we actually developed—we spent a lot of time on this, and we had funding from the American Cancer Society, and then later we had funding from the National Cancer Institute to actually develop a clinical trial for adoptive immunotherapy. We had some very good preclinical information, obviously, to support it. We developed a technique for growing the cells to very large numbers, and we were able to develop—grow something like ten to the ten—between ten to the ten and ten to the eleven activated T cells from these patients. It had to come from the tumors. So, in other words, these patients had to be candidates for surgery in order to get them. And we did find, though, that it was difficult to grow them from the solid tumors, but we could grow the cells quite nicely from the fluid around the tumors.

Tacey Ann Rosolowski, PhD

0:14:09.6

What were the special dimensions of your technique?

Ralph Freedman, MD

0:14:11.9

Well, we used a device—a special culture device that had media flowing through it, and it had to be monitored so many times a week to measure its glucose because you couldn't wait until the cells were dying. You had to come in sometimes on the weekend. I had dedicated technicians who would come in on a Saturday and Sunday and check the cells, and then if the cells were ready, we had to call the patient in to go and be treated. So it was a laborious and very labor intensive—but very good personnel—actually one of them was Steve Tomasovic's wife, Barbara [Tomasovic].

Tacey Ann Rosolowski, PhD

0:14:47.9

No.

Interview Session: 01
Interview Date: February 24, 2012

Ralph Freedman, MD

0:14:49.3

Barbara—she's retired now. And she was fantastic because she kept every single detail and with all of that information, we were actually able to describe our technique in *Journal of Immunology Methods*. So it is there for everyone to read and see—how do you do these things? What types of cells do you get out of it? But essentially there was a little bit of activity but really nothing remarkable, and it was very costly. It cost in time, and it cost a good few thousand dollars per patient. Now, Steve [Tomasovic] is still doing it, and Patrick Hwu, who works in Immunology here, is still doing it for melanoma. But for ovarian cancer it really—there were logistic issues in that the patient had too much burden. Really, what you wanted to be able to do was to reduce the tumor burden to the point at which you could use the cells. That meant you would have to freeze—you would have to grow the cells up at some point and freeze them down, and then when the patient was in remission from the chemotherapy, you could use the immunotherapy. Logistically this was just too much. You're looking at having facilities to store large numbers of cells. You wouldn't know whether you could even use those cells later on.

0:16:28.0

And I still believe that the immunotherapy approaches which people are still talking about for ovarian cancer are potentially useful, but you would have to use it at a time when the tumor burden had been reduced by surgery and chemotherapy to the point at which it was minimum tumor burden so that the ratio of immune cells to tumor cells was satisfactory. And also, the problem that you have to deal with in ovarian cancer was that the immunosuppressor systems that are in place, and which we now know a lot more about, actually mitigate against using these approaches. So you really have to reduce the tumor burden so that you reduce the amount of tumor suppressive factors that are in the system. We've also tried with IL-12, and we had a grant from the NCI to do that because IL-12 was supposed to drive both NK cells and adaptive immunity. And we tried that in patients with the intraperitoneal approach, but, again, the results were not enough to drive this effort. We also tried whole autologous cells, where we took the tumor cells out of the patient. And we got a grant—an NCI grant—for that study as well. We took the tumor cells directly from the patient and then we put a gene inside those cells to express a factor on the surface that would co-stimulate the immune system. This was developed by Jeffrey Schlom at the NCI. And basically we got the material from him to do it. But, again, we proved that it was not efficient enough to work, and the same problems developed.

0:18:41.6

So, at that particular point, that went on for several years. It supported my academic contributions, if you will—papers and things like that. And the intellectual side of it, which is—you know—you asked me the question, “Why was it better to be in academic practicing than—

Interview Session: 01
Interview Date: February 24, 2012

Tacey Ann Rosolowski, PhD

0:19:04.4

Private practice.

Ralph Freedman, MD

0:19:07.2

—private?" It is a different philosophical— It's a different environment. It's a different way of life. It's different philosophy. Everything is different about it. And one of the good things about an academic practice is that you can ask these questions and you've got time to do this and to think about things and to interact with other scientists and to get excited about things. So I shared—and that was one of the major contributions that Anderson has been to my life is to give me that resource—give me that access to that environment where you can interact, and, of course, to interact with others, even outside the institution. Because Anderson was becoming recognized, as it is today, as a major center. So none of my work contributed to any breakthroughs, but I think we did contribute some building blocks. We learned something about the immune system. Along the way, we developed a monoclonal human antibody to ovarian cancer.

Tacey Ann Rosolowski, PhD

0:20:11.1

What does—? Could you describe what that means?

Ralph Freedman, MD

0:20:13.0

A human antibody is a—up to— Well, I guess in the '80s, most of the antibodies that were used for diagnosis and even for in vivo therapy were raised in mice. And the technique of producing antibody—monoclonal antibody—won Milstein—Cesar Milstein—the Nobel Prize in 1977. And basically what they did is they took immune cells from a mouse and they fused them with the myeloma cell line, which is from a human, so that you had a hybrid cell which had the machinery to make the antibody, but it also had a human genetic—some human genetic machinery in that. And those were the early antibodies. That was the beginning. And it was very appropriate that they received the Nobel Prize because today that same principal has been adopted totally human antibodies. There's no mouse antibody in the system anymore. It's just human antibody, which means that when you put it into the patient they don't get an immune reaction to the antibody. You can use it without getting— Whereas when you used to put the old antibodies into patients, they got what they called HAMA—human antimouse antibody response—which interfered with the activity of subsequent doses. So it was a limiting factor. And today we don't have to deal with that. We did make one antibody—but it was an IgM, and the best antibodies are IgG because they are smaller and they can get into them much more easily. And we had a patent for it, though I think the patent is expired now.

Interview Session: 01
Interview Date: February 24, 2012

Tacey Ann Rosolowski, PhD

0:22:23.0

That was in 1995.

Ralph Freedman, MD

0:22:24.0

Yeah right. Early on. And that was— We got funding from the state of Texas—what's it? Texas Technology, I think. So we actually produced it, and it was available. And we sent it to ATCC for anybody wants to use the hybridoma or the—in producing—the antibody producing hybridoma so they can get access to it. So again, this—

Tacey Ann Rosolowski, PhD

0:22:51.4

I'm sorry. Could I just—? What does IgM and IGg stand for?

Interview Session: 01
Interview Date: February 24, 2012

Ralph Freedman, MD

0:22:56.1

Well IG is immunoglobulin. And it's immunoglobulin-G. The first is an IgM response. It is a larger antibody, and it has a short phase, but it's a large molecule. So when you talk about molecules of that size getting out of the vascular tree and into tumors, for example, it's not going to be too helpful. You've got to be able to use an IGg. IGg is what happens when you get a memory response so you get a long-term immunity to a particular infection or a particular antigenic challenge. So IGgs are more useful in practice. Now, today there are molecular techniques for changing IgMs into IGgs, and industry is much involved in that type of thing.

Tacey Ann Rosolowski, PhD

0:24:07.8

Uh-hunh (affirmative).

Interview Session: 01
Interview Date: February 24, 2012

Ralph Freedman, MD

0:24:08.1

So that carried me through a phase. I think the important thing is a lot of work that's done in the lab is dependent upon collaboration—interaction with others. It's the rare scientist who can do any of this on their own. I think one can always be a little suspicious when you find that a piece of work comes out of one laboratory and there're no collaborators. Because in today's world there's just so many areas of expertise that's needed in order to produce—you know—to advance an idea to the next phase. So I depended—my—as I always say, my career was sort of locked—dependent with the careers of others. Whether it was Sinkovics or whether it was [James] Bowen or Platsoucas, there were always others that were part of this development. We started to get interested—unfortunately it was late in my career—on the inflammatory reactions. Discovered that a lot of—a lot of the changes that take place within tumors actually involve inflammatory changes—inflammatory cells like monocytes and macrophages. And the release of products of the immune response such as eicosanoids—and this is the area, I think, that Dr. [Raymond] DuBois is interested in. I haven't spoken to him about it. And we did some studies. We went back, working with, first of all, researchers at NIH—Franco Marincola and his staff. We actually did microarray studies showing the genetic profile—the RNA genetic profile of ovarian tumors. We were one of the first really to do that. And we focused on the immune and the immune inflammatory environment. So a lot of this supported the work that we had done. And then, also, we saw that there were a lot of inflammatory signals coming out of these tumors. So that led me to look at the eicosanoid story. And actually I worked with Bob Newman who was a pharmacologist at MD Anderson. He left about a year or two ago. And we actually did eicosanoid profiles of ovarian cancer, and actually these profiles—papers published in *Clinical Cancer Research*. And they took some of our work and they put it on the cover sheet of the journal. Because those pathways could be targets for new therapies. We haven't gotten into that area as yet. There's a very close relationship between the immune system and the inflammatory system. They're sort of part of one big system. But the inflammatory system can drive a lot of these tumors, and if you can find a way to interrupt the inflammatory processes, it may be possible that you stop the tumor from growing. Just like people have spent a lot of effort on angiogenesis.

Ralph Freedman, MD

0:28:12.5

This could be another area of similar importance. And there are about fifty products—I read an article—about fifty products that industry has developed that can interfere with inflammatory processes within tumors. So far we haven't seen many of them coming into—well, there were some like the COX-2 inhibitors that they used in colon cancer.

Tacey Ann Rosolowski, PhD

0:28:39.2

I'm sorry. I missed the name of that.

Interview Session: 01
Interview Date: February 24, 2012

Ralph Freedman, MD

0:28:41.0

COX-2 inhibition—and these agents were used to antagonize adenomatous growths in patients with pre colon cancer. So basically that is the—my sort of travels in the lab. We had—over the years we had—I supported I think three or four PhD students, and one was an MD/PhD. We did work on the monocyte, macrophage, in ovarian cancer. Amy Loercher got her PhD for papers published in Journal of Immunology on the monocytes in ovarian cancer. Sheri Butts—she was a PhD student who did the work on dendritic cells in ovarian cancer. And then I had some excellent postdocs from outside. And I can single out Dr. [Gabriella] Ferrandina who was from Italy. And she was from the Pope's hospital in Rome. She was outstanding. She got some good papers—nothing to do with immunology, but just looking at some pharmacology of certain drugs. And then Dr. [Robert] Melichar—he came back a couple of times to work with me, and he's now the chair of Medical Oncology in the Czech Republic, so he has his own department. And he got his PhD, basically, with the work that he completed in my lab. Actually, we went to visit him recently, him and his wife and kids, and they took us around Prague. Phenomenal guy—he could speak—I know a lot of Europeans are able to speak many languages, but he could speak five languages. And I had a Japanese student in the lab. And I saw one day he had a Japanese dictionary. So he was busy studying Japanese while he was working with me.

Tacey Ann Rosolowski, PhD

0:31:51.0

He had a real gift.

Ralph Freedman, MD

0:31:51.7

Yes. And he produced some very important—good papers—while he was there. So it was fun to work with the students, fun to work with the postdocs and have this interaction. And there was always interaction with somebody—on a collaborator scale or whatever. That was that aspect of my career. I don't think we—I think, basically, we contributed some components of knowledge to the disease, but nothing in terms of any earth-breaking treatments. It's fun to look at. It gave me a bit of perspective on how difficult cancer is. Cancer is a difficult disease to treat. And if you can't prevent it, and you've got a disease that causes a significant mortality—and in fact that mortality hasn't changed in the last ten to twenty years—it's a tough road to get into. I know there's a lot of hope that personalized therapies and identifying all these mutations and that be able to— So far what I've seen at the FDA is—because I serve on this Oncology Drug Advisory Committee. It's my third year on it. And a lot of these new drugs come, and they give incremental changes. There are incremental benefits. But you don't get something that wipes out the disease and the patient is cured. So it's been eye-opening to get that side of the picture.

Interview Session: 01
Interview Date: February 24, 2012

Tacey Ann Rosolowski, PhD

0:33:48.3

Well, I was really glad that you've described the intricacy of that process by which you were growing those cells, because I don't think the ordinary person who doesn't spend time in a research lab that's related to cancer understands just how delicate the cells are and what you have to do to kind of create the facsimile of a physical environment in order to grow those tumor cells so that you can work on them. It really gave me a real appreciation for the challenge of how to create something to investigate. And I just don't think most people understand how that works and how laborious it is and how complicated the physical systems are that you're trying to tease apart.

Interview Session: 01
Interview Date: February 24, 2012

Ralph Freedman, MD

0:34:41.8

These cell lines are basic to any type of understanding. And, of course, now we have a registry at MD Anderson of all these lines which we didn't have before. And Ty Hoover who works in the IRB office which I also participate in, he has developed a phenomenal registry now. All these lines that were sitting in people's fridges and so forth have now been identified and catalogued, and they are potentially useful. We have to understand, of course, that a cell line is a little bit artificial because it's been taken out of the host and expanded under culture conditions, and you've selected out certain parts of this—certain cells from that tumor—that are able to grow. And then some of them can't. They don't grow very well. And they may be very important or may be more important than the ones that you actually have in the test tube. So the cell lines are important for studying basic—getting basic information. But at some point you've got to move from them to the tumor itself.

Tacey Ann Rosolowski, PhD

0:35:59.5

You know, I would like to do a quick sound check because we have one of these dreadful leaf blower things.

0:36:08.5 (end of audio 2)

Tacey Ann Rosolowski, PhD

0:00:00.6

Here we go. Okay. I don't know why the record didn't take. So let me ask you again. I neglected to ask you earlier whether—when you shifted from your fellowship to your academic appointment—whether or not you established your own lab or whether you worked collaboratively.

Ralph Freedman, MD

0:00:20.7

Initially, I was with him, and then—

Tacey Ann Rosolowski, PhD

0:00:23.0

This was Dr. Sinkovics.

Interview Session: 01
Interview Date: February 24, 2012

Ralph Freedman, MD

0:00:24.8

Sinkovics. Then at some point, I got my own lab after that, and it was after that that I remained with my own lab assignment. He was there for a few years, and then he moved to Florida—Sinkovics did. So, let me see, the next phase was I occupied part of Jim Bowen's lab, and then after that, I got my own assignment, which remained like that for years after that. We were finding that we had support from external and internal sources.

Tacey Ann Rosolowski, PhD

0:01:07.8

And what was that like, shifting from sharing space to having your own lab? Did that make a difference in the type of work you did?

Ralph Freedman, MD

00:01:15

I think yes. It probably did because you could bring people in to work. For example, you could bring students and postdocs at your own decision, and it wasn't dependent upon somebody else deciding for you.

Tacey Ann Rosolowski, PhD

0:01:37.1

Where was the lab located?

Ralph Freedman, MD

0:01:40.7

The lab was located—let me see—Sinkovics was up on the—was it the seventh or eighth floor of the old Central Core Building? And then we moved around the corner, closer to Virology. I know the area, but I can't describe it to you exactly. But it's in the Central Core of the old building. Then we moved down to four, at the back, behind the operating room area, and actually it was there until I closed my—the lab—before I retired.

Tacey Ann Rosolowski, PhD

0:02:25.7

I was wondering if you could comment on the ways in which the sort of phases in your research career dovetailed with changes in just the understanding of cancer and how cancer as a disease was approached over those decades.

Interview Session: 01
Interview Date: February 24, 2012

Ralph Freedman, MD

0:02:45.5

Yeah, I think that in some ways it's a seamless process because our knowledge influenced what people did, like when we started with the cellular vaccines. There was a lot of interest in cellular vaccines at that time, a lot of excitement because this came after interferon. Interferon started off with using leukocyte interferon in which about two percent of the extract was active interferon that was used by Gutterman. And in the next phase, when they developed the recombinant technology, they shifted from leukocyte interferon to recombinant interferon. And then once they got recombinant interferon, then they made recombinant IL-2 and recombinant IL-12, and the cytokines that they used in vivo today are all recombinant cytokines. So all of these things—and then you had the monoclonal antibody development after '77, I guess the 70s. During the 70s, you had monoclonal antibody development, but first it was mouse antibodies. And then later on people started to develop human. The techniques with doing things in the labs also changed because of the evolving. And depending upon what you wanted to do, the expertise might or might not be available in your lab, and then you had to go to others. And that's why I say that you really today, in today's world, you cannot do this kind of work anymore without interacting with others. I had Platsoucas who was a very important contributor to the research that we did. There was Newman on eicosanoids. There was Franco Marincola from NCI. We were not doing any type of consistent microarrays, so I had the NCI group to do the microarray work and then doing the interpretations of that. I had proteomics. It was a biochemist from Japan, Dr. [Koichi] Kobayashi, who we did proteomics with, and we actually did proteomics analysis on fluids to see what was in them.

Tacey Ann Rosolowski, PhD

0:05:23.9

What is a—? What are proteomics?

Ralph Freedman, MD

0:05:26.1

Proteomics is the study of proteins. There are hundreds of thousands of proteins in our bodies, and these proteins do different things, and they may be involved in signaling. And we actually found one which was called the zeta protein—14-3-3 zeta—and that was an important adapter protein. And that has multiple activities in cellular proliferation. We had a proteomics laboratory at MD Anderson, so we made use of that in order to find out about this protein and its unique pattern in ovarian cancer. So a lot of the work that we did here was absolutely dependent upon the expertise in other labs at Anderson or outside of Anderson, and I think that's a practice that goes on today.

