UNIVERSITY OF WISCONSIN-MADISON ARCHIVES
ORAL HISTORY PROJECT

JOSHUA LEDERBERG

LEDERBERG, Joshua (1925-)
Professor in Genetics Department
At UW: 1947-59

Interviewed: 1998 *Length:* 6 hours
Interviewer: Barry Teicher

Family background; Stuyvesant high school; Early interest in science; Columbia College; Francis J. Ryan; Navy V-12 training program; Columbia University College of Physicians and Surgeons; Early work with *Neurospora*; Leave to work at Yale with Edward L. Tatum; Tatum's work with George Beadle; Discovery of recombination in bacteria; Cold Spring Harbor Symposium; Challenge by Lwoff and Delbrück; Job opening at UW; Other candidates; Interview; Hiring concerns; Job offer; Arrival in Madison; Ira Baldwin; Rudolph Froker; Department of Agricultural Genetics; Jim Crow; Recombination research; Karl Paul Link; Transduction; Norton Zinder; Lambda; Larry Morse; Immunogenetics; Phase variation; Tetsuo Iino; Cell motility; Bruce Stocker; Replica plating; Esther Lederberg; S. G. Bradley; David Skaar; Aleck Bernstein; Bob Wright; Boris Rotman; Tom Nelson; Summer research at Berkeley; Roger Stanier; Protoplasts, L forms and penicillin; Fulbright fellowship in Australia; MacFarlane Burnet; Work with NASA; Moon infall; Carl Sagan; James Watson and Bill Hayes; Numerical Analysis Lab; Teaching; Department of Medical Genetics; John Z. Bowers; Kimball Atwood; Stanford University; Arthur Kornberg; Nobel prize; Trip to Sweden; Honorary degree; Reflections on career at UW.

First Interview Session (June 19, 1998): Tapes 1-2

Tape 1/Side 1

001 Joshua Lederberg (JL) was born in 1925 in Montclair, New Jersey, to parents who had recently immigrated from Israel. His father was a part-time rabbi, taught Hebrew, and supervised the ritual slaughter. His family had moved to Washington Heights in Manhattan by 1925. JL attended New York public schools, which were instruments of Americanization and upward mobility and were very much in keeping with the melting pot tradition in America.

042 JL was a precocious child and even though this caused some difficulties at times, he had some very wise teachers who were sympathetic and made accommodations for his

intellectual gifts. That degree of insight and compassion has always impressed JL. He was academically inclined and spent a great deal of time reading. He learned more from the public library than from school.

061 In 1938, through an entrance examination, JL qualified to enter Stuyvesant High School, which had been founded in 1918 as a special school for science academic development. Stuyvesant housed academically talented youth, and because of that JL felt less lonely than he had in grade school. The teachers were good as well, and were extremely sympathetic to the intellectual nurturance of their students. Besides after school clubs and activities, Stuyvesant also had advanced placement courses, which was unusual for the time. JL estimates that half to two-thirds of his classmates were , like him, second-generation Jewish immigrants. Today you would find a similar phenomena, except the students would be Asian rather than Jewish.

098 Because he was so self-directed, JL cannot directly recall any teachers at Stuyvesant who played significant roles in his intellectual development. However, the teachers played an important role in creating a nurturing environment, which was important to JL. In terms of curriculum, there were lots of electives. JL focused on chemistry and some biology. He talks briefly about the chemistry set he owned in grade school.

121 The discussion turns to the role of religion in JL's early life. His father was an orthodox rabbi and while JL had a good deal of sympathy for the fundamental ethical and philosophical traditions of Judaism, he had difficulty connecting them to the ritual practices that go back to the Middle Ages. Over time he and his father came to respect their differences.

140 JL knew he was going to become a scientist from the time he was literate. One possible explanation for this early interest in becoming a scientist, he notes, is that this was an alternative to orthodox religion, in that Jews had folk heros like Albert Einstein who, while not deeply observant, were highly respected, proud of their Jewish origins, and a credit to the Jewish people.

160 After graduating from Stuyvesant in 1941, JL enrolled in Columbia College. Originally he assumed he would be attending City College until, at the very last moment, he won a scholarship to Columbia. He selected Columbia partly because of his limited knowledge of other possibilities, but partly out of opportunity. He also had an eye on Columbia because he knew that individuals like T. H. Morgan and E. B. Wilson had been there and that they reflected the tradition of Columbia being a great center for research in biology. In high school JL received no advice from his teachers about which college to attend, since they all seemed to assume he would attend City College. City College had some good teachers and a superb peer group, but very limited laboratory facilities and only the semblance of a

research program, especially when compared to the active research programs at Columbia. JL cannot remember the details relating to the scholarship he received from Columbia, but he assumes he had received advice in this area from his mentors at Stuyvesant. One other possibility was that there was a competitive entry into an organization called the *American Institute Science Laboratory*, which was later incorporated into the New York Academy of Sciences. *AISL* won a grant from Westinghouse and IBM to establish a laboratory where high school students could actually dabble in research. JL notes that he graduated from high school in February of 1941 but was not able to enter Columbia until September, partly because he was too young but also because it was midyear. Thus he ended up spending much of his spring working at the *AISL*.

218 Upon entering Columbia, JL had determined that his majors were going to be biology and chemistry. He enrolled in a number of graduate courses as a freshman which, he said, was for the best, since he was not mature enough to appreciate the humanities—which he put off taking until later in his undergraduate career. JL notes he did exceptionally well in the sciences, but the rest of his cultural experiences were not that far ahead of his chronological age. Because of his age, there was some initial skepticism on the part of his professors in the graduate courses he was enrolled in, but that soon disappeared.

235 One of the people at Columbia JL had occasional contact with was Hans Ris, who later enjoyed a successful career at UW. He was among those who initially looked askance at JL because of his age. Over time Ris came to accept him.

245 Regarding instructors, the one outstanding mentor JL had at Columbia was Francis J. Ryan. One of the first courses he took was taught by Franz Schräder, E. B. Wilson's successor. Schräder was a rather stiff, Germanic type. When JL wanted to do experiments with mice, Schräder was not overly enthusiastic about the idea. Salome Waelsh, who suffered discrimination because she was a woman, befriended JL and gave him the mice he needed to conduct his experiment. He explains the experiment he was working on, which in the end did not work out. Just three months ago, JL notes, a paper was published that, in effect, reproduced the experiments JL had done at that time.

272 JL entered Columbia in September of 1941 as a civilian. The Navy advertised an officer training program called V-12. You entered the program through competitive examination and if you were accepted the Navy would put you in uniform and support your education. Later you would have an obligation to service. JL qualified as a pre-med, and eventually a medical student. He was accepted into the program in 1942, with the agreement that he would not be called into active duty until July 1, 1943—at which point he was to be immediately sent back to Columbia College's V-12 program. The only problem was in early June JL received his orders, which said he was to report to Holy Cross College in Worcester, Massachusetts for his pre-medical training. He soon learned, however, that he had received

the wrong orders, and when the situation was corrected he was indeed sent to the V-12 program at Columbia. For the duration JL lived in the barracks in Hartley Hall on the Columbia College campus. Occasionally the Navy would pull JL out of school for a quarter and have him serve as a hospital corpsman at St. Albans Naval Hospital. He was assigned to the clinical laboratory, where he served as the parasitologist and did laboratory diagnoses. Occasionally he took care of patients, but his main job was in the laboratory.

318 JL started attending Columbia Medical School in October, 1944. Columbia Medical School had a very fine reputation and was located in the neighborhood JL grew up in. His idea was to obtain a degree that not only allowed him to practice medicine, but conduct research in neurology. In the meantime, he had become deeply imbued with pursuing genetic work back at Columbia. As it turned out, he continued working in Ryan's laboratory in Morningside Heights on the main Columbia campus while simultaneously attending medical school.

340 Returning to Francis Ryan, JL notes he was at Stanford doing work with George Beadle and Edward Tatum during JL's first year at Columbia. JL had heard about Ryan and was aware of the fact that Beadle and Tatum were studying biochemical mutants in *Neurospora*. As soon as Ryan returned to Columbia, JL camped on Ryan's doorstep "and gave him no peace" until he let JL work in his laboratory. JL calls Ryan the most important mentor in his life, both during his college days and beyond. Some of the reasons Ryan proved so helpful was that he provided JL with discipline, readily exchanged ideas, and taught him how to conduct experiments and record his results—in other words Ryan taught him "what it meant to confront a scientific issue in a highly professional way." When Ryan died at a relatively young age the number of testimonials about his role as a teacher "was absolutely legendary."

