Office of NIH History and Stetten Museum

Oral History with Dr. Rose Mage, NIAID

August 22, 2018

GM:

I am Dr. Gordon Margolin, volunteer in the Office of NIH History and Stetten Museum about to do an oral history with Dr. Rose G. Mage. She served as a Career Investigator in the NIAID Lab of Immunology, starting in 1965, and then as the Section Chief of the Molecular Immunogenetics section from 1988 until her retirement in 2008. We are here in the NIH Library's audio-visual recording center on August 22, 2018.

Thank you, Dr. Mage, for agreeing to record this history about you, your scientific accomplishments, and the time you spent here at NIH.

Let's begin by asking you to tell me a bit of your background, where you were raised, something about your family, and your educational pathway.

RGM:

I was born and raised in New York City. My father was an immigrant from Romania. He arrived in New York when he was 5 years old in 1905. I was named after his mother who died from typhoid in the 1920s. My mother was born in the USA but her family, three of her four older brothers were immigrants.

I decided I wanted to be a scientist when I was about 9 years old, did well in public schools and skipped grades twice. I applied to the Bronx High School of Science and was accepted after taking a written test for admission. It was there that I first learned about bacteria and wanted to

learn more about them and other microorganisms. I also entered the “Science Talent Search” and wrote a proposal to search for “Antibiotics from Actinomycetes”. I didn’t win a prize but thinking back to that time when there were none, I am gratified that there are many now. Among after-school activities I enjoyed the Science Fiction club and still like Sci. Fi.

Since I lived in Manhattan, I traveled by subway train to school and home each day.
There was a polio epidemic during the summer before I started high school and some close friends were hospitalized. I still remember riding to school on the train worrying about them and also whether I was next. I had applied to several Universities and Colleges for admission in the following fall and was waiting to hear from them.

After I graduated in January, I took a class about great books one evening each week and read some classics. I also worked for a travel agent in mid-town Manhattan. I did some typing and ran errands. I was on one such errand the day I learned that I was admitted to my first choice, Cornell University. It happened to be the day of the Saint Patrick’s Day parade. The bands were playing as I hurried joyfully along Fifth Avenue to pick up Steamship tickets.

GM:
You obviously were pointed toward the scientific study of Immunology when you obtained your PhD. What initiated that particular area of interest?

RGM:

I spent a summer at the Jackson Laboratory in Bar Harbor Maine at the end of my sophomore year. My project involved some Immunology. It was able to replicate a new immunological test of rabbit serum that had been reported by Jacques Oudin in Paris one of the discoverers of rabbit allotypes (genetic types of rabbit antibodies). At that time, rabbits were bred there, and I learned about their different rabbit strains. When I had my lab at NIH, I obtained some samples from the Jackson lab rabbits and we did typing tests to characterize their immunoglobulin allotypes using newer methods than the Oudin method. That summer, I also had formal lectures about Genetics.

During my four years at Cornell University, although my major was in "bacteriology", I also learned about Barbara McClintock, maize genetics and "jumping genes" (transposons). During my senior year, I also became aware of and fascinated with the high specificity and diversity of antibodies although nothing was known about their molecular structure and the basis for this. Years later, the "one gene one protein" dogma was overthrown at least not correct in the case of immunoglobulins which were shown to be assembled from several genes. At Cornell, I had also learned about gene conversion in yeast and never thought it would come up as something immunologists would discover in higher organisms. The unusual contribution to antibody diversification by gene conversion that was first shown to occur during chicken antibody diversification was discovered by my lab and others to contribute to the antibody diversification process in rabbits.

My future husband, Mike Mage had to go to Fort Sill for ROTC artillery training. When he graduated and became a lieutenant in the US army, he was able to defer service to continue his education at Columbia University.