Interview Session: 01
Interview Date: February 24, 2012

Tacey Ann Rosolowski, PhD

0:06:26.6

That's leading me to my next question. I believe in one of the materials that Mary Jane shared it talked about sort of characterizing your research as translational research, and I was wondering what your response to that was, because that's all about crossing those disciplinary boundaries and communicating with other—

Ralph Freedman, MD

0:06:50.9

Translation unfortunately has become a funding buzzword. It became incorporated into the NCI funding programs or external funding programs. You know, I served on the National Cancer Advisory Board, so we saw a lot of the things there that it was supporting. And translational research, and maybe it still is now, implies that you take things from the laboratory and then you take it through to the clinic, and I guess the best example would be Dr. [John] Mendelsohn's work with his ImClone product—Erbix. He started working in collaboration with others in California, and he carried it over to New York, and then eventually he had an antibody that he could use in patients. And then trials were done with an antibody, and then, of course, it's now commercially available. So that is, perhaps, the best example of translation work—that it starts and does end up somewhere where you've got something that's either useful or marketable, but a lot of it is research that's done and is contributing something to understanding the disease, understanding potential targets, but maybe doesn't reach the final point of producing. And then even products that are produced and that are commercialized, they have to be replaced in a few years by a small molecule here that does the same thing without these toxicities. So it raises the whole point about what should be the focus of the academic scientist. And I think if we get too obsessed or too taken up with trying to produce a successful outcome, particularly when you're dealing with cancer, it just may be too ambitious for the nature of the disease that we have to deal with. That doesn't mean that you should give up, throw up your hands, and say, "Well, this is just impossible. I'm not going to do it." I think if we accept the fact that each block is a building block to understanding the nature of the disease, and maybe somebody in a few years will take that information and say, "Well, this is another direction that we can go in, in developing a new therapy." Because I strongly believe that most cancer therapy from here onwards is likely to be incremental in this outcome. I don't think we should expect a magic bullet that's going to suddenly wipe out the disease. It's different when you're talking about something like HPV vaccine because there you got one simple target—the virus that you know contributes to the change of a normal cell into a cancer cell. And you know there is a very high probability that that virus is responsible, so if you can prevent that virus from getting in there, it's going to work, but once the cancer is already established, it's got multiple mechanisms for getting around. I think pathologists always used to say that cancer has almost got a mind of its own—that a human being tries to make a strategy towards defeating it, and then it develops another mutation. And that seems to be what happens, because even in patients that have been targeted with drugs like Gleevec or imatinib, they eventually get resistance.

Interview Session: 01
Interview Date: February 24, 2012

Tacey Ann Rosolowski, PhD

0:11:32.6

I didn't know that.

Ralph Freedman, MD

0:11:34.4

And they get resistance. They might get resistance because they are developing mutations, so that same drug is not working anymore, and you have to change to another drug. Well, how many times are you going to have to do that before you actually get rid of those cancer cells? And it will be interesting to see what happens with the personalized therapy approach, because by analyzing the tumor and identifying these different mutations, one has to prioritize them. One has to have a drug that will target it. And even if you have that drug, what's to guarantee that you won't get another mutation to come along and another line of cells that develops that's resistant to that drug? Can you have enough drugs available that can actually annihilate that tumor? So I think we have to see—it's an experiment that's being done now with the IPCT, and we have to see how that works out.

Tacey Ann Rosolowski, PhD

0:12:45.8

You mentioned that you've done both the basic research and research with clinical trials as well. And that's a theme that's come up in a few interviews—it's that connection between basic science and clinical research and how there's kind of a feedback loop between them. I wonder if you have any observations about their respective contributions. How are they related?

Ralph Freedman, MD

0:13:19.1

You know, it's interesting. The previous National Cancer Institute director—actually, he was there when I joined the NCAB. Dr. Richard Klausner said that basic research is a lot like a Lewis and Clark expedition. They didn't really know what they were going to accomplish on this thing, but they had some belief that there was something at the end, but it's not always clearly hypothesis-driven. So we are so used to only look at the research protocol—what's the hypothesis? What's the underlying hypothesis for this label research? Same thing when you talk about translational research. You expect there to be a clear hypothesis. But I think there's a lot of basic research where it's not clear that there's going to be a link. It may provide more understanding of the disease or some component of a disease or some mechanism, and again, it's one of these building blocks, but it's not so clear that it's translational at that particular point. And I think that research is also important. Not all research necessarily has to translate into a new treatment.

Interview Session: 01
Interview Date: February 24, 2012

Tacey Ann Rosolowski, PhD

0:15:11.4

When you were describing the value of— A little bit earlier we were talking about the kind of research that simply opens up a new pathway that maybe the direction of it will become clearer later. It really reminded me of the kind of post-war spirit of doing research where it was just—you're doing research to do research, to just find out what's out there. Then it was really later on in the '70s and the early '80s that the commercial goal of—at least I don't know about it in medicine, but I know in some of the other sciences, the commercial goal became much more powerful, and that started to change. You had to have a purpose for doing your research.

Ralph Freedman, MD

0:15:55.2

Well, there is purpose. This may be hypothesis-generating. So you have hypothesis-based and hypothesis-generating. In other words, you're looking at an area—perhaps you're looking at, to give an example, all these trees that are dying from the summer's heat. We don't know at the time; we just say it's the heat, but somebody assumes that there's some stress involved. So getting information about the environment that these trees are in, where they're growing, how close to water, so forth—maybe this provides important information that can save trees in the future. So it doesn't look directly relevant. It may be because it's a very isolated area, but I don't think you can discount it because, for one thing, it supports intellectual effort. There is some theory behind it, and the hope is that it will, perhaps, provide a number of pathways for further looking at a particular question. But it shouldn't be that we should only consider an effort that starts here and that we already planned that it's going to end up there because that, in biology, it's so complex that you could go in different directions.

Tacey Ann Rosolowski, PhD

0:17:52.3

I was going to say, if you could see that pathway, you wouldn't need to do your experiment.
(laughs)

Ralph Freedman, MD

0:17:56.1

Yeah, right. Exactly. Really, you'd go straight there. So I think it's something—I've thought about this often. If we commit every faculty in the university to developing a new drug or a new treatment—that means their whole career will be spent just on that objective—is that necessarily productive for that individual or even for the community of scientists? Especially when we're dealing with diseases that are very complicated and that we know so relatively little about.

Tacey Ann Rosolowski, PhD

0:18:39.4

What is your most memorable research experience?

Interview Session: 01
Interview Date: February 24, 2012

Ralph Freedman, MD

0:18:45.2

Well, of course, we had these blips of excitement with the production of the antibody, and that was exciting that we had that. Actually, I would say providing patients with some hope in the trials that we did. And when patients, I would say, who did respond and benefitted, and I think that means a lot. I would think—I don't know. As I said, we didn't really accomplish any what I would consider breakthroughs in treatment, but we learned a lot of things. And I think some of the things that we've learned could be useful today.

Tacey Ann Rosolowski, PhD

0:19:52.6

Was there a handful or—you know—one or two discoveries you had in the lab that really kind of shifted your paradigm and how you looked at the disease?

Ralph Freedman, MD

0:20:06.8

I think finding the— When we were able to look at the molecular aspects of these tumors like ovarian cancer, particularly, because most of my career at Anderson was spent on ovarian cancer after the initial few years. And seeing the molecular profiles of these tumors—how many complex interactions there were between cytokines and inflammatory processes and the linkages between all of these factors. The fact that there were so many macrophages which are normally considered to be phagocytic cells—cells that eat up other cells that are damaged or dead—that there were so many of them in the environment of the ovarian tumor was, I think, quite fascinating, even more than the population of T cells. And then we studied them further, and we found that they had so many functional factors that could contribute to tumor promotion. And we constantly thought, “Isn't there a way of possibly harnessing these or trying to control them?” And we found that those cells were dysfunctional to an extent that they couldn't—they weren't as effective as we hoped in killing tumor cells. And was this because of the tumor, the environment that it was in, or was it because they contributed to the tumor promotion—promoted the tumor growth? And these changes we found all in the vicinity of the tumor. When we took biopsies from the lining of the peritoneum in the vicinity of these tumors—the tumor metastases—we frequently found these inflammatory changes already there. So the question was, was the tumor doing it? It was a chicken-and-the-egg situation. Or were these predisposing now to further growth of the tumor? And if that's the case, then really we should be targeting the inflammatory changes around the cancers in the same ways people have been targeting the angiogenesis factor. But—you know—you have so much time to do these things and think about them before your research career is over. But we published—

Interview Session: 01
Interview Date: February 24, 2012

Tacey Ann Rosolowski, PhD

0:23:07.2

So you were saying then that when the research career is over—

Ralph Freedman, MD

0:23:09.5

Yeah, and then it's—you come to a point when you say, "Well, this is as much as I can do, and now I need to step down from it." And at the point that I retired, I made sure that we completed everything, that it was done. And I don't think we left any loose bits lying around, but the idea was to publish everything that had—the way patients had contributed. I think that the important thing is that the patients who contribute tissues and cells—we act in a fiduciary role or we act in a role where we're protecting the interests, and I hate the thought of discarding stuff that they have given you to complete. So we did make arrangements to transfer our bank to another investigator who was able to use and, in fact, just sent a paper to me the other day to look at a manuscript from work that we had collected several years back. And it's a big issue today—what happens when a lab does close? What happens to those specimens? And I told my IRB colleagues, I said, "I really think that the patient expects that that work goes on or that something comes out; people continue to work with what they've donated, and hopefully it will be some useful information." So we've worked out a system where that can happen. The IRB gives authorization to transfer that material to somebody else.

Interview Session: 01
Interview Date: February 24, 2012

Tacey Ann Rosolowski, PhD

00:25:06

When did you begin thinking that way about the specimens that patients have contributed?

Ralph Freedman, MD

0:25:13.0

Oh, probably several years. I mean, we worked out systems, I guess, several years back for transferring banks into the institutional tissue bank or to other investigators. I think investigators have the wrong idea. They think that they own this tissue. They really are given privileges over using it, and they have to be respectful to the people, the donors, who've given them those tissues. And if they can't use them anymore, there needs to be a way of giving them another function. Now, of course, people argue, "Well, maybe somebody can do something that the patients or the subject didn't authorize or wouldn't have liked to have done with it." So we do give subjects an opportunity to withdraw the tissues or their consent. This is getting into IRB business. And we do have restrictions on them doing anything that could affect their families—certain genetic diseases, for example, they might be affected by or a family member could be affected by. But most of the research that's done at Anderson doesn't have any bearing on that. It's basically asking questions about cancer, and that's what I think the donors gave the tissues for, so I think to respect their wishes—we should treat it as donations but continue to make sure that it's properly utilized.

Tacey Ann Rosolowski, PhD

0:27:17.1

It's almost 3:30, and would this be a good time to stop? I mean, we can start up with IRB next time and see how the other roles—(talking at the same time)

Ralph Freedman, MD

0:27:26.3

Yeah. Sure. Sure.

Tacey Ann Rosolowski, PhD

0:27:29.0

Okay. So I'm going to be turning off the recorder right now, and it's about twenty-two minutes after 3:00.

0:27:38.9 (end of audio 3)

Ralph Freedman, MD

Session 2—March 1, 2012

Chapter 00B **Interview Identifier**

Tacey Ann Rosolowski, PhD

0:00:04.0

This is Tacey Ann Rosolowski, and today is March 1, 2012. The time is just about 1:30, and I'm speaking with Ralph Freedman at his home in Houston. This is our second session together.

Interview Session: 02
Interview Date: March 1, 2012

Chapter 4

0:00:04.0+ to 0:17:38.1+

B: Building the Institution

Setting Up Testing Laboratories and Clinics; Building Research into Gynecologic Cancers

Story Codes

A: The Administrator

A: The Researcher

A: The Clinician

A: Definitions, Explanations, Translations

B: MD Anderson History

B: MD Anderson and Government

B: MD Anderson Snapshot

B: Devices, Drugs, Procedures

A: Overview

Tacey Ann Rosolowski, PhD

0:00:04.0+

We had just started talking about the various titles in different departments, and I had noted from your CV that you are chief and director of immunology and molecular biology research, and you were starting to talk about kind of the workings of that in the department.

Ralph Freedman, MD

Commented [T4]: In this segment, Dr. Freedman explains how he came to assume the positions of Director and Chief of Immunology and Molecular Biology Research ('88-'07). This narrative brings together various details: treatment of rare gynecological cancers, billing practices, regulation of laboratory testing, and research.

Interview Session: 02
Interview Date: March 1, 2012

0:00:38.2

So when I came to MD Anderson, it was '76, 1975. I mentioned to you last time that I was working in Dr. Sinkovics' lab, and our department itself didn't have a research lab as such. What they had was a trophoblastic laboratory, and this laboratory actually was one of 7 centers throughout the United States, which was involved in monitoring a very rare type of malignancy in females called gestational trophoblastic disease. That's where post-conception, instead of the fetus and placenta developing normally, the fetus doesn't develop, and the placenta develops into a tumor, and most of the time, it has a benign course. It evacuates itself or it gets removed by intervention, but in some cases, it actually developed into a highly malignant condition called choriocarcinoma. And when I came, it was Dr. [Felix] Rutledge, Dr. Julian Smith, who was the next in seniority on staff at the time, and then there was Taylor Wharton, who later became chair. So Julian Smith ran the trophoblastic disease center. What used to happen there was these patients produced human choriogonadotropin hormone, and as the same thing happens in normal pregnancy, they produce that hormone. So in the case of malignancy, because this was specific to pregnancy states, it was actually used to monitor the disease condition, so when you gave these patients chemotherapy, you could monitor their response by the drop in the HGC. In effect, it was the only condition in cancer where you could actually make a diagnosis based on history and the presence of this hormone in the blood and doesn't require pathology, but for this condition, you wouldn't require it. And you initiate treatment based on clinical history, clinical findings and elevated HGC, so, in fact, you shouldn't actually biopsy these, because they were vascular, and they could bleed. So there was a thing between Julian [Smith] and Taylor Wharton. You had two people who aspired to the leadership of that department when Dr. Rutledge eventually stepped down, and both of them basically were, I think, vying for this position. And Julian—which he left and moved on. I was left with his lab that did the monitoring. Now at that time, this lab actually could bill for services, but we didn't have the certificate from the state, so my job was to get the certificate for the state.

Tacey Ann Rosolowski, PhD

0:04:40.1

And to clarify, that certificate allowed you to—

Interview Session: 02
Interview Date: March 1, 2012

Ralph Freedman, MD

0:04:42.4

To actually do the test that could be used to monitor and treat patients, and they could actually bill for those tests. So we were told, look, you don't have a certificate, so you can't do it. So I worked with the techs that were there, and we actually produced the information that was required in order to get the state certificate which allowed us to continue the job. The institution, however, rightly decided that all tests that were done for clinical purposes should be done in the same pathology laboratories, and I wanted that to be part of it. So what happened was they did some kind of a deal, and they left us with the lab space. They took over the assay, said was now done in clinical chemistry actually under Dr. [Karen] Fritchie, and then we were left with that and also a state-supported technician. And that was the beginning of my research program.

Tacey Ann Rosolowski, PhD

0:06:02.5

Hmm, interesting.

Ralph Freedman, MD

0:06:06.3

But fortunately we had something to deal with basically, we demonstrated—well, we got the certificate. If we give this up now—this functioning—we also lose our lab, so the institution came back and allowed us to keep the space and the state-supported position.

Interview Session: 02
Interview Date: March 1, 2012

Tacey Ann Rosolowski, PhD

0:06:23.3

Could I ask you, you said earlier that the institution rightly decided that the central pathology lab should do this. Why was that the right decision?

Ralph Freedman, MD

0:06:31.9

Well, I think today, first of all, the law states, same as laws—that's the authority for Medicare decisions on payments—that any test that is done for clinical purposes for decision making needs to be done in a CLIA-approved lab. CLIA is Clinical Laboratory Improvement Amendment. And you may not use those tests, and you may not document them in the charts or put them in the results unless you have CLIA approval, and that's a law that goes back into, I think, the 1990s—it's '80s or '90s. But this happened actually just before that. So the institution's labs have now come into compliance with it, and actually, currently we're facing the same problem with Dr. Mendelsohn's lab, which are doing these mutational analyses on patients. And it's not in a CLIA approved facility, so we've had to come up with a compromise situation in which those results are done, but they're not put into the patient's charts. The physician is informed through what they call a research station which is separate from clinic station. Clinic station is part of the medical record, but research station is not, so the physician whose patient it is is informed of that result and does not enter the result in the chart but informs Dr. [Stanley] Hamilton's lab that is a CLIA approved facility. And they repeat the test, and then that test can be provided to the physician so that they can act on it—they can treat them with some new drug or put them onto a new protocol that uses a drug that targets their particular mutation. You probably know about some of the stuff that they're doing.

Tacey Ann Rosolowski, PhD

0:08:59.2

I'm imagining why the mechanism works the way it does, but if you could just confirm why what I'm imagining—

Ralph Freedman, MD

0:09:07.5

It's for standardization purposes. It's so that the tests that are used to treat patients—doesn't mean to say that the test that's done in a CLIA approved lab is necessarily better or better done. You may have some superb scientist who does all the quality controls and actually has an assay that's better than another lab that is CLIA approved, but the CLIA—what it does is it provides standardization and accountability. In other words, every test that goes out, whether it be hemoglobin or blood sugar or mutation analysis—it has a signature on it, and that implies that they have followed strict quality controls to do that test.

Interview Session: 02
Interview Date: March 1, 2012

Tacey Ann Rosolowski, PhD

0:09:51.5

Is there also a sense that if a test is part of some kind of scientific study that has a clear goal, that somehow its objectivities might be compromised or there might be some interpretation applied to it? That was just another perspective.

Ralph Freedman, MD

0:10:09.6

Well, you've got investigators, of course, always enthusiastic about their work, and unfortunately, sometimes the enthusiasm takes control over their objectivity. What CLIA does—CLIA was actually designed for billing purposes. It's a CMS requirement. CMS provides the authority for Medicare/Medicaid decisions for reimbursement, and they'll pay just so much for a test, but it has to be done according to certain objectives. Dr. Hamilton can probably enlighten you better on this whole subject. So CLIA—I'm not sure where we are in this discussion, but—

Tacey Ann Rosolowski, PhD

0:11:01.4

Oh, I had— You were talking about the reporting of the various results to research station versus clinical station, just talking about the mechanisms of how a test would be repeated if it were done in a—

Ralph Freedman, MD

0:11:15.1

Yes, just because research lab tests can be reported to researchers and to patients in aggregate. It's permitted, and I've actually seen the presentation, but I've seen others. They say that it's okay to report these results in aggregate. In other words, you have ten people, you've got one or two mutations, but what they don't want you to do is they don't want research labs to go out there and open up because you'd have no control. The government would have no control over these research labs and the quality, so yes, you might have one lab here that's very, very good and then ten over here out in the countryside that are supposedly doing quality work upon which decisions are being made and the public is trusting. This provides the public with an opportunity to—an indicator of trust that the result that you're getting has made certain quality assurance requirements, and you're paying for that. Its effect determining what treatment is done to you, so the results have to be as accurate as possible, and also—and of course, the billing side of it.