353 The discussion turns briefly to Kimball Atwood, who also worked with Ryan. Atwood was at Columbia doing experimental work at the same time as he was attending New York University Medical School. At one point, after JL had enrolled in medical school, he and Atwood roomed together. Later Atwood again worked with Ryan on periodic selection in the chemostat and some other "very fine experiments" which, JL notes, had nothing to do with medicine. JL cannot understand why Atwood bothered attending medical school, since he had little interest in it and no intention of using his medical education.

364 JL's first publication, "Reverse-mutation and adaptation in leucineless *Neurospora*," was with Francis Ryan. JL began as a dishwasher and assistant in Ryan's lab, and Ryan gradually let him do more things, including sharing ideas with him. Ryan had observed a phenomenon of what was called adaptation, where leucine-requiring strains of *Neurospora* when planted in a leucine-free media would not grow, or grow to a very limited degree, because they did not have the leucine they needed to make their protein. But occasionally an event would occur where an outgrowth of leucine-independent organisms grew very happily without leucine. So the question became was this really a reverse mutation?

Although this seems very commonplace today, it was a new concept at the time. JL was assigned the job of investigating whether it was a reverse mutation, which basically involved doing back crosses between the adapted strains and the wild type strains to make sure there was no hidden leucine-dependant genetic material in those strains. The answer, JL discovered, was that there wasn't, and the best they could tell the adaptive change was a mutation in the same gene that had mutated in the first place.

382 JL names some other professors he worked with at Columbia. Ryan was the person he spent the most time with, however. At Columbia Medical School no one professor stands out. The students "were herded into a very large lecture room," but still he got to know some members of the faculty, such as David Rittenberg, David Shemin and Sam Graff.

392 Most of JL's work in medical school was pretty didactic, and he cannot recall developing any deep intellectual relationships. There was also a different peer group, and while they were smart they were not primarily scientifically oriented. Some of his classmates later became important in academic medicine, but they were the exceptions rather than the rule.

399 There were two reasons why JL took a year's leave from Columbia Medical School and transferred to Yale. One reason had to do with the fact that World War II ended, which allowed him more flexibility in pursuing his medical education. The second reason is he already had begun experiments looking for recombination in bacteria and wanted to continue. The work was more or less an extrapolation of work he had done with Ryan on *Neurospora* reversions, which had been influenced by Avery, McCarty and MacLeod's paper on DNA causing genetic transformation in pneumococci.

412 End of side.

Tape 1/Side 2

001 The most burning question in biology at the time was the authentication that a chemically defined substance was the carrier of genetic material (Avery *et al*, 1941). This needed to be approached from a variety of perspectives. At first JL tried transforming *Neurospora* with extracts of wild type *Neurospora*. He attempted this in Ryan's laboratory and with Ryan's strong encouragement. JL extrapolated those experiments into one trying to transform *Neurospora*, which for a variety of technical reasons did not work. He then thought he could perhaps turn this around and see if bacteria could change genetic material by mating as do other organisms. The textbooks dismissed this possibility, but as JL started to delve into the matter he began to realize there was no intellectual foundation for the claim that bacteria were asexual. He was reinforced in this approach by Rene Dubos, who had just left Rockefeller University for Harvard and who had laid out arguments pro and con for sexuality in his book, *The Bacterial Cell*, thus confirming JL's inference that there was no hard

evidence one way or the other, and that it was a problem worth pursuing with powerful genetic methodology—which he had learned from working with Ryan.

048 The experiments got underway without giving clear-cut results. When the war ended one of the scheduling options presented to JL was an elective quarter. This was done partly to give the overworked medical faculty a rest. Francis Ryan proposed to JL that he consider working with Edward L. Tatum, who had just moved from Stanford to Yale. Very importantly, Tatum had just developed some mutant strains of *Escherichia coli* that would be ideal for the experiments JL was planning to conduct. Instead of just asking Tatum for the strains, Ryan suggested to Tatum that he take JL into his laboratory. JL wrote a letter outlining the research proposal and Tatum accepted him for the quarter beginning in March or April, 1946.

077 The discussion turns briefly to Tatum and his background. Tatum's father, Arthur L., was a distinguished professor of pharmacology in the medical school at UW. Tatum had been raised in Madison and done his undergraduate and graduate work at UW. He had worked with E. B. Fred and William Peterson for his doctorate, which was on nutrition in lactobacilli, and he was among the first to discover that bacteria needed vitamins for their growth. JL notes that Tatum was doing a post-doc after completing his graduate work with Fritz Kögl on the nutrition of fungi when he received word that George Beadle was starting a program of research on the biochemistry of eye colors in drosopha, in which he was working out the genetic control and gene-enzyme relationship. This was in 1936-37. In 1937 Beadle ended up recruiting Tatum to come to Stanford and work out pathways of eye pigment biosynthesis. This had nothing immediately to do with Tatum's background in microbial nutrition, JL notes, but the latter had everything to do with the transition to research on *Neurospora*. Beadle eventually became frustrated with the complexities of working with eye pigments and decided to shift to *Neurospora*, where Tatum's background in nutritional requirements of fungi fitted perfectly into that scheme. Thus in January or February of 1941, Beadle and Tatum started their experiments on looking for biochemical mutants in *Neurospora*—and by June or July they had collected a good sampling of them. They published their first report in October or November in the *Proceedings of the National Academy of Science*, which made for a very quick breakthrough.

127 Tatum, who had been denied promotion to associate professor at Stanford, possibly because there was at the time a fair amount of prejudice against chemists in biology departments, accepted Yale's offer to a full professorship. He set up his program at Yale and JL was one of his early recruits. Tatum was only at Yale for a couple of years before accepting an offer to return to Stanford.

143 JL came to Tatum's lab at age 21 with a prepared proposal and a definite protocol for his experiments. Working with Tatum, JL learned a lot about conducting experiments. Tatum

was a very insightful investigator and had "a green thumb." It took only six weeks to complete the experiments. By the first of July, JL "was ready to talk about them." The opportunity to so came at the Cold Spring Harbor Symposium, held in early July, 1946. JL did not think they were going to get the chance to talk about the experiments at the Symposium, but Al Hershey talked about recombination of bacteriphage and some of those in attendance started saying how unfortunate it was that bacteria did not do things like that. At this point Tatum and JL could not keep their experiment quiet any longer. JL notes how try as he might, he could not think of another experiment "that would nail it down any further than we had." He knew that they had reproducible phenomena, that they had done experiments with more and more markers, and that they had clear segregation of unselected as well as selected markers. One of the joys of this kind of experiment, JL notes, is that you can do it overnight, meaning you can conduct numerous experiments in a month, if need be.

180 Tatum managed to secure a place on the program, and there was a great debate following their presentation. The informal, post-session seminar lasted three to four hours. Andre Lwoff argued that JL had not proven he had gotten single cells that had the characters of two parental cells, and he was just dealing with contaminated mixed cultures that were cross feeding each other. That had been, JL notes, one of his initial concerns. Indeed, he designed his first experiments to make sure that would be readily detected if it occurred.

202 The way the discussion ran was Lwoff said you had to isolate single cells, and JL responded by saying there was other evidence that these were pure clones and could not possibly be mixtures, after which Lwoff said he could not believe it till JL isolated single cells. Eventually Max Zelle raised his hand and said he would show JL how to isolate single cells, or they would isolate them together—which is exactly what happened. JL had overestimated the complexity of isolating single cells and found it easy to do, and he has done it routinely many hundreds of times since. Most accepted the results of JL's experiment. The main holdout was the Cal Tech group. Max Delbrück in particular expressed great skepticism. JL said Delbrück, who was doing research on phage at the time, said essentially that JL had not done the experiments he, Delbrück, wanted him to do. JL notes that many of the top people in the field were supportive and encouraged him in his work. Regarding the experiment itself, technically it could have been done fifty years earlier, but there had not been the correct approach in thinking about bacteria as genetic entities. JL explains how, historically, the discovery of recombination could have occurred.