When I left Cornell for graduate school, I also chose Columbia University after interviewing at NYU where there were some important immunologists including Jeannette Thorbecke, and the three I was to get know when they later moved to NIH (namely Baruch Benacerraf, Ira Green and William Paul). I took required classes at both the medical school and on the main campus. I also assisted in the microbiology lab that the medical students were taking (including our own historian Alan Schechter). Before choosing to work on my PhD project in the lab of Professor Elvin Kabat, I rotated through several labs, worked on patient samples from a deadly flu epidemic, and in Pathology lab, saw the lungs of patients who died there from Flu. Dr. Kabat had been a student of Michael Heidelberger who I got to know because he visited our lab on Saturday mornings (and was later on the committee for my thesis defense). Although Dr. Kabat wanted me to write my thesis in the form of two papers for submission to journals, I had written a longer version of the introduction before he saw my first draft. I did not regret this since at my defense Dr. Heidelberger asked me about the early history of the discovery of pneumococcus which dated back to 1914. When I was a student in the Kabat lab, he had no NIH support because the McCarthy era purges of anyone thought to have been a communist sympathizer at any time.

GM:

How did you happen to come to NIH? What were the circumstances?

RGM

My husband Mike had started at Columbia a year before me and had completed his studies. He had taken both post-sophomore research and postdoctoral research years because it took longer for me to complete my research in the Kabat lab. When it was time to move on, he followed the advice of his mentors to go to NIH and he joined the Public Health service. We moved in the summer of 1962 and I wrote my thesis while he started a new job in his own lab. I visited several labs and in fact, wanted to join Marshal Nirenberg's group where the DNA code was being discovered but he had no openings. It was he who suggested I go upstairs to the 11th floor to meet the immunologists in the Laboratory of Immunology (where I ended up working for the rest of my career). Dr. Sheldon Dray accepted me into his research group. We went up to New York for my thesis defense in the spring of 1963 and I started my postdoc with Dr. Sheldon Dray that summer.

GM:

After your two years in the laboratory of Immunology as a post-doc of Dr. Sheldon Dray, you became an integral part of the faculty here. In reviewing your publications, which exceed 200, and your many presentations and offerings, I note that your life's work was always in the area of the immune system and immunogenetics. Would you be able to summarize briefly where Immunology stood when you started?

RGM:

Nothing was known about T cells and their receptors and the structure of antibodies was not yet known. Dr. Kabat had shown that dextran could not be used as a plasma extender. He showed that it was antigenic, and he immunized me as well as some medical students, I made antibodies

to dextran and still note it as a potential allergy on medical questionnaires. This finding about dextrans led to series of studies in the Kabat lab about antibodies to dextrans. Part of my thesis work on rabbit anti-dextran antibodies showed that they bound to five or six hexose units. Of course, we now know a lot more about three-dimensional structures of antibodies as well as the great heterogeneity of their combining site structures. My other project was about type 3 pneumococcal polysaccharide. One of the postdocs in the lab Gerald Schiffman went on to contribute to pneumococcal vaccine development.

GM:

You also knew a number of the prominent researchers. Can you talk about work or relationship with Sheldon Dray, Ralph Reisfeld, Rose Lieberman, Michael Potter, Baruch Benacerraf, and William Paul?

RGM:

Sheldon Dray was my postdoctoral adviser and when I arrived, he had just returned from a meeting that established the nomenclature for the rabbit genetic variants of antibodies (allotypes). I worked on allotype suppression. In several papers I showed that if you injected anti-allotype antibodies into baby rabbits (newborn or a few days old), that were heterozygous at the light chain or heavy chain loci. you could suppress expression of that allele and favor expression of the other). Some years later my group experimented with injecting embryos and suppression of both alleles and found upregulation of rare alternative genes.

Ralph Reisfeld, after an earlier stint at NIH and a negative experience in industry, had returned to NIH and joined the Dray lab. I learned a lot from him and we published papers together along with others at NIH. He became acting lab chief during the period between when Maurice Landy left, and the Institute hired Baruch Benacerraf. When Benacerraf arrived, Reisfeld left for a position at the Scripps Research Institute in California and spent the rest of his long career there. He conducted cancer research. I found a recent reference to a therapeutic monoclonal antibody "… originally 'made' by Ralph Reisfeld of the Scripps Institute in San Diego, California, in 1985, that binds to the GD2 antigen of neuroblastoma cells and labels them for the desired subsequent attack by the immune system".