Tacey Ann Rosolowski, PhD

0:12:41.2

Now, was the process in the very early days when you had—were organizing getting the certificate, so you could perform the test for the—I'm looking at the form of—the trophoblastic—

Interview Session: 02
Interview Date: March 1, 2012

Ralph Freedman, MD

0:12:54.9

Yeah, the trophoblastic lab was called—

Tacey Ann Rosolowski, PhD

0:12:57.0

—related disease.

Ralph Freedman, MD

0:12:58.0

—the trophoblastic—and the center— There were seven centers around the country doing pretty much the same thing, so it means all the patients with trophoblastic disease used to go to one of these 7 centers.

Tacey Ann Rosolowski, PhD

0:13:07.9

That doesn't sound like an awful lot to me, seven centers in the entire country.

Ralph Freedman, MD

0:13:11.7

Except that it's a rare condition.

Tacey Ann Rosolowski, PhD

0:13:14.3

Okay.

Ralph Freedman, MD

0:13:15.1

It's overall— The benign form is more common than the very malignant form, but the—it presents itself as what they call a hydatidiform mole. That's the common version of trophoblastic disease, which is easily managed, but these patients have to be followed very closely with weekly measurements of the HGC to make sure that they don't transition into a malignant version of that disease.

Tacey Ann Rosolowski, PhD

0:13:41.8

How did that particular lab come to be established through the—?

Interview Session: 02
Interview Date: March 1, 2012

Ralph Freedman, MD

0:13:44.7

Well, Julian actually established that lab. He got technicians, and at that time, they were doing a radioimmunoassay, which is, of course, no longer done anymore. It's now all ELISA assays. It's an antibody targeting an antigen. When those two combine, you get a reaction with a substrate and you get a blue color. You get a color reaction, and that's measured with a spectrometer. But at the time this was being done, you had to measure regular activity that was released in the sample, and from that, a standard curve had to be generated, and then you would get a value. Well, we tended to use less and less radioactivity in the lab for obvious reasons. The next step was developed—ELISA assays—to conduct these same assays, which in the past have been done with crude antibodies, which were not monoclonal and of course had a lot of background activity and other interactions, so the ELISA processes was a natural development from monoclonal technology. [Georges] Kohler and [Cesar] Milstein got a Nobel Prize in about, I think, '75 for developing hybridomas, which were the combination of a cell and that can manufacture antibody with another cell that's been immunized from the spleen of a mouse. Then the hybridoma would generate antibody, and this is the technique that we had used to generate our human antibody early on. So that's sort of the background to this lab, and then from there, with the different research programs that I mentioned the last time, initially, we started off with vaccines, and then there was the antibody, which developed with funding from the state. And then, later on, I got into—well, we were into the vaccine phase. These vaccines were crude extracts, so they had to be purified, and that's why we tried to develop antibodies from patients that had been immunized to see if we could go back again, isolate the antigens of importance. But in the meantime, we were moving along into a more specific therapy which is with T cells, and that was the story that I gave you last time about the adoptive therapy approaches and the work that I did with Platsoucas. So, yeah, that lab then was what was called the immunology laboratory. It was the lab that I used—took basically 'til I retired. It was down on the fourth floor behind the operating room suite, and—

Interview Session: 02
Interview Date: March 1, 2012

Tacey Ann Rosolowski, PhD

0:17:37.4

In which building?

Ralph Freedman, MD

0:17:38.1

That was in the Central Core Building, and our lab is right at the back. There are also— I didn't mention at the time, Dr. Lovell Jones was recruited. He's a biochemist. So he came to occupy the original space of the trophoblastic lab and was brought in because of the department's interest in estrogen receptors, progesterone receptors. As you know, those have been used in order to predict which patients might benefit from hormone therapy, breast cancer, and then we tried it in ovarian cancers. I worked with Jones for a while on trying to do hormone therapy in ovarian cancer, so this was an area that was not immunology, basically, but the treatments were simple. There was— We used drugs like ethinylestradiol, progesterone in patients that we knew had receptors that could be targets for their treatment, and we did some interesting results in patients with ovarian cancer, but these had to be patients who had high expression of these receptors. The majority of patients, unfortunately, don't have high expression. They're undifferentiated tumors, and expression of their receptors is low, but we found that these patients did respond to a number of different hormone therapies—the two that I mentioned. Tamoxifen is another example, and we applied the same principle to treating endometrial cancer, but that was really the extent of the collaboration that I had with Dr. Jones.

Interview Session: 02
Interview Date: March 1, 2012

Chapter 5

0:19:40.7 to 0:41:14.0+

B: Building the Institution

Focusing A Department on Immunological Approaches to Gynecologic Cancers

Story Codes

A: The Administrator

A: The Researcher

A: Definitions, Explanations, Translations

B: MD Anderson History

C: The Professional at Work

C: Professional Practice

Tacey Ann Rosolowski, PhD

0:19:40.7

I was asked—going to ask you about the role that you served. You were chief and director of immunology and molecular biology research, and could you tell me the difference between a chief and a director?

Ralph Freedman, MD

0:19:53.7

I don't know. It's— The departments came up with these titles at some stage, and as I said, we were lots of chiefs in this institution even to this day, and lots of directors and lots of this and that, but basically, what it amounts to is getting the work done. I'm sure that these are also used for budgetary purposes. When a department has an area of research, and they've got titles and personnel attached to it, these things can be used in order to expand. I mean, there was really no research in those days 'til I got there. Now, you've got Dr. [Anil] Sood, who's got a very big program, and Dr. Karen Lu, who got the endometrium program, and each of those people have now got their own space and personnel where they're doing their research. Each of them will give a title to a lab which they feel suits the area very— Immunology research, it suited us, because that's what we did 80-90 percent of the time and the graduate students that we had and the postdoctorals that came, that was the area that they focused on.

Tacey Ann Rosolowski, PhD

0:21:17.1

When you took on that role, did you have a sense of your goals that—something you wanted to achieve in guiding the direction of research and all that?

Commented [T5]: Dr. Freedman begins this segment by sketching the hopes he had as Director and Chief: to understand the biology of the diseases from an immunological perspective and try to identify new strategies to treat ovarian and uterine cancer, with their (continued) dismal outcomes (in comparison to advances made with cervical and endometrial cancer). He notes that the main contribution IMBR made to ovarian cancer was to demonstrate that T-cells can be activated in the patient, a fact indicating that a vaccine approach might potentially be used. He goes into detail about the biological mechanisms of the tumors and of the patient's immunological system. He notes that it is important for researchers to determine adequate ways to measure clinical benefit of treatments.

Interview Session: 02
Interview Date: March 1, 2012

Ralph Freedman, MD

0:21:26.4

Yeah, I was hoping—I was hopeful at that stage that immunology was going to contribute more to the outcomes of disease like ovarian cancer, because at that time and as today, progress was so dismal, and we were looking out for new therapeutic strategies. I don't know if you know about the history of ovarian cancer therapy, but we started off with drugs like Cisplatin, which is no longer used today because it's toxic to the kidneys and toxic to the nervous system. But that's what was approved back in the '80s. And then you had the combination with another drug called Cytoxan, and that was standard of care for a long time, and then, suddenly, Carboplatin came along, which was a less toxic version of what had a different toxicity profile to Cisplatin. It was also related to Cisplatin and was much easier to use, and the patients didn't get so sick with it, so that replaced Cisplatin. But then there was still Cytoxan and Carboplatin until Taxol came along, and that was considered to be a major breakthrough. And in fact, there was what we call an expanded access. At that time, it was called a compassionate protocol. The results were looking so interesting that they wanted to make sure that the drug could get to patients even though it hadn't yet been approved by the FDA, so they developed a compassionate protocol which allowed patients to be treated with Taxol. And this, I think, was in the late '80s, because in the '90s, it became approved. And it wasn't long after that then Taxol was combined with Carbo—first of all with Cisplatin and later with Carboplatin, and that was because of its toxicity profiles. Well, that's taken thirty years just to get through those several drugs, and the 5-year survival really hasn't changed all that much. It's better with Taxol and Carboplatin than it had been with Cisplatin by itself, but there's still about twenty-five percent of patients who survive five years who have advanced ovarian cancer, so throughout this period, there's always been a look around for new drugs, new strategies. They tried different chemotherapies—Doxil, hexamethylmelamine—hexamethylmelamine's hardly used anymore, although it was approved for ovarian—Gemcitabine. A number of these different drugs have been tried, and the most recent effort now is to combine Avastin—Bevacizumab—with the Carboplatin-Taxol. And from my understanding, it doesn't improve the survival of patients, but it may improve by a few months of progression-free survival.

0:25:06.8

Interview Session: 02
Interview Date: March 1, 2012

People have tried different—even things that are non-chemotherapeutic. That's how we got into immunotherapy. Does immunotherapy have a role? There are logistic issues with using immunotherapy on ovarian cancer. I kind of mentioned to you last time that the large tumor burden that you have, which overwhelms the immune system in these patients, so you've got so many tumors secreting all kinds of proteins—a number of which can interfere with the immune response, so it's hard to deal with that unless you can eliminate or reduce the amount of tumor. People have tried to develop vaccine strategies post-surgery, post-chemotherapy when the tumor burden was small but where the patients are still going to die of their cancer, and unfortunately, none of those have turned out yet to be efficacious, so ovary remains. In cervix cancer fortunately we're seeing, over the years, a dramatic decrease in the frequency and in the death rate so that in terms of frequency and death rate, it is now number three. Ovarian cancer is number one in death rate. Endometrial cancer is number one in frequency and second in death rate, and then you have cervix cancer, which is, I think, about 1,500 deaths a years. It's much less—this is—I'm just talking about the US, but of course, if you go outside the US and go to South America and Africa, the disease is still very prevalent, and that's because of lack of screening, adequate screening. The simple Pap smear has probably made an enormous difference. Only about ten percent of women in this country now no longer have any type of screening, and then, of course, you've got the antibodies to the virus, using the vaccine to stimulate antibodies to the virus, which is probably—we don't know for sure that it's going to reduce the death rate even further, but we do know that it's reducing the incidence of pre-invasion cancers, so we can speculate that it may reduce the incidence of invasive cancer even further. But otherwise, for ovarian and uterine cancer, they haven't seen the same amount of decrease.

Tacey Ann Rosolowski, PhD

0:28:26.3

Were there other goals that you had guiding the search when you were directing the activities of the lab?

Interview Session: 02
Interview Date: March 1, 2012

Ralph Freedman, MD

0:28:33.2

Yeah, the important goal was to understand the biology of these diseases from an immunological standpoint, and we did discover—my lab discovered that there were T cells that were activated in this disease, but you had to take them out of the body and show that they had the potential to be activated. And from that, they've now developed strategies to use peptides, which are parts of proteins, which kind of fit into the little cleavage areas on the T cell and are able to stimulate those cells to kill target tumor cells. So we did a lot of that type of work and published a Journal of Immunology, Clinical Cancer Research. At the time, I had a postdoc that came from Dr. [Chris] Platsoucas' lab, Constantin Ionnides, who worked on that aspect in my lab. He identified the peptides, the particular sequence that had the capacity to stimulate the activated T cell, so what it is is a very small proportion of these T cells that are in the circulation. And what we've tried to do was to expand the—in those bio-reactors that were— And we were able to expand the cells to something like ten to the ten cells, so we thought with that large number of cells we're sure to be able to wipe out things, but there were two major difficulties that we came across. One was that you had to be able to grow those cells from tumor, and so you had to have access to a large amount of tumor in order to do it. Well, that's not also a good condition to be able to treat those patients, see, and have some way of storing those cells or keeping them going in culture or storing them until the patient's tumor had collapsed. So these are logistic issues that we came across. We found that directly treating them—the patients—with the expanded T cells, and they had high tumor burden, you got a lot of interferon being released, which indicated that they were producing cytokines. But we didn't see any appreciable shrinkage, and I think part of that is the fact that— And we even put the cells directly into the abdomen, where the tumors were, in the hope that they would go there and would go actually into the tumors, but the problem is that you've got the host is—that the cancer is like a parasite. It basically utilizes the resources of the host in order to support itself, so all these suppressor factors are released. Amy Loercher, who was a PhD student with me, she did her research on IL 10 and the macrophage. We found there were very large numbers of these monocyte macrophages in patients that secreted IL 10, and these were immunosuppressant—these cells behaved in immunosuppressant form—so we speculated or postulated that, in fact, in ovarian cancer, where we saw large numbers of these macrophages, they were secreting IL 10. They were probably primarily the source of the IL 10 that we saw secreted in these patients, and they probably contributed to an immunosuppressive environment, so you would have to find a way to overcome this immunosuppression either by effective debulking the tumor or by finding a technique to inhibit those immunosuppressive cells. And that's not—it's not a trivial issue because there are multiple mechanisms that the tumor uses to suppress the environment to the tumor. IL 10 is one, and another is IL 6, and they actually suppress T cells, and the suppressor macrophages seem to be expanded in conditions of malignancy. So in other words, you have to be able to knock each one of these and the more pathways that there were for immunosuppression, the more complicated it became from a logistic point of view. So I think that our main contribution was the fact that, yes, we demonstrated that in ovarian cancer, there were activated T cells produced in the host, and they

Interview Session: 02
Interview Date: March 1, 2012

were kind of sitting there in a dormant fashion, probably suppressed by this immune environment that they could be taken out of the host and expanded into activated cells.

0:34:06.0

There was a possibility that if you were able to shrink the tumor down to very small amounts—we don't know what that amount actually is—that you could use a vaccine approach potentially to target these. This hasn't been effectively done at this stage because there are multiple peptides and multiple T-cell clones, basically, that can only be activated by certain peptides. And then of course, the description of the immunosuppressant environment and this is providing new channels of research for many others, such as our recent progress in cancer research. I'm listed as a collaborator because they used samples from my lab and expanded on some of the ideas that we had developed to actually demonstrate the suppressor T regulatory cell. It's a small subset of T cells that has a highly suppressive effect on the T-cells bonds, and these cells have been isolated from ovarian cancer patients from tissues. You can demonstrate them actually in the tissues in the vicinity of the tumor, so we know they're there. So you're looking at this, you're looking at angiogenesis, you're looking at mutation, and you're looking at inflammatory processes that support the tumor that are recruited from the patient—from the host—in order to support the tumor. So it sort of raises a little pessimism, I guess, about being able to overcome those tumors that are so very heterogeneous. The more heterogeneous the tumor, the more likely that you will have multiple mechanisms that will support the growth of that cancer. Where you have monoclonal tumors—certain lymphomas, certain leukemias—you've got a better potential for targeting the cancer, but if the cancer has a habit of mutating and changing—changing its face all the time—that's going to be a difficult problem to keep up with, and that's where we have to see now with the new patient-directed therapy whether you're going to be— You see, I think that the only way that you can defeat cancer is to eliminate it. We've talked about making it into a chronic disease. I think there's a little bit of glibness in that hypothesis because it seems that the relationship between survival of the cancer and survival of the host is so tenuous unless you totally destroy that disease. In other words, if it gets out of control, how do you control it? So that's where I think we contributed understanding of the immune system, natural killer cells that we did with Eva Lotzova and the T-cell environment, the immunosuppressive environment in this disease—the fact that in spite of that all, there is a state of immunization that takes place in these patients but it's overwhelmed by the immunosuppressive environment that you have, so it's possible that in the future multivalent vaccines can be developed which target different types of cells. But it's that one clone of cells that might escape and grow that's ultimately the concern.

Interview Session: 02
Interview Date: March 1, 2012

Tacey Ann Rosolowski, PhD

0:38:20.3

I just wonder how much of the general public understands the many faces that cancer can present. I think that I've mentioned before that when I started doing research for this—and I had no idea how complex the disease was and what you've just described, the way it can morph and present these very, very different challenges to any attempt to control it, let alone eradicate it, so—

Ralph Freedman, MD

0:38:48.5

If you don't try, you can never learn.

Tacey Ann Rosolowski, PhD

0:38:52.0

Well, certainly.

Ralph Freedman, MD

0:38:54.1

And that's why I think we have to keep on trying, and of course, we don't want to destroy people's optimism and present a totally pessimistic view of things to the public. I think generally those patients who develop these terrible diseases that have low cure rates, they search for areas of optimism, and we've got to try to keep the optimism, but do it in a truthful manner, because some patients are happy with a few months. When they've got that disease they're happy with a few months longer that they can have with their families provided, of course, they've got good quality of life. What's missing in a lot of our trials is adequate ways to measure clinical benefit. It's not sufficient to just show the tumor shrinks here. We've actually got to know how the patient is benefiting. They have these quality-of-life instruments, and we have some researchers that are working in that area. From a regulatory point of view, they fall short because they don't find sufficiently the symptoms or the complex of symptoms that goes into creating those instruments like you may have pain. You may have just feeling good or not feeling good, but each of these is separate. If a drug is approved on the basis of improved quality of life, you've actually got to show it, and a good example would be, for example, esophageal cancer. If a patient can't swallow, and as a result of their treatments now they can swallow, that's clear evidence of benefit—clinical benefit. And unfortunately, there may be half a dozen or so drugs that have been approved by the FDA and actually have been approved using patient-reported outcomes or from quality of life improvements. That's an area that the agency is struggling with now, and they've provided guidances.

Tacey Ann Rosolowski, PhD

0:41:13.8

Which conference is it?



Interview Session: 02
Interview Date: March 1, 2012

Ralph Freedman, MD

0:41:14.0

This is the ECOR Conference that's— ECOR stands for Ethics Compliance in Oncology Research and will be in October. We've got Pazdur from the FDA, people from OHRP, and we've got a panel on patient-reported outcomes, because it is so important that our trials not just provide end points that are satisfying to the physicians, but end points that are meaningful to the patients, and that's where we fall short with a lot of trials up to now.

Interview Session: 02
Interview Date: March 1, 2012

Chapter 6

0:41:59.8 to 1:43:20.4+

B: Building the Institution **Two Decades Overseeing Human-Subject Research**

B: Building/Transforming the Institution
B: MD Anderson History
B: MD Anderson Snapshot
B: MD Anderson and Government
D: Understanding Cancer, the History of Science, Cancer Research
D: The History of Health Care, Patient Care
C: Leadership
D: Ethics
B: Ethics
C: Professional Practice
C: The Professional at Work

Tacey Ann Rosolowski, PhD

0:41:59.8

Now here we're starting to broach your work on the Institutional Review Board. Would you like to dive into that area and—?