253 JL said that when he began the experiment, he had no idea if it was going to work. He merely wanted to test the proposition. He was prepared for the long haul and was startled when he achieved such immediate success. This early success, he notes, was "pure luck." JL did not know how lucky he was in coming to Tatum because he not only had interesting mutants, but the very strain he had chosen, *E. coli* K-12, which was just one of the stock culture collections out of Stanford, proved to be almost unique due to a number of properties

that lent itself to this kind of experimentation. In retrospect, for the way they did the experiment, if random strains had been chosen the chance of success would have been one in twenty. JL notes that he was well aware of the prospects of strain specificity. For all he knew there were male strains and female strains and he would have had to mix them with the right gender combinations. He was again surprised when it worked with a single strain. JL has no idea how persistent he would have been had the experiment not met with early success.

274 JL immediately understood the importance of the experiment. He remembers linking it to what Avery and his people had done. He views himself as a genetic counterpart to Avery's biochemical work.

283 The first appearance in print was in *Nature*, which was published in November, 1946. It was a very brief article summarizing what they had spoken about at Cold Spring Harbor. In the spring of 1947, the proceedings of Cold Spring Harbor were published. JL notes he did all the experiments by himself and he brought the concepts of the experiment to the lab. Tatum provided the strains and the lab space, as well as guidance and oversight. They talked over the results and reviewed the manuscripts together. JL did the preliminary writing and Tatum polished it up. JL and Tatum alternated senior authorship for the first couple of papers. JL does not recall Tatum ever publishing anything afterwards on recombination.

301 The issue when JL approached Tatum initially about the experiment was not did Tatum think the experiment would be a success. Rather, the issue was did Tatum think JL had a good experimental test. And they were going to find out something one way or another about nature by applying that test. In that sense the experiment would work, since it would answer the question of whether or not one can find genetic recombination in bacteria.

309 The issue was that nobody in natural history had seen any clear evidence of reassortment of genes. Is there anything else in the natural history of bacteria, the question became, that might lead one to guess whether recombination is occurring? JL discusses some research published in 1941, which demonstrated how, when one does serological typing of what were then called species of *Salmonella*, one can see some natural historical suggestion that some kind of reassortment of immunogenic factors was taking place within the *Salmonella* group. That was the only hint he had at the time. This was also the reason that the next organism after *E. coli* JL wanted to study was *Salmonella*.

339 Returning to the summer of 1946, because so many issues needed to be resolved in relation to his and Tatum's recombination experiment, JL elected to ask Columbia Medical School for another year's leave of absence. This was the year he worked out the linkage map of *E. coli* and published it in *Genetics*. During this same time period, he met Esther Zimmer and they were married in December, 1946.

354 JL notes that Tatum was an extremely important and supportive influence during this period. Among other things, Tatum got him the fellowship that enabled him to come to Yale in the first place, then arranged that the fellowship be renewed the following year. JL comments that he could not have done his experiments had it not been for Tatum's deep involvement and support. Still, Tatum was not immediately involved in the experimental or the intellectual work. He was much more of a biochemist than a geneticist so even though he was concerned about gene-enzyme relationships, he was not thinking about mapping or several of JL's other interests and concerns. JL briefly discusses what he sees as Beadle's and Tatum's most significant contributions to science.

375 JL's dissertation was a compilation of the work he had already completed. In 1947 he was faced with a new crisis: does he return to medical school or not—and if he does not then what does he do next? At some point during that summer, Tatum received a solicitation from Alexander Brink of the University of Wisconsin asking about prospective candidates for a position in the Agricultural Genetics Department. Tatum sent Brink JL's name along with some background material. It was not until July of 1947 that JL was personally contacted about applying for the job. It was around this time that Tatum suggested that if JL was interested in securing a job, he might want to finalize his dissertation. Tatum then arranged with the Yale authorities for JL to register retroactively as a graduate student, so that all the time he was at Yale he was in an informal status as a visiting medical student from Columbia. In order to complete the retroactive registration, JL had to come up with an $800 tuition fee.

395 End of side. End of tape.

Tape 2/Side 1

001 The discussion returns to the 1946 experiment and JL's thoughts when the first positive results came in. Fear, he says, was probably his dominant emotion. The fear was of having his expectations raised only to have them dashed later by not being able to replicate the results. Thus he tried restraining his emotions and assumed it was probably a mistake or an artifact. He was especially fearful that his judgment might be clouded by his high expectations. After repeating the experiment four or five times, there was no escaping it: the experiment was a success.

026 From there JL allowed himself to think about its implications and ask the question "What do you do next?" He was eager to talk with others and get their input and suggestions, and indeed he did just that. The Cold Spring Harbor Symposium was a wonderful opportunity because essentially everybody in the field congregated for the first time since the war. The Symposium was important in two ways: first, it gave JL access to supportive and critical judgments made by people he respected and admired; and second, the debate that followed

the presentation settled the matter once and for all. Had his findings first appeared in a journal, for example, the debate on a matter this controversial might have dragged on for months.

063 A position in the Agricultural Genetics Department at the University of Wisconsin came open when Leon Cole retired. The decision was made to replace him with a person more versed in basic, as opposed to applied, genetics. JL suspects that Cole might have been responsible for this decision to some extent. Although he did not know it at there time, several other names were submitted for the position. These included Max Zelle, J. M. Severens, John R. Laughnan, Adrian Srb, A. H. Doermann and David Regnery. JL later came to know some of these candidates very well. David Regnery ended up at Stanford University and was on the faculty there for some time. Adrian Srb went to Cornell, where he had a distinguished career in *Neurospora* genetics. Gus Doermann did some fine work on T-phages, and worked on *Neurospora* as well. Max Zelle is a bit surprising in that he did not make a strong mark scientifically, although he assumed some important administrative positions in biology and medicine in the Atomic Energy Commission.

102 Prior to JL's interview, Tatum told him a lot about UW and how much he had enjoyed living in Madison. JL, who had never visited the Midwest, had never met any of the people he would be working with in Madison. He was excited about going for the interview, especially in light of the fact that there were no other jobs available in bacterial genetics—nor was there a guarantee that there would be a job in this area in the foreseeable future. The only alternative he had at the time was to return to medical school.

129 JL left for the interview in Madison by train. He brought his wife, Esther, and many people commented on what an asset she was to the 21 year old candidate's credibility. JL was impressed by the friendly nature of the people in the Midwest. He thought, correctly, that he could enjoy Madison very much. JL's first impression of Brink was as a very responsible, albeit initially formidable personality. JL came to like him immediately. Though forewarned, he was still somewhat dismayed by the lab facilities and he found himself working in primitive quarters for quite some time.

170 Regarding his appointment into a college of agriculture, he says he was not the least bit dismayed about conducting basic research in a department that featured applied research. Besides, he notes, the University and the College of Agriculture already had outstanding reputations. JL knew a fair bit about the College's work in various areas so he knew he would have intellectual companionship, even if he was on the basic side of the spectrum.

190 Even though he wanted the job in Madison as soon as he was greeted there, he was still torn about returning to Columbia and finishing medical school. He does not recall making a final choice until the very last moment. There were, in addition, other matters he needed to

consider. He had applied for a Merck Fellowship that would have provided financial support for his time at Columbia, and at nearly the last minute the Jane Coffin Childs Fund said they would arrange some funding for him. JL was disappointed to learn he did not get the Merck Fellowship, as he had considered returning to Ryan's lab and continuing his work on *E. coli*, while at the same time completing medical school.

220 Regarding the Madison job, JL's correspondence indicates that he vaguely agreed to a verbal offer in Madison, probably from M. R. Irwin, and that this was followed up by a formal written offer. The salary offer was for $3500, roughly twice what he had been making as a fellow. He was hired as an assistant professor and as such was expected to teach and conduct research. During his first years at UW he started a course in genetics and microorganisms, which was cross listed with bacteriology. He also lectured occasionally in other courses.