Rose Lieberman and Michael Potter were working together on immunogenetics of the mouse. Dr. Dray was helping and advising them, so I was taken to meet them both in her lab. A few years later (March 1971) I was invited to speak at a NY Academy of Sciences meeting and Michael Sela from the Weitzman Institute in Israel, was there. After my talk, he came up to me and asked me to contribute to a book that was published in 1973 entitled "The Antigens". He wanted the chapter to cover rabbit, mouse and human so I asked Rose Lieberman and Mike Potter to write the part about mice and William Terry who was in the Immunology Branch of the NCI to write the section on human.

Mike Potter didn't like to travel (though he did go to Basel when antibody workshops were held there). He responded to a request from the WHO to teach immunology in Lausanne Switzerland by suggesting me. So, I got to travel to Geneva and Lausanne and lecture for several years. One student from those days ended up at NIH and said he remembered my lectures back in Lausanne.

He recognized me when we were sitting at a large round dinner table during an immunology retreat.

I had colleagues in Geneva who I visited, and several times continued to the Basel Institute where an important contributor to the field of rabbit immunogenetics, Andrew Kelus, worked. He discovered a mutant rabbit named Basilea and sent breeders to me. With Edmundo Lamoy we discovered the mutation that silenced the major kappa 1 light chain gene expression. When Edmundo came to me with the sequence he said, “there is no difference”. But when we looked more carefully, we saw that the difference was not in the coding region but at the 5 prime location where the kappa variable region is spliced to the kappa constant region. The paper we wrote was published in the Journal of Experimental Medicine. Another alternative light chain that we called kappa 2 was upregulated in expression in the Basilea rabbits along with higher expression of lambda light chains. We believe kappa 2 was the primordial light chain gene because it is more similar to those of other species and that the predominately expressed Kappa 1 genes developed to be the dominantly expressed ones with an unusual extra disulfide bond that stabilizes the protein structure, When we finally saw the genome assembly we confirmed what another postdoc Nicky Hole had found, that there was a large distance between the two.

I had first heard about Baruch Benacerraf when I was in the Kabat lab because he had studied there before me. Since he was quite wealthy, he sometimes took off to take care of business in Venezuela, but he didn’t let his wealth interfere with his study of Immunology. He went on to win a Nobel prize based in part upon work done using two strains of guinea pigs that were maintained at NIH. They, like the rabbits I maintained are no longer maintained at NIH.

Benacerraf arrived at NIH with the two of his trainees from his NYU lab that I mentioned Ira Green and William Paul. When Benacerraf left NIH for Harvard, it was William Paul, who became our lab chief at the age of 34 and remained in that position until his death on Sept 19, 2015. Ira Green remained in the lab until he retired.

GM:

I see you have worked almost exclusively with the rabbit in all this time. Why did you select this particular animal? Is there a close tie with the human system?

RGM: Yes, among small animal models, rabbits are closer to human genetically and are the best model for some human diseases. Some of the latest information is covered in two recent reviews I wrote in 2018 ("The wide utility of rabbits as models of human diseases" and "Rabbit Models of Human Diseases for Diagnostics and Therapeutics Development").

In addition, they make great antibodies that can be of higher affinity and specificity than those raised in other species. I have given invited lectures and seminars entitled "Why rabbits make great antibodies" both at NIH, at conferences, and at various institutes and companies around the world. We did use sheep, goats and even chickens to obtain antibodies against molecules of the rabbit immune system. They were housed at the NIH animal center in Poolesville.

GM:

We would like to hear more about inclusion of both minorities and women in the more professional ladders. What can you tell us about Glendowlyn O. Young-Cooper and Cornelius Alexander?

RGM:

Glen had been hired by Sheldon Dray and was already in the laboratory when I started working as a post-doc. She was from Oklahoma but moved to DC and earned a Masters' degree from Howard University. Dr. Dray told me that when he set up his lab. he phoned Howard U and asked them to send over their top graduates. She was the one he hired. She was in charge of managing the breeding and testing of the allotype-defined rabbit colony and continued working with our group at NIH when Dr. Dray moved from NIH to Chicago. She did a variety of lab tests to detect what allotypes were inherited in offspring of breedings, participated in many roles and was first author on one of our papers and coauthor along with Cornelius Alexander on one of the first papers I published in a Nature Journal. This was a breakthrough observation "Mage, R.G., Young-Cooper, G.O. and Alexander, C.: Genetic Control of Variable and Constant Regions of Immunoglobulin H Chains. Nature New Biology 230: 63-64, l97l". It described discovery of a recombinant between the variable and constant region in one of our rabbit litters providing some of the best evidence for more than one gene contributing to the antibody heavy chain sequence. Subsequently another lab discovered a recombinant and years later we found two more.