Ralph Freedman, MD

0:42:09.3

Yeah, well, that—

Tacey Ann Rosolowski, PhD

0:42:11.1

When did you start on it?

Ralph Freedman, MD

0:42:12.6

Yeah, well, I guess I've had about twenty-five years of that, although it may be more. When I came to the department they asked me to—like they often do is the person at the bottom of the totem pole gets—well, which committees can we put you on that aren't the best board to be on? Or maybe they do want to be, but they haven't got the time to do it. So I ended up on the research committee, and at that time, it was early in its development, '74 or '75, and that's when Congress came up with their regulations on human subject research. So it actually took from '45 to '75—that's almost thirty years—for us in this country to develop our own principles for conducting human subject research. When I was overseas we really didn't know too much. We just did what we thought was ethical, but we didn't have any guidelines, so our consents were

Commented [T6]: In this segment, Dr. Freedman discusses his more than twenty-five years of experience overseeing human subject research on the Institutional Review Board (IRB). He sketches the history of human subject guidelines and clarifies IRB procedures, potential conflicts of interest (between IRB members and the institution), and the kinds of research protocols of concern to the IRB, whose primary function is the protection of human subjects. He then takes a broader view and for approximately thirty minutes discusses his belief that regulation is very necessary, but that it has currently gone too far. He points out that different protocols represent different levels of risk, some of which may not require IRB regulation, such as experiments in which the main risk is to patient privacy. Dr. Freedman offers rich detail about the challenges to researchers and describes systems that might satisfy the public's need for privacy and information security while easing the burden on researchers who want to move ahead quickly with their work. "We needed these systems yesterday," Dr. Freedman asserts. He gives examples of how his understanding of the need for regulation and its potential complexity evolved as his experience as a researcher grew, then expands his focus again and discusses how regulation can influence how a researcher focuses his or her career.

Interview Session: 02
Interview Date: March 1, 2012

very rudimentary. We asked the patient, “Do you consent to have a biopsy or do a procedure?” Here, it’s been evolving to what it is today, where it’s a very regulated process. And there are strict rules, and what was regulations and now policies, based on regulations as to how research should be conducted in an institution. So in ’75 when I came to MD Anderson, we had a research committee which had started in the ‘60s, so that committee actually had started off even before the Belmont Report came into place, and that’s dealt with really nicely in Jim Olson’s book. He talks about the origin of the research committee; so basically, the committee was there to review human subject research— There was one committee at that time. It was the— It was called the Surveillance Committee. That’s right. They called it the Surveillance Committee. What does surveillance mean? It means just—

Tacey Ann Rosolowski, PhD
0:44:37.6
Oversight, yeah.

Ralph Freedman, MD
0:44:38.1
—oversight, and it used to review all clinical protocols that could be conducted at Anderson. And of course, they were a much smaller number than they are today. There were a number of events that happened—and I don’t want to go over this because it’s all well-described in his book—but there were some events which embarrassed the institution. Dr. [Charles A.] LeMaistre had to go up to Washington and appear before Congress with Dr. [James] Bowen, because a drug that was given to patients, one of the departments that had been obtained from NIH in order to do pre-clinical studies in animals—it should’ve never gone into humans—and it ended up going into humans, and—

Tacey Ann Rosolowski, PhD
0:45:29.7
Just for the record, I wanted to say that James Olson’s book is Making Cancer History, so we have that on the recording.

Ralph Freedman, MD
0:45:38.3
Right, and he did a great job in describing the evolution of that. So we had two or three people working in the office. Today, there are about fifty, and that fifty have come about basically through unfunded mandates. The government has said, “This is what you’re going to do,” and in the institution to protect the patients and to protect itself has created this structure, which we now have today, with five IRBs that—initially just one. Now they have five: three clinical, one psychosocial, and one executive IRB that I chair. And the executive IRB basically determines policy and makes decisions where they cross department and protocol boundaries. So you have two protocols that have an issue that would affect both—the same issue that would affect them.

Interview Session: 02
Interview Date: March 1, 2012

For example, adverse events—the reporting of adverse events—you want a uniform policy for reporting those events across the hospital. You want for— When a researcher doesn't follow the protocol exactly, it's a deviation, and it may be a minor thing—it doesn't affect patient safety—but they have to make a report. So you want people to follow that policy across the institution, and that's what we do is we create the policies which are based on federal regulation and guidances and good clinical practice documents so that they are followed across the institution. So early on we had a very small structure, and then the feeling was that they needed much more. Dr. [Leonard] Zwelling became the vice president for research at that time, and that's when it was suddenly expanded, and then we landed—we found that the IRB had so much work to do because it had to review a host of new protocols. It's required to review existing protocols on an annual basis—at least annually—and then it has to deal with all these adverse events—changes to the informed consent based on adverse event-reporting by sponsors and deviations and all kinds of thing—that there was less and less time to discuss the science. So they created a separate committee, or the clinical research committee, which is made up of faculty and scientists from around the institution, and that's where they discussed the science. And it's a sort of a seamless process, where protocol gets discussed in the departments we pursue. Then it goes to biostatistical review. Then it ends up in the clinical research committee, when you would expect a protocol to have basically the format and the content that it would have almost in its final form but with the science being discussed and any revisions that are recommended by the committee being dealt with. And then, within a few weeks, it goes to the IRB, where they look primarily at the consent and the form of the consent and any other issues of ethical concern. So that extra effort was really very necessary. I served as a member first, and then I served as a chair. Then there was a situation where I was no longer a chair, and then eventually I came back to be a chair for the committee. This was six or seven years ago, and I've been chair of this committee now for about five years. We don't have term limits for people on the IRB, I think, in part because it's not easy to get people to serve in this role.

Tacey Ann Rosolowski, PhD

0:50:12.5

Why?

Interview Session: 02
Interview Date: March 1, 2012

Ralph Freedman, MD

0:50:12.5

Well, it's demanding. There's a lot of time involved. It's largely voluntary, what you do there. There is a small stipend that they give to me, but it's due to the chairs, particularly. It's one of the things that they discussed in their recent review—Dr. Hong's review of the research—whether there shouldn't be more remuneration given to members of these committees. There's a difficulty here because the IRB is supposed to function independently, and it's supposed to serve the interests of the subjects, not the institution. It's not the IRB's mission to protect the institution. You have Compliance and other groups who protect the interests of the institution, so if the IRB is going to serve the benefits of the subjects, it has to keep the institution at some arm's length. So if— We're all employees of the institution, so it's a sort of a—

Tacey Ann Rosolowski, PhD

0:51:35.4

Almost a conflict of interest.

Ralph Freedman, MD

0:51:36.6

—conflict of interest to be a member, but it's—

Tacey Ann Rosolowski, PhD

0:51:39.4

What are you going to do? Yeah.

Ralph Freedman, MD

0:51:42.2

I mean, I guess the only other alternative is to have all the reviews done outside the institution by the so-called Central IRBs. Now, they deal with very large studies that are done in multiple institutions, but they also have their own issues—a number of issues—with regard to conflict of interest and how they organize and so forth, so it's— What we have done is that we found that the system that works well for us is—

0:52:24.1

Interview Session: 02
Interview Date: March 1, 2012

Our primary interest is the protection of human subjects, and sometimes those interests are not exactly in line with those of the institution. The IRB is the only committee in the institution that can approve a study. The institution can decide for various reasons—financial—but if they don't want a study to be done, in terms of actual approval, no one else can approve a study to be done. No study can commence at the institution without it being approved by the IRB. When it comes to conflict of interest, for example, the president can waive some conflicts of interest, but it will be dependent upon the IRB approval. So if the IRB says this conflict cannot be resolved, we cannot do the study at MD Anderson. It has to be done elsewhere. The IRB has the final say, so this is the only place in the institution, ironically, where a decision by the IRB can supersede that of the president of the institution.

Tacey Ann Rosolowski, PhD

0:53:38.4

Is there— ? Are you able, without breaching any confidences, to give a kind of example of this sort—that kind of dilemma that you've confronted?

Ralph Freedman, MD

0:53:47.7

Well, we've had cases where an individual had conflicts, and the president said, okay, they can have a waiver. Actually, what happened was originally the waivers were going through without the IRB seeing them, and then we'd point it out to Dr. [John] Mendelsohn that this could be problematic especially if safety issues occur, so the rules were changed. Conflict-of-interest rules were actually changed so that the waivers would only be permitted if the IRB approved, and all our decisions are made in strict confidence. Even the votes are done electronically and anonymously so that no one knows who said what, and also, we have a limited number of people from outside who are present at the IRB meetings. Sometimes we've found that in the past, that sometimes the presence of an official with a significant authority in the institution could influence the decision making in the IRB, and that was not always in the best interest of the patients.

Tacey Ann Rosolowski, PhD

0:55:14.2

How are these external parties selected?

Ralph Freedman, MD

0:55:17.5

Well, these would've been ex officia. In other words, they were there because of their position.

Tacey Ann Rosolowski, PhD

0:55:26.5

Oh, I see.

Interview Session: 02
Interview Date: March 1, 2012

Ralph Freedman, MD

0:55:26.9

So a vice president, a lawyer from Compliance—we used to have the lawyers from Compliance in the committee, and the problem—as I told Jessica—is the issue for us is that Compliance, their mission is to protect the institution overall, primarily. I mean, they do protect patients. When the patient has a complaint, they take these things out, but I think, at the end of the day, the primary purpose is to protect the institution from lawsuits, from bad publicity, whatever it is. Our role is to protect the subjects and not to—although indirectly, we protect the institution but not to have the protection of the institution as the direct object of our deliberations. Obviously, we're not going to do anything stupid that would put the patient—the institution in jeopardy, but it's not our main objective. So what's happened is those individuals, they get invited on an as needed basis, like if there's an issue that comes up that we feel the expertise is not in the IRB, we have the authority to ask to bring in those experts from wherever. It could be from Compliance, it could be from across the road, from anywhere in order to assist the committee in making its deliberations, and that is actually stated in the regulations that you can do that. But these individuals would not have voting rights, so they can come and present, and they'll be asked questions, and then we let them go out, and there's further discussion. Then the motion comes up, and the vote is taken with these people out of the room.

Tacey Ann Rosolowski, PhD

0:57:31.2

What's the relationship between the IRB and the ethics and compliance and clinical research?
That was the conference that you were talking about earlier.

Ralph Freedman, MD

0:57:42.1

Oh, okay.

Tacey Ann Rosolowski, PhD

0:57:42.7

Is there a link between those or—?

Interview Session: 02
Interview Date: March 1, 2012

Ralph Freedman, MD

0:57:44.0

Yeah, so the IRB—so the vice president, Dr. [Aman] Buzdar got together with the chairs of the IRB, and we came up with a program. This would be after the conference. It's an international conference, and the idea is to choose topics that are maybe a bit controversial, but they're not—we feel that faculty may need to know more about the subjects, and the IRB—certainly members—would maybe need to know more about it so that they can make decisions, the appropriate decisions. A lot of what human subject research is, there's different aspects of it. One is basically the regulation, the law, following the regulation, following the guidance with the intent that subjects are notified, but there's a lot of education, as well. Our primary role is not punitive; it's not to discipline people. Our primary role is to ensure that patients are protected through good practices, so often we have to teach those practices. And it may be an individual protocol, issues that arise with that protocol, and a corrective action plan is required, so you hope they go through that experience, that the investigator and the team members will have learned from that, so the next time they face that situation, they won't have to deal with it. So our last resort is a punitive decision where you close down some research. And in most instances, literally ninety-nine out of 100 instances, we're able to correct the behavior of individuals and actually provide them with new pathways and new guidelines for doing things. I mean, their regulations are not really guidelines but just change their behavior so that the ultimate result is that the subjects are protected.

Tacey Ann Rosolowski, PhD

1:00:28.6

What's the landscape of the protocols that come under your eyes? I mean, what percentage of them go through, and they're well-designed, and they satisfy guidelines? What's the percentage that need some tweaking? What's the percentage where people actually need some intervention, and what are the numbers that actually have to closed down?

Ralph Freedman, MD

1:00:57.4

Oh, first of all, there's virtually no protocol. That doesn't have some contingency attached to it because there's always some improvement that people can do. We don't try to change the science. Once it's gone through the scientific committees, and the science is accepted, although the IRB has the prerogative to look into the science, and sometimes we've sent the protocol back to the science committee to re-review it, but I would say that, in most cases, it's an approval with a contingency. There are few that are rejected. If a protocol is rejected, that's a big issue because. For one thing, we have to forward it to the OHRP that we've actually rejected a study.

Tacey Ann Rosolowski, PhD

1:01:47.0

What is the OHRP?

Interview Session: 02
Interview Date: March 1, 2012

Ralph Freedman, MD

1:01:48.3

The Office for Human Research Protection in Washington, and the reason for that is that what people have done is they've gone around and done IRB shopping to get their protocol approved. And some of the companies have even done that, so they'll go to a central IRB that's got a better record of approving studies than others with the least amount of difficulty. So I would say most—there are really few that are actually—so in most cases, you would approval with contingency, and you might have defer—defer which is another action. In other words, there are real concerns about the study but not something that can't be retrieved and redesigned and amended, and then they'll come back, and often they'll get approved.

Tacey Ann Rosolowski, PhD

1:02:43.3

What are some of the issues that come up that can be of concern?

Ralph Freedman, MD

1:02:46.7

Well, is it ethical to do the work? In other words, is it appropriate to have a placebo control? When is it appropriate to have a placebo control in a study? And basically a placebo control, it's ethical if there is clinical equipoise. In other words, you have a group of experts who cannot decide which arm of a treatment is better. So you might allow a placebo in that situation with an opportunity to cross over for those patients, or if it's, say, near the end of life, and you're looking at a treatment that has subjective component to it but is a placebo effect, you might allow comparison with a placebo because it's over a short period of time and it's the only way that you can show a difference between the arms. The placebo might be accepted there. Or you might permit a placebo to combine with an active drug, so two active drugs and one arm, one active drug plus a placebo in the other arm where you're mainly interested in the matching to the placebo with the only arm that has the two drugs—the one drug of the two that's new, and the one that goes along with the placebo would be a standard drug. So you'd have standard plus test drug, standard plus placebo in the other arm, and that's done not infrequently today. So there are situations with placebos not only ethical but it's necessary in order to show benefit.

Tacey Ann Rosolowski, PhD

1:04:57.5

All right. We're back after a brief break.

Interview Session: 02
Interview Date: March 1, 2012

Ralph Freedman, MD

1:05:02.8

So I think the IRB actually—if we understand that the test—its role is certainly protection of human subjects—that’s certainly number one—but also educating physicians and their teams. Today, it’s a team—most research that’s done on patients is a team approach—and it should be because it’s—there are few studies today that can be done by a single person. For example, you need a research nurse. We couldn’t do without research nurses because there’s so much documentation and submission of forms, submission of reports, and the physicians are also seeing patients in for standard of care in addition to doing clinical research, so they need as much help as they can get in making sure that they do things adequately. They need all this support, and then, of course, you need other investigators to help you do that work. And there are different levels of research, and they are basically related to risk. The newest drugs first in human trials are going to be at the top in certain IND studies. Investigation of a new drug—which, by the way, all that IND means is permission that the FDA gives an investigator was sponsor to take a drug across state lines, so they can do the study in different states. That’s what the IND does. This is compared, say, to new drug application where a new sponsor wants to obtain approval for a specific indication related to a new drug. They first have to have the IND in order to conduct the studies, and then they come up with a new drug application once they’ve got the studies underway in order to see if the FDA will approve the indication that’s being approved for that drug. FDA doesn’t actually approve the drug. They approve the indication for the drug.

Tacey Ann Rosolowski, PhD

1:07:53.2

I think it was last time you had mentioned something about how very needed regulation was but that had gone too far, and is this a time to maybe talk about this issue?

Ralph Freedman, MD

1:08:05.4

Yeah, yeah, yeah. I think there’s—look, it’s with everything. It’s like a pendulum, and there comes a point where you’ve had a chance to work within a system and you can see what works and what doesn’t work. I think a lot of the research that we do is so-called minimal-risk research or low-risk research. Basically, the only issue of concern there is privacy, and I think many individuals today—the people who work with computers and have bank accounts and have to work with government or state at some level have an understanding for what is possible to protect their privacy or not. People used to talk a lot about don’t give out your social security number, and now I just heard that from Google, they can actually know so much about you—your profile and more. So when the patient agrees to provide samples or clinical information to an investigator to do research, I think they should have an understanding that the researcher—or the environment where that research is done—will do the best that it can in order to protect their privacy. But nothing is absolute. We cannot guarantee that privacy will be protected. With the new high tech act that came in last year, they’re subjecting institutions to big penalties for

Interview Session: 02
Interview Date: March 1, 2012

breakdowns in privacy, so this—and the problem is that it's gotten—to protect privacy involves so much technical know-how and technology that it's no longer fitting that the IRBs be responsible entirely for protecting that privacy. This came out last year when the HHS submitted a proposal to change the rules to broaden the area of minimal risk and they actually raised the question whether IRB should still be responsible for this. For that type of research— And the other thing is that we've got regulation on board, because you were asking me specifically about regulation. The HIPAA regulation—Health Insurance Portability Act—was basically designed for insurance purposes, not for conducting human subject research, so they have different definitions of what a human subject is to what the HHS has. By the way, they're all in the same group because HIPAA comes under the Office of Civil Rights under the HHS, you've got different offices. You got the Food and Drug Administration; you've got the Office for Human Research Protection; you've got the Office for Research Integrity—and they deal with fraudulent issues—and then you have the Office of Civil Rights.