234 The question relates to concerns people had about JL's hiring, concerns which focused on his age, his unfamiliarity with farms and agriculture, his "aggressive" personality and the fact he was Jewish. JL notes that he was totally unaware of any of these concerns. In retrospect he understands that some of the people he had contact with on a daily basis might have had some misgivings about hiring a Jew, but if they did they never betrayed those feelings to him. Regarding his so called aggressiveness, JL said it stemmed from his relentlessness about the logic of the situation, in that he did not hesitate to speak his mind if the situation called for it. Over time he learned there were other ways to get one's point across. He could take as well as give, he notes, and in the context of scientific discussion he always expected to be dealt with critically, openly, and forcefully—and he did not hesitate to treat others in a similar fashion.

279 JL reflects on his relationship with the University of Wisconsin and how things might have worked out better than they eventually did. He also notes that *he might not have been aggressive enough* when it came to matters relating to resources, such as space and help. He notes that he did not push hard enough, and too often took "no" for an answer and let it stand at that. There were others on campus, he notes, who were more diligent in pressing for their needs. The net result was that instead of being as aggressive as perhaps he should have been, he ended up leaving and going to other places where he did not have to argue as hard for his needs.

296 End of side. End of tape. End of interview.

Second Interview Session (September 30, 1998): Tapes 3-5

Tape 3/Side 1

001 JL briefly discusses the Merck fellowship he applied for at approximately the same time he applied for the job at UW. The Merck fellowship, JL notes, was a newly instituted program of post-doctoral fellowships. He hoped the fellowship would finance his return to New York City to continue his medical studies at the Columbia College for Physicians and Surgeons. JL was not awarded a fellowship. That left him in a quandary as to how he would be able to afford to return to medical school. At that time he was also afforded the opportunity to accept a position at the University of Wisconsin. At the last moment, the Jane Coffin Childs Fund in New York City made an offer for a research fellowship that would have helped out considerably, yet it would have been difficult to cover tuition and living expenses with what the Childs fund was offering. In the end, JL decided to accept the job in UW's Department of Agricultural Genetics.

052 The discussion returns to Max Delbrück's challenge of JL's recombination findings at the 1946 Cold Spring Harbor Symposium. JL recalls that Delbrück did not say much, critically or otherwise, during his presentation. Thus Delbrück was not a factor in the overt debate. It was only somewhat later, when JL wrote Delbrück for advice on some aspect of the work, that Delbrück wrote back saying he did not believe a word of the recombination theory and did not want to discuss it. Delbrück noted that JL was not doing the experiments on the kinetics that he wanted him to do. JL does not recall ever having a clear message from Delbrück of what, exactly, he had in mind.

086 JL remembers Cal Tech, where Delbrück was from, as being rather quizzical about his findings from the outset. He later learned, from a letter Ray Owen had written Alexander Brink regarding JL's possible hire, that everybody at Cal Tech was opposed to his theory—a fact that puzzled Ray Owen. People at Cal Tech, JL notes, sometimes had difficulty understanding there might be important discoveries being made elsewhere.

107 The discussion moves to C. N. Hinshelwood, a very influential figure in science. Hinshelwood wrote "a curious book" in the mid-40s on the chemical kinetics of the bacterial cell. In it he denied the existence of genes in bacteria. It was evident in the book that he had not given much thought to recombination.

139 The question asked was what was happening in genetics in 1946 that prompted Brink and the Department of Agricultural Genetics to hire someone with JL's background and expertise. The most visible and important innovations in genetics during the early 1940s, JL notes, were in the field of *Neurospora*. Also, the biochemical kinetics represented by Beadle and Tatum were making a stir, in that they offered the possibility of understanding pathways of gene action and brought genetics closer to biochemistry. Tatum was, in a way, an exemplar of that, and had he been available at an affordable rank, Wisconsin would have gone after him. Bacterial genetics almost didn't exist, with the exception of JL's 1946 work. There had been a few studies in mutation in bacteria, but the conclusions were less than far reaching.

There was also work on phage, but the genetics of phage was, again, a recent phenomena, and it is unlikely its results would have spread very widely at that point. In terms of the overall discipline of genetics, the part that had a chance to ripen and sink in since 1941 was the biochemical genetics of *Neurospora*. Indeed the record has shown that some of the other candidates for the UW position had come from that field, which presented a very legitimate alternative.

171 JL and his wife, Esther, arrived in Madison prior to the start of the fall semester in 1947. There was a tremendous housing shortage in Madison at the time, due to the large number of GIs on campus. JL and Esther moved first into emergency housing at the Truax Field barracks, along with numerous graduate students, for the first couple of weeks. They then had a rental for a year before moving into Eagle Heights, which was a new housing development on campus.

188 JL's original appointment was for an academic year. This was quickly changed to a twelve month appointment. Starting at a salary of $3,500, JL soon got a raise to $4,800, which was for a twelve month appointment. Compared to what he had been living on, JL had no complaints about what he earned at UW.

204 The discussion moves to various individuals in positions of power during JL's years in Madison. Ira Baldwin was dean of the College of Agriculture at the time JL was hired. As a new hire, JL had little to nothing to do with the dean. E. B. Fred was president from the time JL arrived on campus nearly to JL's departure in 1958. Again, JL did not have many dealings with Fred and that level of administration until when he wanted to establish a new program in a new department. When he wanted something, JL generally worked through the department heads, Brink and Irwin.

238 JL knew Conrad Elvehjem more as a professor than as Graduate School dean. JL saw people like Baldwin, Fred and Elvehjem as very correct, polite and reserved—something he did not fully appreciate until he had achieved similar status. Indeed, there is something inherent in these jobs that makes one careful about what one says. JL also notes that the Madison administrators were men of their word who did not go back on their promises.

256 The one other administrator discussed is Rudolph Froker, who succeeded Ira Baldwin as dean of the College of Agriculture. JL saw a little bit more of Froker than the others. Froker, JL notes, saw his job as running the Ag School and the Ag Experiment Station and serving the needs of agriculture for the state of Wisconsin.. He thinks Froker might have been a little puzzled about his appointment. In hindsight, JL sees Baldwin as perhaps being more research oriented than Froker. JL relates an incident in which a professor was seeking support from the Ag Experiment Station to conduct research on plant improvement through protoplast fusion. JL thought it was a good idea and made some intervention to try and get

the project some support. It was turned down, however, which, JL notes, may in part color his reaction.

280 Regarding the applied versus basic research debate, JL thinks that applied research, aimed at making a good name for the school in terms by showing what it could do for the farmers of the state, was what Froker saw as his mission. JL is certainly not opposed to that mission. In fact, it might be the only politically viable stance to take. There was no question that you could get a Baldwin or an Elvehjem interested in a scientific development, whereas Froker was someone who came with a different perspective.

296 When JL was hired, he took the position that had been held by Leon J. Cole. Cole had retired the year before and died a few years later. JL has a vague recollection of meeting him once or twice after arriving on campus, but he remembers Cole's spirit as being "all over the place." Brink and Irwin frequently referred to Cole and his vision of incorporating more basic science into the Department's overall activities. JL came to learn that Cole had even written a paper about bacteria in 1916, and while it was rather primitive it was still ahead of most thinking at the time. The very fact that Cole worked in the area of bacteria at all set him apart from many others at the time. Cole, JL notes, was very sympathetic to an eclectic view of what genetics needed, and he certainly had a vision of the ever growing importance of genetics in biology and human affairs.

320 The discussion turns to members of the Department of Agricultural Genetics in 1947. Almost everybody in the Department was much older than JL when he arrived on campus and were thus, in his view, venerable. This was certainly the case with Alexander Brink, with whom JL had an avuncular relationship of sorts. Like so many others in the Department, Brink dealt with JL kindly and generously. Brink, who took a serious view of science, had, in his own work, "spanned the gamut of some very important applications in breeding work," in addition to studying cattle poisoning from sweet alfalfa and other practical work. With his work on transposable genes, Brink was on to the same line of work as Barbara McClintock. McClintock won a Noble prize for her work, and, JL notes, it would have been totally credible for Brink to have shared the prize with her.

353 The discussion of other members of the Department begins with Lester Casida, whom JL characterizes as a bit of an anomaly because he was more of a reproductive physiologist than a geneticist. Casida conducted important research that was published in basic science and application journals.

368 JL did not have much contact with Arthur Chapman, Delmer Cooper, Norman Neal and Gustav Rieman, perhaps because they spent a good deal of time in the farm fields conducting their research. JL knew Richard Shackelford a little better. He describes Shackelford as a lively person whose main line of work was mink breeding. He was interested in pigment

mutations and hair color and he was as much a geneticist as a breeder. Shackelford, JL notes, uncovered some interesting developmental mutations in mink.