Cornelius Alexander was transferred to my lab when Baruch Benacerraf became our lab chief. As you can see from my bibliography, Alex: as he liked to be called, was a coauthor on a number

of papers. He was an outstanding lab assistant (and a great Redskins fan too. He had season tickets that were hard to get back then. We always knew he would be in good spirits on Monday when they had won over the weekend. When he retired, he didn't want any farewell event, but a few years later, his wife and son surprised him with one and our lab members were invited. We gave him a bound book containing reprints of all the papers he was coauthor on plus two books of photos. He was an excellent photographer and took photos including via photo-microscopy.

Sequencing the whole rabbit genome obviously ties in with the human genome project. Can you elaborate on that?

When decisions were being made about what additional species to sequence in 2005, Yukari Manabe of Johns Hopkins, Jean Chang of the Broad Institute and I wrote a "White Paper" documenting the value of the rabbit as an animal model. Yuka was studying Tuberculosis in a rabbit model and is a coauthor of the 2018 review on animal models of human diseases documenting the continued value of the rabbit as an animal model. After the rabbit was chosen and the low coverage 2x sequence was nearing completion, some of us were invited to the Broad Institute where I gave a keynote address, became acquainted with, and heard talks from a number of other invited people interested in the deeper sequencing they were undertaking (to about 7X coverage).

More recently a rabbit genome biology network was funded as a European "Cost Action". I was contacted by one of the co-chairs when they were writing the application and helped edit and improve their English usage. I became one of the few non-European members of the group and

was able to attend several meetings including one where the decision to sequence the entire order of Lagomorph species was organized. I helped communicate with the Journal and to write the report that was published in 2016 in the Journal of Heredity. “LaGomiCs - Lagomorph Genomics Consortium: an international collaborative effort for sequencing the genomes of an entire mammalian order. J Heredity 107: 295-308”.

GM: You were involved in more than just science at NIH, as you sought to make it a more inclusive place. Can you tell us about the development of EEO programs and policies in 1970’s and your involvement?

I served on the committee and became chair, but I really don’t know how much of an effect this had on increasing the diversity of the work force. However, over the years the tenured scientific staff does have better representation of women and under-represented minorities.

GM:

Your honors and scientific achievements are listed in your CV, which, of course, in our files will be attached to today’s document. Which recognition have you valued the most?

Probably my selection as a fellow of the AAAS

GM:

How would you summarize the NIH venue as a place to work?

RGM:

NIH is a great place to work. When I arrived, there were very few women to get to know as role models and although Rose Lieberman transferred to our lab for a while, I was the only woman on the Senior staff of our lab for much of my career. I was generally well respected; however, after one of our external Board of Scientific Councilors reviews that occurred about every 4 years, my review noted that my salary was not commensurate with those of full professors at Universities. Shortly thereafter the "Senior Scientific Service" was established and I was promoted with a raise in pay included.

GM: Have you seen changes here over these years?

RGM:

Yes. One example is that there are more women in permanent positions as tenured scientists and clinicians. Other positive examples are the formal graduate student programs, the inter-institute Interest Groups such as the Immunology Interest Group (and there are many others). There are more examples of positive changes, but my pet peeve is that it appears to me that there has been an increase in the many-layered bureaucracy. I think this leads to a lot of support staff turnover and some are poorly trained and inefficient. I am talking about the non-scientists administrative staff responsible for things like ordering and paying bills. In contrast, many highly talented lab technicians remain here for years but some of the burden for ordering falls on these lab staff members who should be doing experiments instead of paperwork.

GM:

What would you have done differently, if at all?