1:12:19.3

Interview Session: 02
Interview Date: March 1, 2012

And HIPAA is controlled by them, but all of this falls under the general umbrella of the HHS, so you've got agencies for all, and yet, they have different sets of rules and different sets of regulations. So for example, we have a federal-wide assurance, which says that we will be compliant with CFR 45, 46, which are the regulations that relate to human subject research that is funded by the government. We could actually opt out of that by just signing one little box, but we haven't, and so in the federal-wide assurance that the institution official signs, it says that we will comply with all these rules and if there are unanticipated problems, that we will report these to the government. They have—the first part of this is what's called the common rule, which basically talks about definitions of human subject research, IRBs, how they should be formed and the responsibilities of the individuals, and then we get to vulnerable populations and so forth. In the HHS definition it says that only a living person is a subject. According to HIPAA, even if you're deceased, you're still a human subject, so the problem then for researchers who do a lot of edemiology-type research is that the population that they're studying includes deceased people who, because of the research—and you've got to get authorization from family members in order to get access to that information, whereas under the HHS you don't need it because a deceased person is not a human subject, so then they allow you to get waivers—HIPAA will allow you and the other will allow you to get a waiver for informed consent or authorization. Informed consent is what we generally get from a participant. Authorization is what we require under HIPAA—authorization to access their records, authorization to use those for research—and the HIPAA requires you to be very specific about what you're going to do with it. So whereas the HHS rules may be satisfied if you said I was going to do the laboratory research or there's nothing going into patients—there's no risk to them; it's just privacy issue and protect the privacy the best we can—HIPAA will say no, you got to say exactly what lab experiments, and then if you want to change your research by adding different reagents or something, you're supposed to come in and get their permission. That's the way it is, so you can get a waiver if it's not feasible to do the research without accessing the private information, and they use that terminology, practicable—they use the word practicable, which means that it's impossible, basically, to do it without getting access or without getting the PHI—the private information. Well, it's always possible, and that's where the problem is because it may take you two months to get authorization, find out who the family member is who's responsible, who's the legal authorized representative in order to grant you access when what we're talking about is not any research that's going to affect either the family members or the community, perhaps, because in those cases, we treat it separately, and we might actually require consent. For example, the Huntington's chorea is a genetic disorder, and it occurs in families, so if you're going to do research on that type of situation, you would want to get permission from them and also inform them how you would deal with that with the results, how you would disseminate them back—that problem happened with that in a South American country some years back—so there's no harmony between the two groups. Basically, what we need is a system that the public can have confidence in. So we're talking about hardware; we're talking about software; we're talking about processes—hardware computers, so now they are busy installing Windows 7—Windows 8—

Interview Session: 02
Interview Date: March 1, 2012

Tacey Ann Rosolowski, PhD

1:17:57.1

I think eight.

Ralph Freedman, MD

1:17:57.2

—onto all the computers. Not all the computers can take it, so they've got to abandon those computers and now get new ones, but those can be encrypted—the information can be encrypted at least, so there needs to be—and we've talked about this—it needs the institution to come up with systems in place. This is the equipment that you are permitted to store patient information on. It has to be in a password protected area; it has to be encrypted. If you happen to have this on your laptop and you leave the facility and your laptop gets stolen, gets lost, nobody can get access to that information or it's unlikely—really difficult. And then you have to have software that can be—also protect the individuals, and in the case of the FDA, they want you to be compliant with part eleven, which is that nobody can manipulate data. In other words, there's signing in and signing out for every event that happens where that data's taken out—if it's worked on, calculations done with it, there's a signature pathway that goes with it, so you've got information security; you've got information technology; you've got the people who buy the equipment—the contractors. But most of this is outside the domain of the IRB. Institutions should really have to pick up the ball here and provide the resources to the investigators or provide the investigators with solid guidelines as to what is acceptable practice to protect the subjects' purity. Once we've got all this in place, I think you could come to the public with a strong argument and say we've got processes in place, which are equivalent to what your government has, what your state has, what your bank has, and we can't guarantee that your privacy be protected, but if you want to participate in this research, this is what we've got in order to protect your privacy.

Tacey Ann Rosolowski, PhD

1:20:30.2

What's the situation with all of those components at MD Anderson right now?

Ralph Freedman, MD

1:20:36.6

Right now, it's evolving. Unfortunately, I think when a person view—and that is not mine or any others—is that we've lost a lot of time building these systems and building these processes. It's taken events to happen, to get into the media to encourage us to do these things. There are committees that are working on this. We needed it yesterday—the moment we started working with this private information, so that—

Interview Session: 02
Interview Date: March 1, 2012

Tacey Ann Rosolowski, PhD

1:21:15.7

But why has there been such a slow process to come up with— ?

Ralph Freedman, MD

1:21:21.0

Well, it changed after 2003. HIPAA was enacted in 2003, and HIPAA changed everything because things were much easier. Now I don't know that HIPAA has solved problems or has prevented problems from occurring to a great extent. It's an extra layer of—it's become an extra burden, basically, to researchers, and IRBs have to spend so much more time reviewing these things, so instead of taking care of physical and other risks to subjects, we're spending a lot of time on privacy risk, where if the systems were in place, we shouldn't be bothering about this. We should allow somebody who wants to submit a study to look at data from the institution, and if they're going to comply with all these things, it should be able to go through on a templated-based system, and there may need to be a record of access and release, but the risks basically would not be very—they'd be very minor. So I think this is part of the thing is to have the systems in place for the researchers to use, and then regulations, so these regulations which we're not sure protect anyone or they are certainly burdensome, and there should be a way of removing unnecessary—or there should be at least a very careful look at what we have to see where these things can be amended or changed so that patients can still be protected but not with additional burden to the researchers. That way, the research can get done more quickly. You can access the necessary patient information. We talk about honest broker systems—honest broker systems, which can—we don't have any such thing at Anderson, but data tissue banks basically could be operated by honest brokers, and they don't have to be a person, but it could be a technical thing that allows people access to only certain information but keep PHI back.

Tacey Ann Rosolowski, PhD

1:24:08.2

Okay. Because I have not heard that phrase before. I wasn't—

Ralph Freedman, MD

1:24:11.8

Yeah, so that's—I mean—it's one of the recommendations of the NIH for developing tissue repositories as the honest broker system's being placed. The only problem with the honest broker system that I see is that investigators need to have access to a lot of information, and the honest broker—if you've got many investigators, you may not have enough people doing—separating the PHI out from the information that the investigators are requesting, so it may not be feasible. On the other hand, if you have secure computers and secure programs, that may cover it, and I would say a lot of research today, you need more than just a pathology diagnosis. You may want to know, for example, what happens to these patients long term, so you may need a followup. If you only need the tissue in order to study something there, and that's probably a minority of

Interview Session: 02
Interview Date: March 1, 2012

research that goes on, then it's okay, because you can go to the tissue bank and say I want x number of tumors from certain a type of cancer, and I don't want the identifiers, so they give them to you, and then you do the research. You probably should go with research exempt, so the exempt category, you don't continuing review. You can be administratively approved, and you can go through, so the idea that was submitted in the federal register last year was to broaden this category—somehow to broaden it so that there were less barriers in the way to separating the investigators from the research material. So this is a major issue—getting to grips with the privacy issue, even case reports.

1:26:21.3

I mean, you may have someone who was treated at MD Anderson with an unusual history and the investigator wants to publish a case report. Well, according to the HIPAA law, you've got to get authorization even though the patient is deceased. You've got to get authorization from the family. Now, they've gone through a tough time maybe, and maybe they don't want to talk to anybody over here about things at this time, and we're going to bother them now with forms which do nothing to protect the subject. I mean, it's a case report. There'll be no identifying information in the case report, no pictures. If there are pictures in there—and, of course, you require authorization—but it's just a case report. It's important for teaching. The fellows often will want to write case reports, and there are some journals that like to take them. They may be hypothesis-generating, but they don't prove anything. One or two cases that are reported of a certain condition doesn't amount to a proven statement on that disease, but often, it's very useful for people who are learning to study these cases. So those things have to get authorization, and you think from the other side, well, that's—so this is all low risk research, basically, getting access to tissues, getting access to clinical information from charts, records. Then the other side of it is you have the higher-risk research, and we start to talk about that, and it's related to—first-in-human studies carries the highest risk—and then you go through those studies that have already been done before. So there's information about not just animal data, but human data, and in finding you end up with the Phase II studies where you're looking at some efficacy and safety, and then finally the definitive Phase III, or the randomized control trial, which may be placebo controlled or not. Those studies require a lot of expertise in doing them. Investigators who do those studies have to be very familiar with the drugs that they're using because you get a look at toxicity effects. You need to be able to know whether it's the disease or the drug that may be contributing—is this a new toxicity so that you can report it as an unexpected event related to the treatment. You have to be experienced enough to do that, so these are individuals who've been recognized by the FDA as investigators. An investigator with trial is the individual who's responsible for the conduct of the trial. The sponsor is a person who—or the company, organization that supports the conduct of the trial, maybe provides the drug, so a sponsor can be a company that wants to market the drug, and then they are identifying investigator around the country. Maybe MD Anderson will be—they have a principle investigator there, and this person would sign a 1572, which is a form that says, I will follow the good medical practice and all the regulations that relate to the administration of this drug and then sign any other individuals who

Interview Session: 02
Interview Date: March 1, 2012

would be necessary to participate. These are called sub-investigators. They don't sign a separate form. And that investigator actually has the total authority and is totally responsible for the management of the study, for the assessment of the effects, the end points or the toxicities, and for any problems that happen during—for the consenting process, for delegation of authority to others, that person is the principle investigator and special role. If there's a problem, the principle investigator takes the responsibility. Now MD Anderson can be a sponsor, also, of studies. If we develop a drug and if we—well, let me not put it that way, but some studies we cannot do, where we develop the drug. We are apt to get another institution to do them because of the conflict of interest. But if we have a funded study that's, say, funded by the NIH, NIH can be the sponsor or we can be the sponsor. If we submit the IND—that's the investigational new drug exemption—then we are—MD Anderson is the sponsor, so we would be the sponsor. We would also have a principle investigator responsible for the study. The trials require a lot of input, and a lot of this has evolved over years of learning how to conduct these studies—what resources you need, the support personnel that you need to do these studies. And in the old days, they were done with a shoestring, so as a result, a lot of things were missed—toxicities were missed or end points were missed.

Tacey Ann Rosolowski, PhD

1:32:23.7

Since you've had such a long relationship with this process and then finally with the institution or review boards, what is your special interest in protecting patients' rights through these mechanisms? How did that start, and why have you kept up with it?

Ralph Freedman, MD

1:32:41.7

Yeah, I think—I actually saw it evolving with me as I was learning to do—become a better researcher. I saw a necessary or—these are necessary rules that we need to comply with.

Tacey Ann Rosolowski, PhD

1:33:01.2

What kinds of things did you notice?

Ralph Freedman, MD

1:33:05.2

Well, I would say that we noticed you probably learn from others' mistakes more than our own because that probably prevented us doing things that we aren't correct just by learning what others had done and what they've done to correct. We saw events happening where, for example, a principle investigator took on the responsibility of being principle investigator but wasn't familiar with all the interventions that were being done in the study, and as a result, patients were potentially harmed. And so I think learning that the responsibility of an investigator—someone who wants to be an investigator on a trial—you have to be certain that you have the resources to

Interview Session: 02
Interview Date: March 1, 2012

do it. If you don't have the resources, you may not be able to do the study. Maybe someone else can do it but not you. But to go back to your questions, I guess I like a certain amount of order in things. It's nice when you have an instruction about what to do and what to do correctly. I familiarize myself with guidances and, of course, with the regs over the years, and I still go back to them from time to time to—when a certain situation comes back and see what is the guidance for this particular issue. And they're always coming out with new guides, so we're learning—well, I'd say we're learning continually how to conduct trials, how to conduct them correctly, and—I mean—conflict of interest, for example, has become a very big issue today. It wasn't ten years ago. We only had our conflict-of-interest committee established something like—I think it was about ten or fifteen years ago. We didn't have a committee at the institution. Now we have very, very strong regulations. I sit on that committee, as well, as an ad hoc member from the IRB, so when a human subject issue comes up, I don't vote with it. But after the Gelsinger case—that was the case from University of Pennsylvania. I think it got a lot of attention. [James M.] Wilson was a scientist who developed a gene therapy to transfer a gene for enzyme deficiency into patient. He had a nineteen-year-old whose name was Gelsinger—the investigator's name was actually Wilson—and he went to U-Penn. It became so successful that the university got interested in it and he was able to develop a company. He was conducting trials at U-Penn himself as an investigator until one day he took a nineteen-year-old boy—his name was [Jesse] Gelsinger—his father didn't accompany him, went up to the hospital. He got this gene therapy, and he died from liver toxicity, and they went back and found that some of the animal experiments had suggested that this might happen. Well, it was a big problem—problem for the University of Pennsylvania—and I don't know if you know about the case.

Tacey Ann Rosolowski, PhD
1:37:22.3
No.

Interview Session: 02
Interview Date: March 1, 2012

Ralph Freedman, MD

1:37:23.9

He was suspended from research—well, they found the conflict of interest, that he had his company—he shouldn't have been involved. He ignored certain experiments—pre-clinical experiments—so he was suspended from research initially from a certain amount of—from getting grants from NIH. Then he had to write a paper, which has been published—that's Dr. Wilson. He had to write a paper describing what he had done wrong. He actually wrote it, and that was one of the corrective action plans, so after—I guess that case was a wake-up call to a lot of institutions around the country—I mean—the many other instances where physicians are getting large amounts of money from industry to—even in standard of care—orthopedics, cardiology, example—and these you see in the newspapers all the time, but it raised the question whether these conflicts could actually contribute to safety issues in subjects. In most cases, conflict of interest is a perception. It's a perception by the public—somebody else—that the conflict could interfere with the objectivity in research, and sometimes the safety, but the problem is that once the perception is out there—in particular when it gets into the media—it's irretrievable. You cannot recover easily from that, and there have made many academics who've lost their careers because of discovery of conflict of interest.

Tacey Ann Rosolowski, PhD

1:39:33.9

Do you suspect that the conflict of interest is sometimes overblown, that it maybe is not so much of an issue or—?

Ralph Freedman, MD

1:39:42.9

It can be, but the problem then is it's a perception that's created in many cases. We've had our own situations, which have been very clear, and actually, they have been the potential for harm to subjects as a result of those situations, and they take a lot of time to try to repair the situations. We've had 483's, which is a notice of concern that the FDA gives you when you have a problem that they come and inspect and they find the problem. It isn't a warning. It isn't the same as a warning from them, but it's a notice of concern. And then you have an opportunity to fix—and in most cases, we've been able to do that, but with a lot of effort—is to give them a response, which shows that we can adequately take care of the problem, and then you don't end up with a warning because once you get a warning, that's hard to recover from that. In response to your question, there's no—there's limited amount of evidence that conflicts actually have harmed people. Mainly, it's created a perception that objectivity can be a victim, and there could be harm, but there are some cases where you say it's very likely that the subject could've been harmed—Gelsing case is one example—so as to try to avoid this problem. So all of this has actually been amplified now because of the Bayh-Dole Act—the Bayh, B-A-Y-H—Senator Bayh and Senator Dole, responsible for that in the '80's. Basically what that act did is they said that there were lots of patents being developed for universities, but they were not being

Interview Session: 02
Interview Date: March 1, 2012

exploited. And a Democrat and Republican coming together to pass this act which enables institutions and individuals—inventors—to get some financial reward from the inventions—Institutions like it because it increases the size of their coffers, but itself, it created a dilemma now because now that this act has been passed and been around for some years, the HHS has come back and said now you have to have rules dealing with conflicts of interest. So when it comes to first-in-human studies or even definitive studies, we cannot be the lead site anymore with those trials. So it's one of the things that I wonder about, and I know that Dr. [Ronald] DePinho was interested in developing new drugs, but I'm not sure where they plan to test all these drugs because under the current conflict of interest rules for the institution—

Tacey Ann Rosolowski, PhD

1:43:18.8

MD Anderson can't be the site.

Ralph Freedman, MD

1:43:20.4

—and we may not be able to be the site, and maybe that's not what he's thinking of. He's interested in the developing of the drugs and marketing them for institution and is having the trials done elsewhere, which can be done, but it does raise some issue about where the—for faculty, what their emphasis should be in their academic careers.

Interview Session: 02
Interview Date: March 1, 2012

Chapter 7

A: Professional Service beyond MD Anderson

1:43:55.0 to 2:36:54.9+

Service On the National Cancer Advisory Board and Other National Bodies

Story Codes

- A: Contributions
- B: Beyond the Institution
- D: Understanding Cancer, the History of Science, Cancer Research
- D: The History of Health Care, Patient Care
- D: Business of Research
- D: Fiscal Realities in Healthcare
- B: MD Anderson and Government
- C: Professional Practice
- C: The Professional at Work
- C: Critical Perspectives
- C: Faith, Values, Beliefs
- D: Ethics
- A: Post Retirement Activities

Tacey Ann Rosolowski, PhD

1:43:55.0

Would you like to speak now about your role on the National Cancer Advisory Board?

Ralph Freedman, MD

1:44:03.0

Yeah.

Tacey Ann Rosolowski, PhD

1:44:05.1

You were appointed to that in 2000, served between 2000 and 2006 and—

Ralph Freedman, MD

1:44:11.3

Yeah, that was very—

Tacey Ann Rosolowski, PhD

1:44:12.2

Kind of amazing.

Commented [T7]: In this segment, Dr. Freedman discusses his role as a presidential appointee to National Cancer Advisory Board (President Bill Clinton, '00 – '06). He begins with a brief sketch of the birth of the NCAB (and the National Cancer Institute) in the National Cancer Act, then covers NCAB review processes and grant procedures and compares the different styles of the Directors of the National Cancer Institute, who work with the NCAB. He shares his view that all the institutes need to reconsider the kinds of clinical research they are supporting. This discussion leads naturally to his post-retirement role on the Oncologic Drug Advisory Board (since '09), "one of the most productive Boards at the FDA," in Dr. Freedman's words. He notes that he had to divest himself of certain stocks and remove himself from committees to satisfy the Board's conflict of guidelines. He also talks about the Board's procedures for questioning drug companies, offering several examples (including a drug company's challenge to a rejection). He concludes that "They [the FDA] do a terrific job of protecting the public."

Interview Session: 02
Interview Date: March 1, 2012

Ralph Freedman, MD

1:44:13.3

Well, that was very interesting. I was nominated to the board. I don't know the process, but my office got a call telling me that I've been nominated for that and to supply information. The members of the board are presidential appointees—actually, I still have the certificate here; it's back in my study—and so it was done under Clinton's presidency, and I didn't give any money at that time. I did give Hilary [Clinton] some money later on, but she disappointed me. But that was years later after I was off the board. It was 2008, of course.

Tacey Ann Rosolowski, PhD

1:45:01.8

I notice that you're careful to dot those conflict-of-interest I's and cross those T's.