391 The discussion turns to Jim Crow, whom JL first met at Cold Spring Harbor in 1947. Crow was extremely lively and had a breadth of interests. He was a fruit fly geneticist who later went into human genetics. He is very articulate, thoughtful and generous. During JL's first year in Madison another vacancy occurred, and the Department wanted to find somebody who could teach formal genetics. This was to be a joint appointment with Letters and Science. JL brought up Jim Crow right away, and the Department liked Crow from the outset. JL thinks his being in the Department was part of the draw, in that they had a lot of common and fundamental interests. Crow was also an excellent teacher, and JL often comes across people who had their first genetics course from Crow and remember him clearly.

412 End of side.

Tape 3/Side 2

001 Continuing with the discussion of Jim Crow, JL notes that Crow taught the introductory course in genetics, which was in all likelihood cross listed in zoology. Crow's research was in population genetics in *Drosophila*, and he conducted experiments on natural selection with cages with artificial populations of various mutants and how they evolved over time. JL explains how Crow's research expanded when he ran into certain kinds of mutants that showed departures from normal Mendelian behavior. Crow worked with Larry Sandler, one of his early students, on a phenomenon called meiotic drive, which is a situation in *Drosophila* genetics where you do not get one-to-one ratios because the presence of the gene actually alters the details of spermatogenesis and competition between sperm, with some carrying and some not carrying the gene. JL says it was lucky Mendel did not run into that early on or he never would have discovered his laws because they would not have applied. Crow was interested in anomalies like that. He also became more and more theoretical about how mutations affect any reproductive process and enter into the mathematical theory of natural selection. He did a good deal on the foundations following Sewall Wright, R. A. Fisher, and others in the elaboration of that theory.

036 This then drove an interest in his part in human genetics and human evolution from a similar perspective—such as studies of mutation in a human, for which he is still regarded as a world expert. He also became more and more involved in advisory work to the government. JL believes he was chairman of several successions of the National Academy committees on biological affects of atomic radiation, which were very important in setting standards of radiation exposure. So he had a very broad ranging set of interests. In addition, JL said he talked over his own experiments with Crow all the time, and vice versa.

054 JL thinks the Department of Ag Genetics functioned well and that Brink and Irwin were both good managers. Both men practiced shared decision making with members of the Department. It was not necessary to take everything to a formal vote, as there was enough informal consensus to run the Department. Thus, both Brink and Irwin could speak authoritatively whether or not there had been a formal vote on the matter under discussion.

075 The issue of funding in Ag Genetics is discussed. JL says he was more fortunate than most because he had access to NIH grants, which provided a major part of his funding during his years on campus. People doing more applied work received funding through the Agricultural Experiment Station. These funds were usually a little on the scarce side. In addition, there was less of a merit system involved, which might have proven a little discouraging for those doing cutting edge work. Again, JL was not involved much in the administrative end of the budget. He had much to do in the lab and focused his energies there. He got more work done in his years at Wisconsin, JL notes, than at any comparable period in his career.

107 The discussion turns to JL's research. JL's first lab at Wisconsin "was pretty primitive." It had no air conditioning and "was not much more than a couple hundred square feet, all together." It had facilities for glassware washing, autoclaving and media preparation and the like. His lab also contained two lab benches, and for a long time JL did not have a hood. It was difficult to do much chemistry under those conditions, but he was able to do microbiology. Probably the most irksome thing, from JL's perspective, was the summers. It was not just a matter of personal comfort, but the agar plates would not jell. The temperatures were around 35-40 degrees centigrade. Nevertheless this period proved to be the most fruitful of his career.

136 The work JL brought with him to Madison was the work he had done his dissertation on, which was the discovery of the recombination of bacteria. He spent the 1946-'47 academic year working out how to do linear mapping from the crosses of different *E. coli* strains. After that there was the question of "what do you do next with that system?" That was still a time when, although the strains were publicly available, there was no competition. Luca Cavalli was just beginning to conduct experiments in this area and it would be two or three years before anybody else really picked it up.

148 A line of inquiry JL had in mind to start with, and which had its beginnings at Yale, was to work out still more sharply the actual physical or physiological system—the mechanics—of recombination. Could you see the cells joining up with one another under the microscope? What was the fertilization process like at that level? This proved very difficult because it was a rare phenomenon with the strain he had at that time. You could tell from the frequency of recombinance when you made mixed cultures that only about one out of a million cells in a culture would participate. So how are you going to go around looking for unique morphology when you have a haystack of a million and one needle in that haystack and no

obvious way to pick it out morphologically? JL says they ran a blank on that for quite awhile, but then several things started happening in very quick succession. One was the discovery that there were, in fact, mating types in *E. coli*. In one level this was not a very great surprise, because JL had started his work with *Neurospora* where there were well established mating types and you can only get a cross if you mix a plus and a minus strain together. In the *Neurospora* case you don't talk about one as being male and the other female, you just have arbitrary alternate types.

174 With *E. coli* it turned out there was a polarization that, besides there being a mating type difference, that the plus cell, called the F+ cell for fertility factor, was actually contributing genetic material to an F- cell which was receiving it. JL knew that because the contribution was often much less than the complete genome. As a result, there existed progeny that were the result of a quarter, a third, a half of the genetic material of the donor of the F+ cell being represented in the overall progeny of the fertilized F-cell. So he started calling them male and female. This was greatly helped by Cavalli's discovery of a strain that showed a very high frequency of recombination—which got as high as 1 percent or even a few percent, making it so JL could at least start dreaming of being able to see the conjugal mechanism under the microscope. Eventually he succeeded in doing that and actually finding pairs of cells stuck to one another. He describes using a strain of *E. coli* other than K-12 where, when looked at under the microscope, one could see the cells that would agglutinate with one another. But every now and then you would be able to see a clear mating pair where there was a plumb one and a thin one stuck together. You could then isolate and follow that pair and their offspring under microscopic control. The result was a good correlation between the occurrence of these pairs and the occurrence of genetic recombination in the progeny.

207 This was one line of research that put physical meaning into the very abstract recombination process. Until then it had been a black box where you put two genotypes into the black box and ended up getting different genotypes out of it. This way you could get a little more insight into what was going on in between. However they were still unable to get a clear picture of exactly how the DNA was transferred from one cell to another because for most of their lifetime these pairs, although they are swimming together, maintained a physical gap between them. For awhile, JL thought maybe one of them was getting stuck on the flagella of the other. We now know it is not the flagella, but other much shorter hairs that are all over the surface of the cell, which apparently are the recognition sites for F+ and F- cells. Thus "he" recognizes "she" through the mediation of these hairs. Looking at the problem today, from the best we can tell the hairs allow the two cells a little later on to get very close to one another—and then something else happens and there is a pore opened up as the cells are in close approximation and a single stand of DNA unravels from the double strand and works its way through to the recipient cell and increasing amounts of it appear in the donor cell that initiates fertilization. The conjugal mechanism, JL notes, has ended up rather more complicated than he had initially expected. His visual model had been that the two cells

actually fuse with one another, as in fungi and protozoa. The complete fusion is not seen, however. To this day, JL is attempting to find systems where complete fusion occurs—but that is not the standard even in *E. coli* crossing. This issue became very complicated with the contributions of other workers. JL mentions some, including Bill Hayes' discovery of the F system. He also discusses experiments conducted by François Jacob and E. L. Wollman, in which they timed the progressive entry of different genes from the donor cell into the F- cell. At first JL resisted this approach, thinking there might be other explanations for the genetic ratios they were getting, but over time he came to accept it. That was the underlying platform of JL's continued research on *E. coli* recombination upon his move to Madison.