RGM:

Maybe it would have been good to take a sabbatical but being far away from home was difficult when children were still home and coordinating to be away with a husband was also a consideration. On the other hand, either alone or together and sometimes with children, we did travel to many small and large national and international meetings and now have colleagues residing all around the world,

GM:

Can you tell us about your continued relationship with the NIH and the world of Immunology since your retirement?

RGM:

It is a little more than 10 years since I retired at the beginning of June 2008. I was very pleased that a very rare event occurred a few days later. The last paper I wrote before retiring was accepted with no revisions. I became Scientist Emerita and continued coming to NIH each day for about a year and a half in order to clear out, store, or discard the accumulated files, notebooks and such as well as the equipment in two double modules. Some valuable equipment was transferred to others in the lab including to a newly hired scientist who is now tenured. What remained (such as microscopes and specialized equipment) was advertised and transferred to members of other labs and a few things went to the office of NIH History.

By 2010, I had upgraded my home office and added shelves where I saved my original lab notebooks and displayed some photos and awards. I added new file drawers to hold reprints of my publications. Once I had a newly upgraded home office, I still came to NIH frequently. As the rabbit Genome was now available at 6.5X coverage, I was interested in looking at some regions of immunological interest. I wrote a formal request to the Lab chief, William Paul and to the NCBI directors' office and was encouraged to work with NCBI scientists. I had become acquainted with Alejandro Schaffer at seminars he came to about B-cell biology. He had already been working on annotation of the assembly of Feline (Cat) genome and agreed to help with the rabbit genome. His staff scientist Mike Gertz and another NCBI scientist Richa Agarawal worked with me. After looking at the genetic region encoding IL4 that was of interest to Dr. Paul (who with Maureen Howard had discovered this important immune system regulator) we noticed that there was a base missing that would have caused deletion of one exon. Working with Mike Mage (since I no longer had a lab), we obtained a sample of the DNA of the donor rabbit plus another rabbit from Broad Institute that they had not chosen to sequence (they chose the rabbit that appeared to be most inbred … least heterozygous). We amplified and sequenced a segment surrounding the region of interest along with DNA of a rabbit from an inbred strain from Japan (that I received when the investigator who had trained with Jacques Oudin in Paris retired). We concluded that the sequence assembly was incorrect and there was not a deletion.

We then went on to examine the rabbit heavy and light chain genetic regions. Since the heavy chain locus was not assigned to a chromosome in the assembly, we obtained help from scientists in France, (Claire Rogel-Gaillard, Amelie Bonnet-Garnier, Helene Hayes) who found by fluorescence in situ hybridization that the IgH locus mapped to the telomeric end of

Chromosome 20. These, and some other genes expected by synteny to be located there were absent from that region.

GM:

What were the International Congresses of Immunology?

RGM:

The first International Congress of Immunology was in D.C., initiated by Benacerraf. I attended many, chaired workshops, and when I spoke in Australia, I was delighted to see another former NIH scientist Tasuku Honjo presenting at the same symposium. [Note added November 2018: Honjo was awarded the Nobel prize this year.] Some veterinary immunology meetings were scheduled in parallel before or after. I remember the International Congress in Delhi, followed by the Veterinary Immunology conference in Lucknow where I was an invited lecturer. I was happy to hear the veterinarians referring to mice as "vermin". They preferred other animal models. Also, a few thoughts about the age DNA sequencing: My lab set up for DNA work before Mark Davis arrived. I visited Leroy Hood's lab and met Mark Davis. I urged him to consider coming back East as a post-doc (he graduated from John Hopkins). Bill Paul was perceptive enough of his talent to let him choose and pursue his own project, and he reported the initial cloning of a T cell receptor beta chain at the 1983 International Congress of Immunology in Japan. "The T-lymphocyte antigen receptor – elusive no more" was a News and Views Commentary on two articles published back-to-back in the March 8, 1984 issue of Nature. These articles described the cloning of the genes encoding the beta chains of the human and mouse TCR. The author of the Commentary was the late Alan F. Williams, a highly respected immunologist who was keenly

interested in the hunt for the TCR. March 8, 1984 was a day that had been anticipated by immunologists for over a decade, a day that signaled the end of a long and frustrating drought and the beginning of a new chapter in immunology.