Ralph Freedman, MD

1:45:06.9

So anyway, the National Cancer Advisory Board was created as a result of the Cancer Act in 19— I think it was 1970. I might be wrong on the date, 1970, '71. Basically what the Cancer Act did was—this was [Richard] Nixon's effort to eliminate cancer, and of course, we hear that many times now—and what it did for—R. Lee Clark was involved—and I think that's also nicely dealt with Jim's book. But what it did, it created a separate budget line for the National Cancer Institute. I think they were hoping to get, initially, a separate institute from the NIH entirely that was totally independent. But the American College of Professors and others around the country, I think there was a lot of competitiveness or antagonism from people out of the cancer field as to why should cancer be so prominent. I mean, you can imagine the cardiologists thinking, Well, why not us? We need a separate institute. So NCI is one of the twenty-eight to twenty-nine institutes but they have a separate budget line. So the director of the institute submits a budget which goes to the White House. The NIH director submits a budget on behalf of all the institutes separately, and so that's a potential advantage, and it's probably served in the interest. That's why they have—I don't know exactly today what the budget is, but I think it's about five billion dollars a year, the NCI, and I think that the NIH budget must be around thirty billion dollars, so that's a sizeable proportion considering how many institutes there actually are. So it's been beneficial. I learned a lot of interesting things there. First of all, at the NCAB there's a board of the President's Advisory Board, and Margaret Kripke was on that committee. There are three members, and they go around the country. Then there's the NCAB, and then you also have a Board of Scientific Counselors. And what the NCAB actually does is the second level of review of grants. So the grants go through the review process, they get triaged, and they go to their study sections and they get scored. Then the NCAB, in collaboration with the administrators, determine what the cutoff level is going to be how much money they've got, because a lot of money has to be set aside for continuing renewals. For example, you get a grant this year, and it takes—it's for three years or four years—they have to have money next year and the year after to fund them, so really, a very small proportion of the money actually goes towards new grants. Ten

Interview Session: 02
Interview Date: March 1, 2012

percent gets taken off automatically to go to the intramural program. That's what goes on at those buildings, and they do a certain amount of research up there. They don't have to compete for grants. They actually are competitors today with the institutions around the country, the fifty or so cancer centers around the country. We've got these institutions where they do clinical trials. They have their own one at NIH. They have a clinical research center, and patients can get their—they get free treatments there, and I'm not sure if they also get their transport paid, but at least they—I think they get their accommodation covered. So in a way, they're competitors. But they have the ten percent of the budget, and that's been a bone of contention for a while—and also, because dynamics have changed. In the early days, when Dr. [Emil J] Freireich was at NIH and people like Roth and Grimm were with the NIH, you had a large number of prominent researchers working at NIH and NCI. And basically, the main discoveries were being made there. Taxol—Horwitz discovered Taxol—it came out of there. And the cytokines have been developed there, and therapeutic approaches in leukemia, so there was a time when they had a critical mass of scientists. Now those scientists are getting older—like all of us, getting older—and they're getting close to retirement, and the question is what are they going to do? What's the future going to be for NIH? So NCAB would get reports at its regular meetings as to what was going on.

1:51:00.3

The meetings would occur every quarter, and they also went along the grant cycle because they had to do the second level of review and approval of those grants and determine what I think they qualify for. That was all done behind closed doors. The first part of the session was a public session in which innovative research from around the country was being presented. Sometimes they'd bring investigators up to present, and that was fascinating. That was exciting and interesting. We had different— During my tenure there, we had two directors. Andy von Eschenbach was the last one, and before that was Dr. [Richard] Klausner, and he was actually very excellent. They had different styles. The directors had different styles. These are political appointments, also, so the director of The National Cancer Institute is an appointee of that administration as are the members of the NCAB. So you listen to all this stuff, and you hear reports from the preventive group and from the biology group or areas of importance. I attended something called colorectal screening in which they reviewed all the approaches towards early detection of colon cancer. And it was very informative because on that day that the specialty that I come from—OB/GYN—was actually doing the worst job in screening patients because they would do a single digital exam and do an occult test in the rooms, which is totally inadequate. His patient had that sigmoidoscopy every five years and colonoscopy every ten years if nothing was— So all of that data was presented at a special meeting, and then the guidelines came out of that. HPV vaccines were discovered while I was there, so we heard all of these interesting and fascinating things, but in terms of actually making policy, the board doesn't really do that. The director has a lot of—he has his own boards inside that determine a lot about what they do at NIH. There have been some interesting books written about the NCI. There's a fellow, Epstein, who wrote about the politics of cancer—actually wrote two books—and he was an

Interview Session: 02
Interview Date: March 1, 2012

epidemiologist. Of course he felt that more of the funds should go towards prevention and early detection in epidemiology research, which may not be the wrong thing considering now that most of the drug innovation is actually done by pharmaceutical companies who develop the drugs today and it costs so much to conduct clinical trials. It's a question whether government-supported trials can actually have enough resources in order to conduct large trials effectively, and some of these issues have come up. And some of the observations that I've made where some of the studies were done by some of the groups that are supported by the NIH—oncology groups—they've now consolidated them in the last year because of budgetary reasons. Well, it takes a lot of money and resources to conduct a big study, and certainly I think industry has got an advantage there because they can rely on the R & D funds and the profits that they get out of marketing their other products, unless it's a single product in an early company. So I think it's time that the NCI does look at their whole portfolio, looks at their whole structure, and in Britain, for example, you have the MRC. I've participated in reviews for them, and you have ten pages. You answer questions about the conduct and the study that's being proposed for funding, and they give you a very succinct list of questions. You send your review in, and then it's looked at it in England by the MRC group. Here, you've got to invite people up to study sanctions. There's always the question of how the study sections are constituted and how fair are they. You can have very prominent researchers that can suddenly lose their funding, and it's not always—or else they may get a score that they don't get funding this time. Then they've got to wait another year before—eventually they do get funding. In the meantime, the process is slowed down. It doesn't seem to be a very efficient system for today, but the basic question is what type of research should the institutes be supporting now? Can they still do a good job in supporting clinical trials? They get their drugs from industry through what they call a Crada mechanism. It's a cooperative research agreement, so a company provides NRH with a group of drugs, and then they have the investigators at different institutions apply or send in a—by the way, the name of the previous director was Klausner, Richard Klausner.

Tacey Ann Rosolowski, PhD

1:57:44.8
Thank you.

Ralph Freedman, MD

1:57:45.1
It came back to me, K-L-A-U-S-N-E-R. He had to leave. He was actually a phenomenal guy, brilliant, very brilliant. I remember he gave one talk once on Lewis and Clark, and he related basic science to the Lewis and Clark expedition, though it's fact-finding, not clearly hypothesis-driven, and it was absolutely a brilliant presentation that he gave.

Tacey Ann Rosolowski, PhD

1:58:18.2
You mentioned Lewis and Clark in our last session.

Interview Session: 02
Interview Date: March 1, 2012

[Redacted]

Tacey Ann Rosolowski, PhD

1:59:20.4

Oh, the cooperative research appointments.

Ralph Freedman, MD

1:59:22.0

Right, right, so that's the company's— NCI would have arrangements with industry to allow their drugs to be used in clinical trials, and they have a review process at NCI, which they would do, and the company, I think, would have some kind of final decision on where the drug goes. Now I think if you think about it logically—and certainly, not everything is logical—or intuitively, you have a company that has a drug that they think is very important. Are they going to release that drug to be done by investigators that they have little choice over because the NCI picks the investigators to test the drug? And with the chance that the study may—the way it's designed and the way it's constructed or other variables may apply—may lead to a false negative outcome for that drug? So I'm a little suspicious of this mechanism. I think that the companies, if they have a really good drug, are going to keep that drug close to their chests, and they're going to wait until the drug is approved and then maybe release it to the NCI or other people to work with it, say, for other indications. I suspect that that's what happens. I don't know this for a fact, but they are the creators—makers—so the thing is that people have to write a notice of intent, LOI—letter of intent—that they want to study the drug, and they put down a few things there—how they want to study—and it gets reviewed by the NCI committee. And then again, it's done on a competitive basis, and then they give the drug out for the study to be done. Well, then you have to have money to do that study. Can the NCI provide enough monetary support to do these studies? Why did they have to consolidate the cooperative groups? Often there's a limit to grants. There's a ceiling on which you can actually get, so you—and I've had experience because I've done—I've had grants through the different mechanisms or ROI or R21 and so forth, and one of the difficulties is that the institutions take big overheads from these grants—sometimes up to ninety percent from some institutions.

Tacey Ann Rosolowski, PhD

2:02:08.6

Wow.

Interview Session: 02
Interview Date: March 1, 2012

Ralph Freedman, MD

2:02:09.0

And the decisions on the overheads is not made by the NCI or NIH. It's made—it's another government level. So an institution can apply and say we want seventy percent overhead, and whoever this body is that grants it—because I know I asked this question in the committee in my naivety, and they get it mainly at NCI, when it awards the funds, has to comply with this. In other words, they give their direct funds, and they have whatever the percentage is allowed by indirect. That indirect goes to the institution for whatever purposes, but very little of that goes back to the researcher. So you've got this system in place, and now we're dealing with a success rate for grants of under ten percent of average, maybe much under that. That's a one in ten chance of getting your study funded, so by the time your study may get funded in another year or so, maybe their drug is irrelevant; there are two or three better ones. So is this the system that we want to support such a system? And it's worth going back and looking at some of Epstein's comments, especially in his first book. The second book was not—he was quite critical of the processes and the politics, and I think there is a lot to that. It's hard for us to—you can't separate politics from all this. It's there inbetween. You get actions that are taken in Congress, for example, to award certain areas of funding. Somehow the NCI had come up with supporting a certain area of research. It's decided not by scientists, but by officials, and they've got the same pot of money to do it. They don't actually get more money to do it, so it means they're going to take from somewhere else to. So maybe a congressman from a certain district—say it's a number of patients with a certain type of cancer, and they think not enough is being done for this. What they did do, which was useful, was to actually provide the amount of support for different disease entities, and we saw that when I was there. And then they did provide programs to cover those areas that they felt had been sort of underrepresented.

Tacey Ann Rosolowski, PhD

2:05:09.8

So this was like a national averaging of what money that was being—

Ralph Freedman, MD

2:05:12.1

Yes, and how much money was actually assigned, say, to pancreatic cancer. And you've still got to go through their review process, and that's the problem. You don't necessarily have all the experts of that disease. I think they try to create some disease site by these—through these groups.

Tacey Ann Rosolowski, PhD

2:05:36.7

Do you happen to recall what the breakdown was? I mean, what struck you at the time about the breakdown of how funds were being directed to different cancers?

Interview Session: 02
Interview Date: March 1, 2012

Ralph Freedman, MD

2:05:45.2

Yeah, for different cancers. I don't have the information. I remember looking at that in gynecologic cancer. At the time, there was relatively little support for uterine cancer, and now some of our researchers have been able to exploit that and to get more grants to cover uterine cancer, and of course, gynecologic cancer; if you take out breast cancer—because most gynecological oncologists treat breast cancer, except for some parts of the country—it's a relatively small part of the whole spectrum of cancer, so therefore, relatively less can go there, but I think whenever you can show results—of course, results mean support for further work in that area.

Tacey Ann Rosolowski, PhD

2:06:40.0

Right. Did you have something else you wanted to add about the National Cancer Advisory Board?

Ralph Freedman, MD

2:06:48.2

Well, we had some very interesting people, and they had Susan Love, I remember. Do you know Susan Love at all?

Tacey Ann Rosolowski, PhD

2:06:56.3

I remember the name.

Ralph Freedman, MD

2:06:58.1

She wrote a lot—she treated breast cancer. She was a surgeon from UCLA.

Tacey Ann Rosolowski, PhD

2:07:13.7

Okay. Yes.

Ralph Freedman, MD

2:07:15.0

—that is it may—and she actually made a very good contribution for women. And she was very eloquent, the things that she said, and that was actually great things. We shared books. She sent me a copy of her book, and after that, I haven't spoken to her for a long time, so it was nice having her on board. And then there were—I can't think of—oh, it was Larry Norton who was from Memorial Sloan-Kettering, quite an intensive knowledge on cancer. I think it was simply a privilege to be there. I don't know how much difference it made whenever they have—because

Interview Session: 02
Interview Date: March 1, 2012

we—second level of review may be the most important part of the work, but seldom were decisions made that had wide impact there and that were not already made somewhere else. When Andy von Eschenbach came out with cure cancer by 2015, he had made that decision already when he came and announced it to the board. The board is a public meeting. You've got people from the newspaper, from Cancer Letter, Goldberg—I think his name is—the editor from the—who sat in the audience and listened to it, so once the directors made this announcement, I just—people, I think, were just frozen to their seats, and you can't really go back on it. It's done, and I think the—I don't know where—who persuaded him to do that, but obviously it's ridiculous. The year 2015 is three years away, and we've got as much cancer now as we had—maybe a little bit less.

Tacey Ann Rosolowski, PhD

2:09:27.0

You're serving now on the Oncologic Drug Advisory Board and carries with the—

Ralph Freedman, MD

2:09:35.2

That's the Food and Drug Administration.

Tacey Ann Rosolowski, PhD

2:09:36.6

And I'm just curious about the comparison of those experiences and also, of course, what your activities are on that.

Ralph Freedman, MD

2:09:42.9

Yeah, this is different. I was asked to—if I wanted to participate in this—and I had to go up to FDA and make a presentation, and I think I was one of—I don't know how many people there were, but I was chosen, and it's a fourteen-or-so-member board. It's the Oncology Drug Advisory Board, which is part of CDER—Center for Drug Evaluation and Research—and it relates to the oncology drugs, primarily. It's primarily because some of the products that we've approved have not been actually oncology drugs—they've been others—and it's advisory, so whatever decision is made is purely advisory. And typically what happens is the FDA advisory group will review a new drug application, employee license to market them in a different application, and then they may have some questions about it. So they'll have some cases which are clear-cut, and they will give it approval. There are others where they're not sure about the study. It may be that the balance between the toxicity and the benefit is a little uncertain, so they'll bring those to the board before each meeting, and we may have—I think we had up to 6 meetings last year. It's actually one of the most productive boards at the FDA, the oncology section. So the company presents its data. The FDA does its own analysis of the raw data, so what you basically get is you get a review from the FDA; you get a review from the drug

Interview Session: 02
Interview Date: March 1, 2012

company—two separate amounts of data, which are quite extensive—and the FDA basically will ask the board members certain questions—do you think that the level of effect is justified by the risks, something like that, so the questions are always different. There's a very tight company intra-screening. I don't keep any drug stocks. When I started, I had one, I think—or two. I just divested them. I had to take myself off the Data Safety Monitoring Board here at Anderson because I was on that just because—they didn't tell me that I had to, but there were so many questions being asked about what drugs that I had reviewed in the past year, and we had so many protocols involving so many drugs, it was just easier to do that. And then they decide if you can participate or not, so the people that go there are their regular board members, and then they bring the experts in—ad hoc members—who have been screened and maybe experts in a particular disease—prostate cancer, kidney cancer. The presentation is made, first of all, by the company, and then it's made by the FDA people, and the way they set up the meeting is kind of interesting. It's in a public forum, and the public are separated from the board members. The FDA people sit at the table. You have the ad hoc members sit at the table. There's supposed to be no communication. We're not supposed to communicate about the product with each other while the session is ongoing and also with others. So if you go out for a break or something, you can't communicate, and of course, once you've got the information they sent you to review, you cannot communicate that to anyone, either. Ayou can understand there are obvious reasons why they don't want that to happen. You've also got insider rules, which could apply if you did divulge anything.

Tacey Ann Rosolowski, PhD

2:14:17.7

I'm curious of what the logic is of not having the committee members talk among themselves, however.

Ralph Freedman, MD

2:14:23.9

You can discuss it in the meeting.

Tacey Ann Rosolowski, PhD

2:14:27.8

Oh, okay.

Ralph Freedman, MD

2:14:29.0

Like for example, not privately.

Tacey Ann Rosolowski, PhD

2:14:30.8

Oh, okay.

Interview Session: 02
Interview Date: March 1, 2012

Ralph Freedman, MD

2:14:32.4

Not privately, but when the case is being presented, there may be questions from one board member to another, but it's all over the microphone.

Interview Session: 02
Interview Date: March 1, 2012

Tacey Ann Rosolowski, PhD

2:14:45.2

So everything's transparent, public mention.

Ralph Freedman, MD

2:14:49.0

Right. Everything is transparent. It's a very—I didn't know about this process—most people don't—but to be open and transparent process. So the FDA do their thing, the sponsors do their thing—and of course, their conclusions may be a little different—and then they present questions to the board. The board discusses. They also have public members. A person who happened to be a patient, perhaps, or represents a group of patients—say, Lymphoma Society or whatever—could make a statement in open forum. They have to indicate that they want to speak, and they are treated respectfully. They're allowed to make their comments over a certain period of time, and then they—there's no questioning of those public members, but they're allowed to make a statement. Then this process can take a full morning or full afternoon—usually, I would say one half day per drug in most cases. Sometimes it goes over, and then you vote, and the vote is public. You press a button, screen comes up, and it's got your name there that you voted yes or no or abstain. Then they go around the table and you have to say why you voted yes or no, and it's over, and that's the recommendation. The committee votes to approve this indication, the committee votes not to approve it, and then after that, the FDA can do—yeah, the FDA, in most cases, will take the decision that's made by the committee. I've seen it happen at the—for various reasons—

Tacey Ann Rosolowski, PhD

2:16:55.1

They overturned it?

Ralph Freedman, MD

2:16:56.0

Overtuned it. Well, it's not like they're overturning it because it is advisory.

Tacey Ann Rosolowski, PhD

2:17:06.8

Advisory?