263 There were equally exciting things going on as well. Once you have a cross breeding mechanism in bacteria, the question becomes what can you use it for? One issue JL brought with him from Yale was to use the genetic control of enzyme reactions. In particular, he decided to concentrate these efforts on lactase. The enzyme was easy to measure and it was one that under some conditions is not vital to the life of the organism, so that lactase negative mutants would be perfectly viable and you could grow them and study them and compare them with the wild type, lactase positive. Shortly after arriving at Wisconsin, JL asked Karl Paul Link for assistance and Link got one of his graduate students to prepare a substrate that would give rise to a color reaction when the enzyme was present. What resulted was a very sensitive and very keen assay for the enzyme. JL very quickly found a great many mutants that were defective in lactose metabolism. At about the same time Jacques Monod, and joining with him shortly thereafter, François Jacob, were beginning to work on the same system. Originally they were doing this without reference to recombination. Starting in the early '50s, they began embracing a program quite similar to JL's, but whereas JL's approach was to learn how many different kinds of mutants he could find and could he classify them in having different impact on the formation of the enzyme, their approach was to go into much further depth on the phenomenon of enzyme induction—about what happens within the cell when lactose or other inducing substrates are added to the bacteria and the enzyme starts to be formed. JL ended up with numerous anomalies and they ended up with a very pretty picture. Their pretty picture is mostly right, but there are still some anomalies that have not been explained very well.

299 The contributions that came out of his work encompass two important points. The first is JL found, on introducing this colorimetric assay for the enzyme, that there was a baseline level of enzyme formed. It was only about 1 percent of the maximum level, but it was not zero. That told JL that the inducing substrate was not carrying information necessary for the specificity of the enzyme. It was acting as a trigger for the production of the enzyme, but its production was going on anyhow at a low level without the inducer. That was a new concept at the time, because most theories of enzyme induction thought the substrate played an active role in shaping the enzyme around it. This was, then, a departure from that point of view.

The other, which went even further, was that among the first mutants JL isolated was one that he called a constitutive mutant. This is a mutant that went full blast in making top levels of the enzyme even without an inducer. This just reinforced the idea that the cell already had all of the information needed to make the enzyme, and the role of a substrate was as a physiological modulator of level of production. This was eventually internalized by everybody, but JL thinks his early experiments in this area set the trend of thinking in that direction. JL started those experiments in 1947. Much of this work is summarized in the 1951 Cold Spring Harbor Symposium.

332 JL notes there are some anomalies that led to some amusing consequences, because besides using lactose he started using other sugars and looking for fermentation defective mutants with respect to those sugars. There was one that, oddly enough, was a non-fermenter, or a very slow fermenter on glucose, but fermented very rapidly on maltose. The question was: if you had a glucose negative mutant how come it was fermenting maltose? In 1950 JL was a summer lecturer at the University of California and he met Mike Doudoroff, who was a member of the biology department or biochemistry department and who was very much into fermatative metabolism. Doudoroff was quite skeptical about what JL told him, but when he viewed the cultures, he and his students went to work on it and discovered a new pathway. It turns out that in *E. coli* a major pathway for the utilization of maltose is to use one of the two glucose residues—maltose is glucose linked to glucose—to synthesize the starch from it, and use the other one and release not glucose but glucose six phosphate. (JL notes that it might possibly be glucose one phosphate.) This was a new pathway that was picked up as a result of the anomalies generated by these units.

354 There were a number of things that JL stumbled onto in the process of this other more designed line of work. He has already mentioned the F factor, it turns out these mating types were controlled by a unique genetic element which was not in the chromosomes, but were floating around in the cytoplasm. The F factor, as later work has shown, is controlled by a little ring of DNA which replicates along with, but is not part of, the bacterial chromosome. JL says it may in fact be present sometimes in multiple copies. So this is a whole new class of genetic elements, and it was a prototype for what JL later called "plasmid".

366 Another thing they stumbled onto—which was the result of astute observation by JL's then-wife Esther—was the presence of phage plaque appearing on plates of certain kinds of crosses. They had no idea where these were coming from. At first Esther thought it was a contamination. JL suggested following that up, and they found that standard strains of *E. coli* were carrying embodied within their genetic structure a bacterial virus, which they called lambda. At first they thought this was another cytoplasmic factor, and they compared it to the kappa that T. M. Sonneborn had been working with in paramecium. That proved to be not quite correct. They soon discovered that if you do crosses between lysogenic

strains—the ones carrying this phage—and sensitive strains, the lambda segregates as if it's on the chromosome—it was linked to a factor called galactose. There was no question that the capacity to produce lambda was linked chromosomally, thus in some way you had something that could be transmitted through the medium, enter the target cell, and then become incorporated into the chromosome.

383 This also ended in some parallel thinking about genetic transduction. The French group concluded that cytoplasmic factors—the ones JL called plasmids—often, or maybe even always, had a Jekyll-Hyde existence in its being able to go into and out of chromosomes. They coined the term "episome" for that transition, which was a perfectly legitimate concept except others started getting confused and using episome to mean transmissable particles whether they got into the chromosome or not, and it got to be a little bit messy. This eventually got straightened. Plasmid is an over arching set of extra chromosomal genetic elements. Some of these can interact with the chromosome, and in the case of lambda they do. In the case of F sometimes they do and sometimes they do not. So when F gets into the chromosome it is stabilized and has a high frequency of recombination associated with it. If it stays out in the cytoplasm, it allows conjugal transfer, but transfer of the chromosome only at a very low rate and transfer of the plasmid itself at a very high rate. They were, thus, able to tie together a number of aspects in what might be called infective heredity.

403 End of side. End of tape.

Tape 4/Side 1

001 The discovery of lambda , which is a prototype for a large number of other viruses that can have a lysogenic stage—with lysogenic meaning capable of producing the phage, where the virus is integrated within the chromosome, and then relating that to the overall plasmid concept—was, JL thinks, important elaborations of cell biology that have had very broad ramifications even beyond microbiology. Indeed, we use these concepts everyday when we think about cancer viruses and so on. But they were unexpected by-products, in that they were not in any way looking for them. These were things simply stumbled into in the course of other work.

021 The discussion turns now to transduction, which was the outcome of a very explicitly designed experimental effort, but which had an outcome they were not counting on. JL had begun his research with *E. coli* because everybody was using *E. coli*, in that it is convenient, it grew on simple media, and the strains JL worked with were totally safe—although it has relatives that are dangerous. But it does not have any great medical interest. It is not, by itself, a source of disease. It can be used technologically for producing various kinds of gene products, but that did not occur until many years later.

045 JL had had his eye on *Salmonella* as a near neighbor, a close cousin of *E. coli*. He saw it as something that, once they had the tools, should be worked on genetically as well. Thus working with *Salmonella* was on his agenda when he began his work at Wisconsin. In 1948 JL recruited his first graduate student, Norton Zinder. JL suggested that Zinder work on recombination in *Salmonella*. *Salmonella*, JL notes, is in many respects just like *E. coli*. Its most obvious difference is that the entire lactase gene and its control elements are deleted from it. Another reason to look at *Salmonella*, besides its importance in food poisoning and typhoid fever and related diseases, was a lot of serological work had been done on it. The serology of the *Salmonella* group had a special interest because the pattern of distribution of different antigens in its natural history was a mosaic kind of matrix that struck JL as indicating that recombination must be taking place to account for the various combinatorial varieties of Salmonella strains that are found in nature. This was an idea JL had before he did his first *E. coli* experiment—in that yes, there should be recombination as part of the natural history of bacteria.

083 JL got Zinder to start working in that area. JL then wrote Kaare Lilleengen, who had a library of different strains of *Salmonella* typhimurium he was happy to share with JL, together with a few bacteria phage which he had also isolated. JL thought these might at a minimum be useful as resistance markers. Zinder and JL set up protocols exactly analogous to those of *E. coli*. They had a tough job getting a new library of mutants, and that inspired developing some new experimental methodology for acquiring mutants. JL remembered a lecture in medical school which noted that penicillin only worked on growing bacteria, so he thought maybe he could exploit that. The question relating to that became: "How do you isolate a needle in a haystack when the needle is a nutritional requirement?" It is easy to isolate the hay, he notes, but how do you isolate the cell that is not growing? Penicillin, JL concluded, only attached cells that were growing. This worked, giving JL a new method for isolating auxotrophs, which was invaluable in developing the library of Salmonella mutants.