Ralph Freedman, MD

2:17:09.1

And I think a lot of people don't also realize that the FDA have really—they have regulations under which they operate in approving drugs, and this goes back a century. Their regs started developing even before the human subject research regulations were published in the register in the '70s, and they started off when they were vaudeville snake-oil salesmen and went around. So I think things which were pretty dangerous— So the first type of rules that they had were safety

Interview Session: 02
Interview Date: March 1, 2012

rules. In other words, they just had—in the 1930's, they had to show that a drug was safe. They didn't have to show that it was effective. A company had to show that it was safe. And then in the '60s, they had to show efficacy, and then later on they defined what efficacy meant, and that's an ongoing process. So when you look at efficacy end points, we're looking at primary and secondary end points. The primary is the main thing that determines whether a drug—if it's successful. If they can show that this is a clinical impact of—a difference between the control—these are usually at randomized controlled studies. That is the difference in survival, for example. That is absolute—people live longer from the treatment. You can't argue too much with that, and then often is the secondary—but sometimes even if a primary end point—they will have what they call progression-free survival. That's the time that it takes for a tumor to actually progress, so it may not be an effect on survival, and it's considered to be a surrogate because it's expected that in some cases, if you have an improvement in time to progression, this might translate into some improvement in survival, but it doesn't always happen. It frequently doesn't happen because you get small increments in time to progression, and therefore, either because it's crossover from one arm to the other or because the difference is so small—maybe two or three months, which is what happened with Avastin and breast cancer—that there really cannot realistically be a difference in survival. So then the question is how significant is that to the patients, and that's where they have to be able to show that the patients are actually getting a defined clinical benefit. And defining clinical benefit is sometimes the most difficult thing in cancer because the patients are getting side effects from the disease, they get side effects from the treatment, and then it's a balance. And that's where people are asked to make a decision, and what's the risk benefit of this? Can you see a clear clinical benefit from this? And—

Tacey Ann Rosolowski, PhD

2:20:26.6

That's kind of going back to those quality of life— You were talking about the need for some kind of systematic way of defining how a patient's quality of life had been improved.

Ralph Freedman, MD

2:20:36.1

Oh, well, the quality-of-life instruments are very complex, and a lot of academic institutions do those studies. But they're not relevant to the approval process because what is approved is the indication, and that indication goes onto the label for that drug. The labeled information basically reflects largely what is presented as part of the new drug application, so how well the drug did in the trial, what was the toxicity profile, what is a whole range of serious toxicities, percentages—all that has to be given to physicians and to patients. And the one thing they are not allowed to look at is the cost effectiveness, because that's not been—Congress has never given that authority, and—

Interview Session: 02
Interview Date: March 1, 2012

Tacey Ann Rosolowski, PhD

2:21:32.6
Why is that?

Ralph Freedman, MD

2:21:34.5
Well, I think a lot of it is political issues. It's a sensitive area.

Tacey Ann Rosolowski, PhD

2:21:51.0
Should I turn off the recorder?

Ralph Freedman, MD

2:21:55.1
Yeah, just in case I may say something.

Tacey Ann Rosolowski, PhD

2:21:59.0
I've turned the recorder back on after a brief pause.

Ralph Freedman, MD

2:22:02.2
They do a great job, I think, in protecting the public. It's a public health issue when you have a drug that's released to thousands and thousands of patients, which may have a significant toxic effect. Like one drug that was disapproved was an antibody, denosumab, which is actually used—this was already in the public arena, and it was at our last session. It was for prostate cancer patients, and the idea was it would reduce osteal occurrences. But they couldn't show that it actually reduced symptoms from developing, so a lot of patients who have prostate cancer may have sub-clinical metastases to bone and don't even realize that when does it become clinically important is when they start to develop fractures or when they get pain from their metastasis. So that wasn't part of the evaluation, or if it was, it didn't show up, and there was no difference in survival, and the difference—the time to developing these osteal metastases was short. It was two months or three months—maybe about three months, perhaps, and there are a lot of questions, right? So the recommendation was against it.

Tacey Ann Rosolowski, PhD

2:23:57.4
Interesting.

Interview Session: 02
Interview Date: March 1, 2012

Ralph Freedman, MD

2:23:58.5

—felt— So I don't think the FDA have come out with their final decision on this drug. It's an antibody, and it's marketed— And another name called Prolia—in order to strengthen bones in post-menopausal women, but in this case, it was used at a higher dose. What it actually did, it caused a high frequency of bone necrosis of the jaw, and that's one of the complications of these drugs. And it was weighing up this three months' time interval versus the other. And we didn't know how long treatment would—these patients would be exposed to treatment, because if they were exposed for three years or four years or whatever it is, the incidence of the bone necrosis may continue to go up accumulatively. So it is a public health issue because there are a lot of prostate—a lot of patients eligible for the treatment. Once it's released up there, then you got to think about how many people are going to be exposed to the drug that could get a significant side effect from that which can sometimes require major surgery. So those are the kind of decisions, but there are backed by legislation. When we had the Avastin—which is a very interesting situation because it's the first time, I think, that they've actually had a public meeting—after the ODA Committee had reviewed this drug twice—

Tacey Ann Rosolowski, PhD

2:25:45.2

What's the name of the drug again?

Interview Session: 02
Interview Date: March 1, 2012

Ralph Freedman, MD

2:25:46.2

It's bevacizumab. It's owned by Genentech Roche, and they submitted it for study in patients with advanced breast cancer. The FDA had given them what they call accelerated approval. In other words, the first study that they basically approved showed a five-month difference in progression-free survival, but under the accelerated approval rules, they have to come back with definitive studies. They can market the drug for that purpose, but if the studies that they do are not strong enough as the first one, the FDA has the authority to withdraw the approval. So when they came back, they had several studies. They were done with different drugs—some was the same drug, some with a different drug, and there were about three or four trials—but the magnitude of difference, instead of being five months now, is one to two months, and there was increased toxicity for some of them. And as I said, this is a population of patients. They could survive twenty-four months with current available chemotherapy, so the right of the committee was to disapprove. This represented an amount of—pretty sure it represented quite a large amount of money to the company, so they challenged it, and they asked for a public meeting, which they had—according to their rules, they had the option to have. And this public meeting had a very interesting format. You're going to have the two groups there—the company and the FDA—each representing their side. And interestingly, the lawyers were the ones that were pushing the main issues. In the— Oh, the other thing was that the usual FDA people that sit around the table couldn't be there. The officer running the meeting had to be from another part of the FDA—nothing to do with oncology drugs—so they had to divide up all this responsibility. And then the ODA—there were several of us that were there—were part of the process but not sitting at any main table. So the lawyers from each side, their main push was why—whether there were inconsistencies in the way the FDA applied the ruling here, with other drugs got it, and these at least didn't. And the FDA came back and said, well, each drug is different and each disease is different. You can't apply necessarily the same rule to each, but basically, we were looking at the same data again, and the conclusions were the same. I did try to see whether I could find something that I could get my hands around, and I did ask some questions, which apparently were thought of as indicating, that maybe I was changing my mind. But all I was doing was trying to see if there were other applications—advantages that had been—perhaps strengthened the support for it. So it was open public meeting, so we had a lot of demonstrators there. We had, oh, a group of women from an advocacy. They sued FDA once before because they wanted access to experimental drugs that hadn't been approved. It's named after a patient, too. He had end-stage disease, basically. And there was a lot of vocal criticism. You had to endure this and just sit and listen passively. There were people outside with placards, and it was really an active demonstration. They were allowed inside as long as they didn't make a noise. Once they started to interfere with the meeting proceedings, then they were escorted out. They had Homeland Security people there who escorted them out.

Interview Session: 02
Interview Date: March 1, 2012

Tacey Ann Rosolowski, PhD

2:31:02.5

What did you take away from that whole experience?

Ralph Freedman, MD

2:31:05.3

Well, I think it's—

Tacey Ann Rosolowski, PhD

2:31:06.5

A bit of wisdom?

Ralph Freedman, MD

2:31:07.6

It's a democratic process, and it's giving them another chance. They still have an option. They could go to court if they want to, but I understand even the usage of the drug and the disease has continued to— See, what happens when a drug is approved, initially there is a lot of enthusiasm for that drug.

Tacey Ann Rosolowski, PhD

2:31:30.5

It's like there's a new miracle cure out or something, yeah.

Ralph Freedman, MD

2:31:32.3

There's a new thing. You got to get it. And then there's—doctors get more used to it. They suddenly find—say, look, there are other drugs that do the same thing, and they can maybe have not as much side effects or whatever. They decide, so there's a lot of off-label usage in this country, and the FDA does not really control it. They consider that medical practice if people want to use a drug that's already no longer in experimental mode—now, insurance companies may not pay for it, but that's not an FDA concern. The FDA doesn't actually liaise directly with Medicare—I mean—in determining how drugs are priced the way they might be. There's no linkage.

Tacey Ann Rosolowski, PhD

2:32:25.1

Well, it sounds like a really amazing experience.

Interview Session: 02
Interview Date: March 1, 2012

Ralph Freedman, MD

2:32:27.1

I think it was, and so these—you know what? Some of these things actually—these have been highlights from the point of view of being able to participate in something that is important to the community—drug safety, what drugs are out there is a very important thing. I mean, after the Thalidomide disaster years, we avoided that by having a review process that prevented the drug from getting here, and probably that's happened a number of times, and it's hard work. They have to do a very detailed analysis on these drugs that's actually done by the FDA themselves. Sometimes a drug is approved in Europe, and it's not approved here and visa versa. There are different standards that are applying to drug approval.

Tacey Ann Rosolowski, PhD

2:33:31.2

Why do you think you were asked to part of that advisory board by—?

Ralph Freedman, MD

2:33:36.6

I don't know because I don't know who nominated me. I knew Buzdar because he had been at MD Anderson, but we were not personal friends or anything. Actually, when I went for the interview, he wasn't available for the actual—the people that interviewed me, he wasn't one of them. You have to go before a—you do a presentation, and then you get interviewed by a group of people who work at the FDA. I mean, I have been involved a lot with clinical trials, and I suspect the clinical experience and maybe people aware of my interests in this area. Perhaps the IRB had some role in it—I don't know. And the fact that we had to deal with some of the type of questions must benefit. You're always looking at this balance, but as I say, I don't know what the actual criteria were. Now, they do choose people who are not involved to any degree with—I can't say, because some of the members actually are quite involved with clinical trials, but the more companies that you're involved with, the less likely—the more difficult it is for you to be there.

Tacey Ann Rosolowski, PhD

2:35:18.5

That makes sense.

Ralph Freedman, MD

2:35:19.4

Because either you cannot review any drug that's made by the company that's making the submission or even competitors—they go beyond what we do. When we exclude people from review of trials at Anderson, we cannot include—we exclude the ones that have relationships with competitors because they would have nobody there on the committee. They can draw from a wider arena, so—

Interview Session: 02
Interview Date: March 1, 2012

Tacey Ann Rosolowski, PhD

2:35:55.3

It sounds like a pretty impressive process you have to—

Ralph Freedman, MD

2:35:58.4

I think the process—I was actually impressed. I had no idea, had no knowledge, really, of the process. I just knew that the FDA did the review somehow and then drugs got approved or didn't get approved, but I didn't know how tight the rules were. So the general rules are applied that can be applied generally, but at the same time, there are disease differences and other differences that can result in a drug being approved under one situation and not in another.

Tacey Ann Rosolowski, PhD

2:36:44.2

Now, just for the record, how long have you served on that committee?

Ralph Freedman, MD

2:36:47.1

Well, this is my third year, so I will finish in June.

Tacey Ann Rosolowski, PhD

2:36:49.9

Oh, okay. Yeah, would you have an interest in serving again, or is it a one—?

Ralph Freedman, MD

2:36:54.9

You can't—I think you cannot go back for—there's a certain amount of time that you cannot go back. You can come back as an ad hoc member, but you cannot come back as a full member.

Interview Session: 02
Interview Date: March 1, 2012

Chapter 8

2:37:09.0 to 2:44:05.0+

A: Post-Retirement Activities

Working with LBJ Hospital and Indigent Care

Story Codes

A: Post Retirement Activities

A: Professional Values, Ethics, Purpose

B: Beyond the Institution

D: The History of Health Care, Patient Care

D: Business of Research

D: Fiscal Realities in Healthcare

Tacey Ann Rosolowski, PhD

2:37:09.0

Another activity that you're taking part in after retirement has been your teaching work at the LBJ Hospital.

Ralph Freedman, MD

2:37:22.3

Yeah, that—

Tacey Ann Rosolowski, PhD

2:37:22.5

Talk a bit about that.

Ralph Freedman, MD

2:37:23.4

Yeah, it's been fun. We have the program down there. I work in Dr. Ramondetta's group. Do you know her? Have you met her?

Tacey Ann Rosolowski, PhD

2:37:32.2

No, I have not.

Ralph Freedman, MD

2:37:33.7

She runs an interesting program down at LBJ, and I think—

Commented [T8]: In this segment, Dr. Freedman talks about the Lyndon Baines Johnson Hospital in Houston, a public county hospital that has many MD Anderson faculty who work part or full time. Dr. Freedman has worked with the gynecological oncology resident training program since his retirement: a choice he made to continue seeing patients, which he felt he could not do at MD Anderson under conditions where patients required continuous monitoring. He notes the economic burden that indigent patients represented for MD Anderson in the past; he has also had an opportunity to note how many more women physicians are in the field.

Interview Session: 02
Interview Date: March 1, 2012

Tacey Ann Rosolowski, PhD

2:37:41.9

And that's a public hospital.

Ralph Freedman, MD

2:37:43.1

It's a public county hospital, and I think the person to talk to more about the arrangement between MD Anderson and the county hospital is Lewis Foxhall, because he's the one in charge of the outreach and the overall program. So basically, we have—essentially, we have a number of people who are faculty at MD Anderson and actually are on the payroll of MD Anderson and who work at LBJ either full-time or part-time and that there are two major departments. One is Gynecologic Oncology, which I work in, and then there's a General Medical Oncology—lungs, skin, breast, GI and other things, and they're also down there at LBJ. The gyn-onc is the only surgical specialty that is actually functioning down there, and I have to say Lois Ramondetta's done a great job. She's very enthusiastic about taking care of these patients, because there's not many people who want to go and devote the full amount of time to working in a place where the facilities are perhaps not as good, not as comfortable, with the ivory tower up there, and then you've County Hospital down here, and—

Tacey Ann Rosolowski, PhD

2:39:18.5

And this is all indigent patients?

Interview Session: 02
Interview Date: March 1, 2012

Ralph Freedman, MD

2:39:21.8

I would say it's a mix. Obviously, these patients don't have adequate insurance to get into MD Anderson, so you've got a lower socioeconomic stratum. There are also a number of patients who are what we call undocumented, and I don't know how well the county actually screens those or permits those to come into the system. They've got to be paid for by the county, and if you're interested in going further into that, Lois would probably give you more details about how that's working out. Of course, with a new—if insurance and a new thing comes about where you expand the Medicaid group, the question that's being asked is those patients don't have to stay there. What'll happen to our county hospitals, and will those patients then be at MD Anderson? I don't think anybody—I'm not sure they know the impact, but you're looking at distribution of resources at that particular point. One of the difficulties that Anderson had that alluded to was when we had—when MD Anderson was carrying the big burden of indigent patients which were not able to pay where they didn't have means of being remunerated, that the hospital actually had financial—was running into financial difficulties, and that's when LeMaistre went to Austin and came up with new arrangements. What we have there is basically we're down there to take care of the patients there. If they need special treatment that they cannot get at County, like radiation, they may get a special pass to allow them to get radiation at Anderson, which happens in some cases, but surgery and everything else, chemotherapy will be done at LBJ. And there are residents from UT Health Science Center—usually one resident at a time. It's been fun working with them. That's been interesting to me—because when we were at Anderson, we didn't come as much into contact with residents—fellows, we had there, but not residents—and everything is changing now. This used to be a male-dominated field, and now I would say seventy-five to eighty percent of the residents are women, and that's how it is, and—

Tacey Ann Rosolowski, PhD

2:42:12.4

Do you notice differences in terms of how—?

Ralph Freedman, MD

2:42:15.5

Oh, they do just as great, just as fine as—I mean—they—some of them may be married, have families, so they got to deal with that and deal with a difficult specialty, but somehow they manage to handle that. And they like to learn things. You have almost a one-on-one relationship with the residents there because you're working next to them in the clinic. They present the cases, and you have the opportunity to do direct teaching. The case of fellows, they are more advanced, so they know a lot more things, and then they want to go in and get the things done that they need to do—certain number of surgeries—they like to be in surgery, of course—and the clinic is down on the priority list. But if they can get the surgery to be an interesting case to do the surgery, that's where they want to be. Oh, of course, that's what you'd expect. It's a surgical field, and also, from time to time, I did courses for them so that they knew when they're going to

Interview Session: 02
Interview Date: March 1, 2012

do the exams, the resident's down there. There are groups of residents would come and do the—I think this is maybe changing now because they've got an oncology group now at the Health Science Center, so they're getting a lot of their teaching directly there.

Tacey Ann Rosolowski, PhD

2:44:00.0

Why did you choose to take on this role?

Ralph Freedman, MD

2:44:05.0

When I retired, I wanted to—there were certain things I didn't want to do. I didn't want to continue surgery because I didn't feel that I could do it on a part-time basis, but I did want to keep up with the field, and I felt that working at LBJ would provide me with an incentive to see patients and to teach. And also, that potential was helpful to Lois, who had nobody else working down there, so she could basically take off time to do her stuff. It's worked out very well. I see patients on a Tuesday; she goes on Wednesday. So I think it wasn't all altruistic. I did want to do it, and I did feel that that would be a good place for me to work and see patients. I didn't feel that I could continue to see the patients that I had that are at MD Anderson because I wasn't going to be able to give them complete care—what they had expected in the past. Like if a patient needs to go back to surgery, I wasn't going to be able to do that anymore, and I think that was a necessary change. I think our— There are subtle changes, and sometimes not-so-subtle changes, that take place in us as we get older. In terms of surgical practice, they can be kind of critical, and I've come to realize this. It may be just a spasm in your hand or something like that, or something else, and especially if you are not involved in surgery on a regular basis, you can't keep up your skills. Then I think it's the patient that doesn't benefit from this.

[The recorder is paused.]

Interview Session: 02
Interview Date: March 1, 2012

Chapter 9

2:46:15.6 to 3:18:13.4

B: Institutional Change

MD Anderson Growth and Changes to Institutional Culture

Story Codes

C: Critical Perspectives
B: MD Anderson History
B: MD Anderson Snapshot
B: Growth and/or Change
B: MD Anderson Culture
B: Multi-disciplinary Approaches
C: Understanding the Institution
C: The Institution and Finances
A: Career and Accomplishments
A: Post Retirement Activities

Tacey Ann Rosolowski, PhD

2:46:15.6

Okay. We're running again. We just turned off the recorder for a very brief break. I wanted to ask you just a few final summary questions. Over your long career at MD Anderson, you've seen it go from a relatively small cancer center to—I like the phrase Frederick Becker used. He said it's gone from being a cancer center to being a cancer city, and I'm wondering what your observations are about that transformation and the culture of MD Anderson, the quality of care and the quality of the environment for researchers.

Ralph Freedman, MD

2:47:00.2

Well, I think certainly the physical plant has expanded, and I think the number of patients that have been seen—in our case, we see different profiles of patients, whereas years ago, we used to see a lot of patients requiring radiotherapy and the complications related to radiotherapy as we were developing new—

Tacey Ann Rosolowski, PhD

2:47:38.4

If you want to wait just a sec 'til it's all finished ringing.

Ralph Freedman, MD

2:47:40.6

I know. It's probably my daughter.

Commented [T9]: In this segment, Dr. Freedman shares his observations about the growth of MD Anderson since he came to the institution in 1975. He notes its particular strength in clinical research and multi-disciplinary approaches (gynecologic oncology being one of the first Departments to put together multi-disciplinary fields). He hopes that MD Anderson will continue to always do the right thing for patients, "since we are there for them, not for ourselves." In the final minutes of the interview, he talks about going to Galveston, Texas, to fish and enjoy the water, as he did when he was young, in Capetown, South Africa. Since retiring, he has been able to indulge his love of history and travel, talking about his trip to Russia. "It's a good thing to leave some time," he says, to have a chance to do other things besides work.

Interview Session: 02
Interview Date: March 1, 2012

Tacey Ann Rosolowski, PhD

2:47:43.1

I'll pause the—okay. We're recording again after a brief break, so—

Ralph Freedman, MD

2:47:49.3

So the physical plant has grown—the numbers of patients seen—the type of patients has changed, the number of faculty has increased tremendously, and the type of faculty is different. I think I mentioned to you last time that a lot of faculty—probably the proportions faculty who are from overseas was probably higher. I don't exactly know what the numbers were, but it seemed to me, at the time, my perception was that there were many more that came from different parts of the world. Now I think the institution has gotten so well-known, they actually have gone out to bring people in of certain backgrounds and experience. So when the institution started with [Gilbert H.] Fletcher, he—of course, this was the center in the country for radiotherapy. I doubt that there was any other center that had the expertise that we had in radiotherapy. That was a very important decision. We had—surgery and radiation therapy were the two major disciplines, and then you had this developing area for chemotherapy, developmental chemotherapeutics—Freireich was chair, and Evan Hirsch was involved with biotherapy and Jordan Gutterman. Then, of course, we started getting into areas of new drug development and sudden expansion—clinical trials, infrastructure and actual clinical trials being done at Anderson, so that's changed. The training programs have expanded, and they now include periods of time in laboratories, and it's something we'll go later to academic areas. I think one of the things is when it was smaller, you knew everybody. Now you know just a fraction of people. Even before I retired, it was already like that that you didn't know—I mean—when we used to get together for our annual dinner, you knew most of the people that were there. They don't have those anymore, because it's too big, so it is, in a way, I guess, like Fred said in that you don't see people from the different departments. I mean, you see individuals. In the IRB, I see people who represent those departments, but I don't know many of the people that are so—now in those departments, and they don't know me, so it has changed in that way. Obviously the budget has expanded, and the salary base has improved for faculty. It's a very good place to work—sources, the supports, all was good. I think there's still, of course, room for improvement. Our medical record system, we don't have an electronic record system that's comparable to what happens elsewhere, but then I'm sure it'll happen, and we'll get that in the near future.

Tacey Ann Rosolowski, PhD

2:51:30.7

What are some other areas of improvement that you would like to see acted on?

Ralph Freedman, MD

2:51:45.2

I'd say it's hard to tell a number-one cancer center that they need to have—I mean, the basic

Interview Session: 02
Interview Date: March 1, 2012

science area, this institution has always been known for its clinical research expertise and been recognized for it, never been recognized, really, for the basic science. We've never had a national academy member. We had one, but he left about the time that was Lenores—and the question is how important that is. I don't know. The regents have obviously decided that we need to emphasize the basic science area. Can we be everything, and I certainly wouldn't like to see the clinical research area be diminished in any way because that's the strength. That's been the strength of the institution. If we lost that, we may lose something we cannot regain. I mean, we've got phenomenal—look at plastic surgery. There are over fifteen plastic surgeons now, and I don't know if we had one when I started. I remember one part-time, possibly, in those old days, because they're doing so much reconstruction, so you've got specialists now—the clinics, the way they're organized—you've got a lot of subspecialty organization. In fact, the surgeons already do breast. Some surgeons already do GI surgery, and yet you still have this multidisciplinary interaction. Actually, GYN was one of the first departments to develop a multidisciplinary concept because Fletcher was interested in radiotherapy and Rutledge was a very excellent surgeon, and the two of them worked very well together to create a multidisciplinary environment. It was probably the model for multidisciplinary environment at Anderson. A lot of decisions were made—and it wasn't hip in those days, but it met in the hallways outside of patients' room—where there was a joint discussion going on about whether it should be radiotherapy or surgery first, and that multidisciplinary concept is very important, especially today. We talk about many conditions that come to Anderson, and you need multimodality. Well, they should be communicating about it right at the beginning, whereas in private practice what often happens is the patient gets surgery first and then sent across to the chemotherapist, and it's not an orderly seamless process. It's just depending upon the way the patient gets referred or how they get referred. Renal surgery, we've got experts. I knew exactly who to go to, and a renal problem, which is a problem with the urinary tract—bladder surgeons—so even within the fields—the general disciplinary fields—and these individuals have developed a lot of expertise and knowledge, but they still participate in multidisciplinary decisions. So I think in that respect, we've continued to grow, develop, and, of course, the regional cancer center's now something new. I think that it's going to be very important because a lot of people don't want to go down to the medical center.

2:56:02.4

Traffic is horrible, and having centers out here that can deal with the more standard types of therapy makes very good sense. And if you have a specialized problem like leukemia and you go to the main hospital, that's different, but many of the other patients can be treated in the surroundings of their house. Now Jennifer, my wife, had breast cancer, and then she got lymphoma. She went to MD Anderson for the initial consultation, and actually, her surgery was done by the late Dick Martin, who was the head of surgery, but the subsequent treatments were actually done by physicians who work—who lived out here and who worked with the physicians down there. In fact, they were all graduates of MD Anderson appropriate like Arthur Hamburger who, by the way, also had some role in my staying at MD Anderson when I was going to go back

Interview Session: 02
Interview Date: March 1, 2012

to South Africa. He's a radiotherapist in practice, and he was part of the radiotherapy program. And then there was—she got her chemotherapy at Memorial City. It was a convenience issue, and she had friends around here that could take her if she needed to go. So I think we have to be realistic about that, and I think that's going to be very successful. They're doing a certain amount of research out there that's not too complex. Peter Pisters is in charge of that, and I've met with him. I've gone out to visit the centers. It's very impressive. It's modeled exactly on MD Anderson. They've got the same systems and procedures in place, so that's also changed, and I think that's for the good. And research, well, we have to see where individualized personalized therapy goes. It's going to be tested; the concept has to be tested, and it may turn out to be a whole new discipline. At Anderson, it would all—maybe it'll be a sub-discipline within different departments where it will be done. Everybody's excited and wants to get into the act, and sometimes it's too tough to make a decision with what resources it's got. You don't want to duplicate or replicate if it's within the institutions because these things cost a lot of money today, and what else could we have? I think what we badly need is an electronic system which would also work for research, and I know there are people who are working on this now, and as I said, we needed it yesterday, but anyway—

Tacey Ann Rosolowski, PhD

2:59:36.5

As you look back over your career, what is something that you're most proud of having achieved?

Ralph Freedman, MD

2:59:43.9

Well, I think I'm most proud of having been chosen to work at Anderson, basically, and to have contributed to many patients, to their outcomes, and also on the national scene, to contribute to public policy—the NCAB and the NCI and FDA. I think being there gives you a feeling that you're contributing not just locally within the institution, but at a national level. And teaching—being able to teach the next generation and see these people developing their skills, watching how they develop over a period of years, it's quite fascinating to watch.

Interview Session: 02
Interview Date: March 1, 2012

Tacey Ann Rosolowski, PhD

3:00:40.1

Is there a specific work that you hope they will carry on that was initiated—? ***Ralph Freedman, MD***

3:00:45.9

I just want them to do the right thing. That's all. Whatever they do, it's always to do the right thing for your patients because those are the principles I was taught and try to pass on to others. Sometimes we're not perfect. It's not a perfect world, and we make some mistakes, and we have to learn from them, but I think to be conscious that we're here for them and not totally for ourselves—I mean—obviously there has to be some ego—a little bit of egocentricity—to drive you, but in the end, it's all about the patients.

Tacey Ann Rosolowski, PhD

3:01:48.6

I wanted to ask just a couple of final questions that are really more about the flip side of your life, not the professional so much but the private life. I was talking to Dean George Stansfeld, Graduate School, Biomedical Sciences, and he happened to mention that you're a fisherman, so I'm wondering where do you go?

Ralph Freedman, MD

3:02:14.8

Oh, Galveston, because it's close. I grew up on the eastern side of South Africa, and I remember as a kid, we used to go to the bay to fish. And, undoubtedly, I can remember having a fishing rod that I made out of a piece of bamboo with those little wheels that came out of movie cameras in those days and screwed it in there and put a fishing line on there until my father got me my first glass rod. Glass rods were solid in those days. Now they're fiberglass or hollow. So we used to go and spend quite a lot of time. I guess that's the way I got introduced to it. And not long after we came here, we got a house down there. The kids used to come down quite a lot, and they used to go crabbing and boating. Now we may go every other week, and there's a colleague of mine—I fish with Jim Abbruzzese, who's chair of GI—and we often go out together on a weekend. I go in his boat; he goes in my boat. We might not catch any fish, but it's getting out. Having that place was very good because working with cancer patients can be quite stressful, and doing the other things that we had to do was quite stressful, and this was a very good way of sort of separating yourself. I do that and also spend more time reading—reading more for pleasure. I'm interested in history still a lot, so we got to visit a country and then read up about it. We were in Moscow and went to Saint Petersburg. In Moscow, we went to the Golden Ring towns and learned some more interesting facts there—for example, that there's not just one Kremlin—that there are many of them. Each little town has its own Kremlin. It's basically a fortified part of the city. Also, red is not originally a political symbol. It had more to do with the ground or whatever, but it became a political symbol.

Interview Session: 02
Interview Date: March 1, 2012

Tacey Ann Rosolowski, PhD

3:05:13.6

Did you visit Russia because your background is Russian?

Ralph Freedman, MD

3:05:18.7

No, didn't go to Lithuania where—we had the opportunity of going on a boat. Because of the boat's visits in Petersburg, I had previously been—well, I went to Sweden, and we went as far as Finland. I had a South African passport; couldn't get into Russia because they—so I always wanted to visit Russia and finding what Russia was about, and it was quite an experience—that basically a country has always been ruled, until recently times, by foreigners. So I got Catherine the Great, and I read the latest fascinating story about—I mean—she was German but learned the language—learned Russian—learned to become an Orthodox Christian person where she had been Protestant and bided her time—very clever woman. I don't know how much you know about her history.

Tacey Ann Rosolowski, PhD

3:06:35.0

She was quite an intellect. I know the great amazing supporter of—

Ralph Freedman, MD

3:06:37.9

She wasn't totally 100 percent good, but then who is? And there's a question whether she had a husband dispatched or whether somebody else dispatched him. It wasn't Peter the Great; it was another Peter. He left instructions, and if anyone tried to rescue him, he needed to be dispatched. And some fool decided he wanted him to be the czar again, so it's never quite clear how much involvement she had. And then, of course, she had these relationships including the subsequent King of Poland who's—what was his name?—and she had a child by him. She had a child by everyone except her husband, who used to like playing with toys. But it was a fascinating story. So anyway, going there and going to The Hermitage and visiting the small towns that are part of the Golden Ring. And it was so interesting to me that the Russians could never get their act together in those early days, and—so visiting, I just wanted—they were only Christian from around a thousand—I'm not Christian myself, but it's interesting that they became Christian only a thousand years ago. But they were basically dominated by the Tatars for 300 years, and they basically lost the country because they couldn't work with each other—the princes—they couldn't work with each other and defend themselves against the Tatars. That's probably why they lost and then successively in history, the same, and so they've never known any Democratic existence to this present day.

Interview Session: 02
Interview Date: March 1, 2012

Tacey Ann Rosolowski, PhD

3:08:56.2

Definitely struggling with it now.

Ralph Freedman, MD

3:08:57.1

You compare with China, who also went through the Cultural Revolution, and they are changing much more rapidly. They are catching on their— They have a wonderful heritage, but then for 30 years they were in the doldrums. But since then they're just going up and up and up, whereas the Russians are much slower. And it's interesting—the roads were not in good repair in those small towns. You see much more when you go inside. Then we visited places like Tchaikovsky's house. There was a family that killed Rasputin. These are stories, and the history there— Oh, and then what was fascinating to me was to read about the Siege of Leningrad, which occurred in Petersburg, and we actually went to Stalin's bunker, which was out of the way. He placed it under a sports field because he didn't think that Hitler would attack him there, and it was kind of very, very subdued. I had a chance to talk with the curator of the place, and she wanted to know who, of course, won the war, and I said, "Well, I guess it was a contribution of everybody." She said, "No." She said, "Do you realize that twenty-five million Russians died here," and of course I knew that, and the Americans had only come in later. So they still have that strong feeling, and, in fact, what is remarkable is that a very high percentage of Russians still admire Stalin even though he killed twenty-five million of them over that whole period of time. So I— This is a chance for me to go back and look at these places. We're going to Normandy in May, and we're of course going to visit the D-Day beaches there. We're going with Tauck Tours. They do a very nice tour, so there'll be some food and cheese—Camembert and all that and Saint-Michel once—

Tacey Ann Rosolowski, PhD

3:11:35.5

Oh, Saint-Michel?

Ralph Freedman, MD

3:11:36.8

Yeah, we've been doing about two—an average of two trips a year since I retired. I never used to be able to—I wasn't able to go away for too long before. We still don't go away for very long, but now at least it's about two weeks at a time. Just did a South American trip and we went to Japan, which is before the tsunami, and that was really interesting. We really liked that. And then we did do a trip up the Danube, which we enjoyed, and visited a postdoc who worked with me from Prague. And also, we went to Vienna. So I've enjoyed it and getting a chance to read more. I like non-fiction, as well as fiction, and if I'm in the mood, I'll start—and for some reason I've enjoyed reading Saramago. I've probably read more of his books than any single author. He's the Portuguese Laureate, and I don't know if you know of him, but he sa—

Interview Session: 02
Interview Date: March 1, 2012

Tacey Ann Rosolowski, PhD

3:13:14.1

No, I don't.

Ralph Freedman, MD

3:13:15.8

He did the— There was a movie based on one of his books called Blindness and then a subsequent one, Seeing. They hadn't made it into a movie, but Blindness was about a whole population that suddenly goes blind, don't know why they do, but almost all of them. And what is interesting, he examines the social interactions between these people who are now blind and have lost one of their most important faculties and how they relate to each other—there are bad people amongst them, and there are good people amongst them—and how they deal with each other. He just died this year. And there was another one that he wrote called The Gospel According to Jesus Christ, which he discusses the two Marys. And he actually got—I think he got excommunicated for that. And the very last one he wrote was—which I just finished—was about Cain, and he tries to—and not in a disrespectful way, but he treats them as perhaps historical things that we don't know too much about—we don't know the details—so he provides an opportunity for them to be real people and to connect with each other, and it's quite interesting. So these are the things that I do these days. I work in the yard, dig holes—well, actually digging too many holes, French drains, and then now, of course, we've got a second grandchild on the way.

Tacey Ann Rosolowski, PhD

3:15:14.3

That's exciting.

Ralph Freedman, MD

3:15:17.0

But it was good seeing— Nobody knows how much time you've got when you're in the next chapter, but it's good thing to leave some time because some people work all the way to the bitter end, and then you wonder how they feel when they just aren't capable of doing anything. Should I have done this? You don't want to be in that position. You want to really say, "Well, at least I had a chance to do other things, and we go on trips together and be together." That's not always a—suddenly, when you're away a lot and now you're at home most of the time, it's not always good for the spouse.

Tacey Ann Rosolowski, PhD

3:16:08.8

No, retirement shock.

Interview Session: 02
Interview Date: March 1, 2012

Ralph Freedman, MD

3:16:10.5
Yeah.

Tacey Ann Rosolowski, PhD

3:16:13.5
Well, it sounds like you have a very productive and pleasant time.

Ralph Freedman, MD

3:16:17.0
Yeah, I'm trying to keep comfortably occupied without being busy. I do—I only call it time, but I don't watch the clock at all and this, but there are times—if they have a meeting at MD Anderson, I may try to link in rather than take a trip down there, because it's at least half an hour to drive there and maybe longer coming back, especially if it's late in the day like 4:00-5:00. You have to fit in with traffic, and they have been very helpful in setting those things up.

Tacey Ann Rosolowski, PhD

3:17:03.9
Is there anything else you'd like to add at this point?

Ralph Freedman, MD

3:17:07.9
Well, I don't know. Does that cover what you want to know about?

Tacey Ann Rosolowski, PhD

3:17:11.1
I've covered my questions, and I just wanted to know if there was anything that had occurred to you that you felt you wanted to add at this point.

Ralph Freedman, MD

3:17:21.1
Well, I think I've covered the most significant events.

Tacey Ann Rosolowski, PhD

3:17:27.9
Okay.

Interview Session: 02
Interview Date: March 1, 2012

Ralph Freedman, MD

3:17:29.6

Yeah, I can't think of anything other than right now enjoying the opportunity to see my family—I used to be home late in the evenings, and there was important—so that I had to do what I had to do, but I think now it's time for others, so—

Tacey Ann Rosolowski, PhD

3:17:58.6

Well, thank you very much for taking the time to be interviewed for the project.

Ralph Freedman, MD

3:18:02.2

Well, my pleasure and good luck with that.

Tacey Ann Rosolowski, PhD

3:18:05.4

Thank you. The time is three minutes of 5:00, and I'm terminating the interview now.

3:18:13.4 (end of audio 4)