112 Zinder continued his work, trying crosses, while JL was very rigid and said he would not believe it unless Zinder could show he had double mutants on both sides, because if you only have a single mutant requirement it may revert spontaneously and be an artifact. The best basic method, as in *E. coli*, was to have growth-dependant strains that would not grow in minimal medium, mix them up, and see if there was any bacterium that would grow in minimal medium. But then you want to make very sure that your controls are completely negative, that they will never revert. If you only have a single mutant, then you can almost always get rare reverse mutations that confuse when you get crossing. JL did not want to go wrong on that, so when Zinder showed him results with some of his single mutant strains that looked like they were giving recombinant prototrophs much more frequently than could be accounted for by reversion, JL would point out that these results were not to be trusted and that Zinder needed to work with double mutants. When Zinder tried it with double mutants, however, it did not work. Zinder finally found one particular double mutant that did work,

with another double mutant strain, and this was a mutant that had both a tryptophane requirement and a tyrosine requirement. This seemed to work quite well. The background was completely negative and they never saw any reversions, and when you mixed the culture they gave a result.

140 It became apparent at this point that they had a new system, but was it exactly the same as the *E. coli* system? One of the very first things one does, and JL did it very early in the *E. coli* work, was to see whether the filtrates of the parent cultures, or even the mixed cultures, could induce change as compared to the intact cells. In other words, are the units of interaction both in intact cells, or can you get something that will pass through a filter that will still interact? Lo and behold, JL notes, unlike *E. coli* the filtrate worked. There was much more of it in a mixed culture, although you could get a little activity with a filtrate on one of the pure strains. Here JL and Zinder had a clean enough system that JL felt confident that a result that had one bacterial strain with just one marker and a filtrate—he got such a big difference between reverse mutants and the effect of the filtrate—could now be trusted. He was unwilling to trust it when he was mixing the two cells together, because for one thing he was not sure how much continued growth was occurring, but this was a much cleaner result.

161 At this point, they were "coming down the home stretch" with totally new phenomena which were very different from *E. coli*. But filtrates of mixed cultures could transform single mutants and could be any one of a number. The only double mutant they could transform was the tyrosine tryptophane. At some point they "smelled a rat." There was something very special about that double mutant, and they had to have stumbled on it in order to get the total picture. It was at this point that JL said he went around in circles for awhile, because there had been a lot of talk about L forms. People in the field had been publishing pictures about very curious morphologies of bacteria under certain conditions, but also in phage lysates—very bizarre shapes and forms. They were offering hints that maybe these were gametes of some kind, and formally this statement was correct. JL and Zinder had a filtrate, it had granules in it, and if they put it in a centrifuge and spun it down hard the filterable activity, the FA, could have this transforming activity. JL had it in his head, however, that this might have something to do with the L forms. Zinder was trying to struggle with it and hone in on exactly what was in the filtrate. They were getting there, because they were actually doing physical fractionation and some people, perhaps even Zinder, were remarking that maybe it was phage.

189 At the 1951 Cold Springs Harbor Symposium, JL presented these results on behalf of the whole group, which was again a hodgepodge of everything they had been working on for the last four years. Zinder followed that further and said that if it was phage, they should be able to grow it. That eventually is what materialized. They now had a situation where they could take a phage, grow it on one *Salmonella* strain, and the phage filtrate, by itself, would

transfer activity to a recipient strain and give this prototrophic progeny. This was a new phenomena and they gave it a new name—transduction. This became another very powerful tool for genetic analysis. Transduction has been found in numerous other species. So what was the "rat" about the tyrosine phenylalanine? It turns out they are very closely linked. The other markers are sort of scattered around the chromosome. It turns out that the size of DNA, which is packaged in a phage particle in transduction, is about 1 percent of the genome. So if you happen to have two markers that are within a segment that is 1 percent, they will go together and you get co-transduction of two separate markers. Co-transduction is also used as a tool: if you want to establish close linkage, show that they are transduced together.

232 Larry Morse was in the lab at the same time and he thought he would see if lambda could transduce. He set up some experiments and found the answer was generally no—with one outstanding exception, which was that if you took a galactose positive lysogenic strain and gave it a shot of ultraviolet light it activated the prophage, the prophage started multiplying, started producing many copies of itself, and what they then discovered was a very high frequency of transduction of the gal marker—but no other marker in *E. coli*. Gal and lambda are very closely linked on the chromosome. They now knew that the transducing particles were defective. The transducing particles made a little mistake in what piece of the chromosome they had integrated. Instead of being the intact lambda and nothing else, it was kind of a shift where they had a defective lambda and a piece of the gal that went along with it. That is a specialized transduction and it only works for a marker very closely linked to the prophage itself. In generalized transduction any piece of bacterial DNA at random can be packaged into an occasional phage particle. Thus, within a short period of time they discovered two new mechanisms of recombination.

272 The discussion moves to JL's work in immunogenetics. JL now had a new mechanism for genetic analysis which could be applied to *Salmonella*. At this point, they started looking through the serological factors and found a connection at the Center For Disease Control in Atlanta, which was the United States reference center for *Salmonella* infection work. The Center was particularly helpful and provided JL with all the re-agents he needed. They started looking at this mosaic structure of different serological types. JL found it easy to take any two *Salmonella* of different serology, grow phage on one and apply it to the other, select against the existing strain so you got rid of the unmodified bacteria, and under the influence of the transducing phage find exactly the new ones that you expected. So if you have somatic antigen *x and y*, and flagella antigen *a and b*, you start out with *x cum a*, and another strain *y cum b*, grow the phage on the latter, and you can get an *x cum b* very readily. You have to select against the *x cum a* with anti-a antiserum just to get rid of the majority of parental cells that are still there. JL notes that you almost always do this in bacterial genetics because the sex life is not that active and they do not need sexual reproduction for the most part to produce new progenies, so you have to somehow get rid of the existing types then see

what new ones are going to be present—which is quite routine in this kind of work. So you could essentially generate any serological type you wanted, whether it already existed or not.

309 Another biologically even more interesting phenomenon was there to be analyzed, this one with the help of Tetsuo Iino, a graduate student from Japan. The issue here is a phenomenon called phase variation. This has to do with there being two different antigenic phases of Salmonella bacteria in the flagella. JL gives an example of this phenomenon. In the mosaic descriptions of different Salmonella strains, JL notes, you write down the somatic antigen of each of the two alternative phases that go along with it, which are interconvertible, in that a cell flips from being what is called specific phage into so called group phase, and vise versa. But it always alternates between the same two alternatives, thus you cannot predict what the second phase is going to be from what the first phase was. You can predict what the second phase is going to be, but only if you know the history of that particular strain.

336 So what it looked like was two alternative states that the bacterium could be in and that the genetic potentiality was there for either or both, but that at any given moment it was expressing either one of the other. JL wanted to correlate that at a genetic level and see what he could find out about mechanism. He was able to do that and establish that there are two separate genes, one for the specific phase allele and one for the group phase allele. Thus if you start out with an I, you could, using different Salmonella strains, alter that to be a, b, c, d, e, f, g—any of the alternatives depending on the donor. He discusses some possible variations. You now have established two different genes—one controlling the specificity of the flagella when it is in the group state, and the other establishing the specificity of the flagella when it is in the non-specific state. JL ended up showing that there was an alternation of states that later on were then shown to be a DNA inversion. Mel Simon, JL notes, gets the most credit for a detailed examination of that phenomenon. So there is a specific enzyme that looks for certain sequences in the flanks of this DNA segment, and is able to cut the DNA and let it reseal in the opposite sense. This can go in one direction—and back again, back again, back again. This is what happens once every thousand divisions, and it is a way in which the bacteria can randomize what they expose to the outside world. They are not stuck with one overcoat, and if antibodies start developing against that overcoat they can go to the alternative one.

361 It has turned out to be a frequently used trick, and there must now be hundreds of examples of phase variation based either on DNA inversion or some other physical movement of a piece of DNA from one part of the chromosome to another part. It is an ancient trick that has been well learned and used in many other contexts. JL thinks it is its biological function for the bacteria. They can draw upon an archive of alternative specificities that has been selected for in history as being a good set of choices. But they do not expose their hand until they are forced to, and an antibody is present that selects against an existing strain, so they go to an alternative one. This was another study that came out of being able to start to use the tool

of transductional analysis. One final word about Tetsuo Iino: he successfully completed his dissertation, returned to Japan, and subsequently became a professor of genetics at Tokyo University. He had a long and distinguished career and much of his work was in the general area described above.

383 End of side.

Tape 4/Side 2

001 JL's work with Iino got them into the genetics of flagella and of motility in *Salmonella*, and that led into something else unexpected. One of the characteristic experiments would be to take the non-motile mutant, which might be one that was lacking both of the two loci previously mentioned—the group phase and the specific phase—or having a mutant that barred motility altogether, and then transducing motility from a competent motile strain into the non-motile one. This could easily be selected for by using a nutrient agar medium, but using very, very soft agar, so that motile cells could quite literally swim through it—actually at a rate of one or two millimeters an hour, which is an immense distance when compared to the bacterial size—and then leaving their progeny behind or accompanying them as they swim. They keep multiplying as they go, and you get a cloudy swarm, or a cloudy growth, through the bulk of the agar, if it is a straight forward transduction of motility. If you have a large inoculant of non-motile cells and just a few motile ones coming along—JL calls those initials—these would appear at the edge of the static growth as new swarms that would break out from the edge and then gradually that cloud would go through the entire medium.

035 You pick up strains that had migrated through the agar and they are very active, motile strains, and retain that characteristic later on. JL was looking at some of those plates in his lab when Bruce Stocker dropped in. The very first day Stocker arrived, he noticed some things on JL's plates that JL had overlooked. In addition to the swarms, there were little clusters of colonies they came to call trails, because they looked just as if something had been moving through the agar but left droppings behind. That indeed proved to be the case—it was a cell that had become motile but had left behind descendants that were non-motile, and eventually petered out to where there was no swarm, no permanently motilized culture derived from it. Stocker instantly reached the conclusion, which turned out to be a correct one in the end, that this was a form of transduction in which a gene had been transferred which was somehow impaired in its ability to replicate, but could confer the physiological property of motility on the cell that was carrying it. The net result was that at every cell division this non-reproducing gene would continue to function, confer motility on its cell, but the other daughter not receiving it would very soon lose motility and remain stationary and form a colony around the place where it was initiated.

068 For awhile JL was pretty skeptical about this very simple minded but, as we now know, correct interpretation. Both he and Stocker embarked on a substantial and laborious series of studies in which they followed the fate of motility cell by cell directly under the microscope. That meant finding a motile initial out of a large pot of cells exposed to the transducing phage, which was not as hard as it sounds. What Stocker and JL did was pick up this really fast moving cell and put it into a fresh droplet of medium, waiting until that cell divided, taking the two progeny cells, watching to see if they were motile, then watching to see what their progeny were like. JL has charts where this goes on for twenty or thirty generations. JL notes that if he had allowed twenty to thirty generations of growth exponentially, it would occupy the universe. What they did was take one cell, the one that was still motile, and see if it retained motility. When a cell was no longer motile, it was essentially discarded.

089 Stocker turned out to be substantially correct. There was a little residual motility—sometimes a daughter would be feebly motile. They thought it was because it still had flagella, although it could not make new ones, and that might even be passed on for one more generation. These very quickly petered out and after two or three generations the non-motile progeny, the ones that by hypothesis were not carrying the non-reproducing gene, would become non-motile. It was an outstanding example of where you could see gene function expressed visibly under the microscope on a single cell. This is a kind of model, JL notes, for asymmetric cell division, and in a paper he wrote he explored several examples where differentiation takes this course—where one product of cell division remains a stem cell and the other product becomes a differentiated cell. He gives an example of this. What this did was open up a general framework of looking at what JL calls linear versus exponential inheritance.

112 JL turns to another theme which has less to do with the use of the recombinational methodology but addresses questions that had come up in the course of broader considerations of bacterial genetics. One of these has to do with the actual origin of drug resistant and phage resistant mutants. These are adaptive mutations, in the sense that once they happen in particular environments they are very good for the survival of the cells that are carrying them. That is particularly important for drug resistance. You put a culture of *E. coli* in the presence of streptomycin, for example, and those organisms are pretty unhappy about having to live through it. But if one of them should become a resistant mutant and survive, then they can be inured to that environmental hazard. But the question that had been kicking around in microbiology for many years was: how can you know whether these mutations would be happening anyhow—or is it possible that they are actually induced by this environmental change? Speaking loosely that is sometimes called a Lamarckian interpretation, where you think that the environment is causing the mutation rather than just selecting for it.

134 This matter, JL says, had been addressed by Luria and Delbrück back in 1943 with a statistical distribution of the number of mutants in parallel cultures derived from small inocula, which turned out to be highly skewed—the so called "jackpot phenomenon"—and has been and remains a strong argument for the prior occurrence of these mutations. The skewness is easily interpreted in terms of spontaneous occurrence. Thinking very simply, if you have a small inoculum, there are so few cells that the odds of a mutation occurring in the first direction are very low. But that is where you have a jackpot, because if by any chance that rare event does take place, then you have all the rest of the growth time, and all the rest of the growth from that inoculum, to expand that clone, and you will then get a very, very large clone. As the culture grows towards saturation then there are many, many more cells, and the likelihood of at least one of them being a mutant is greatly increased—but it will not have very many progeny as a result. What you get, then, is what has been called the Luria-Delbrück distribution, which is the calculated estimate of the skewness of the number of mutants in a series of parallel cultures. It is hard to get a robust statistical test for exact compliance with the distribution just because it is so skewed, but there are a lot of experimental data that are in accord with it.

157 The alternative hypothesis is that the environment is inducing the mutation. Unless there are uncontrolled extraneous variables, and one really does have to worry about that, you should then get essentially a mean tendency, a Gaussian distribution of the number of mutants actually induced. If each culture resembles the next one then they should have the same statistical expectation of the number of mutants present. That was the Luria-Delbrück test. It was not a constructive test, however, in that it did not directly prove the prior occurrence. Rather it just said whatever the mechanism that results in the production of mutants, it is going to give you a skewed distribution. It is, JL notes, not a very robust proof.

172 It occurred to JL at some point that there might be another way to approach that problem. It was one that also would address a technical problem JL was having about how to deal with manipulations that went past picking one colony at a time. If you wanted to test a colony for its growth factor requirements, which is one of the most usual things, or to see if it is sensitive to a phage or to an antibiotic, the usual procedure is to take a colony, make a loop-full of suspended cells with it, and then put it onto a new plate to see how it grows under the particular conditions of that plate. There had been some effort to try and get around this. Novick and Szilard had invented a little device which had a lot of steel hairs on it that would act as an inoculating needle, so in a sense you would have an inoculum from an entire plateful at once, that you could then put on a fresh medium—and that way you could get a hundred colonies transferred all at one time. It was pretty cumbersome, however, and does not work as well as it might, because the needles have to be lined up just right.

187 It occurred to JL one day that a proxy for that machine would be velvet, so you have cloth with all the bristles on it, and you would have a hundred points to the inch instead of one or

two. This could be used for the purpose of testing large numbers of colonies from one to another. They called this replica plating. Today it is one of the classical methods in microbiology. Velvet, JL notes, was used because it is the only fabric that has a pile where you have bristles sticking out but space in between that could absorb extraneous moisture or pick up little bits of the colony growth. He later learned that people like Nick Visconti had been trying similar experiments using filter paper, and it just did not work. You need the bristle structure of the velvet or velveteen to make it work. Bob Burris sent JL what he thinks might be some of the very first samples of velvet which they used for these experiments, and "it worked like a charm." Besides being a technical help in handling a lot of cultures, it then occurred to JL that they could solve the problem of prior occurrence of the mutants in the following way. Suppose, JL notes, that he grows a plateful of bacteria from a small inoculum. It starts out with a few thousand cells, and by the time the plate is covered there may be a billion cells. If this is streptomycin resistant there are likely to be two or three clones of streptomycin resistant cells buried somewhere in the plate. Classically the only way to find them would be to pour streptomycin on the plate and see what would grow up; but that would nix the question you were asking, which was : Was the streptomycin inducing the mutant? How can you tell whether the mutant was there before you add the streptomycin?

216 JL's first test was to take a replica plate, make three copies, and add streptomycin to each of them. If the clone came up in the same place, then the only reasonable explanation was that it was already there on the source original plate. That worked. Then it occurred to him that you could go even further and they could actually isolate the mutant. What they did was in addition to making a copy of the streptomycin plate, they made a copy to a plate without streptomycin. They knew where the clone was hiding, from the copy with the streptomycin. So they put the plates in register, carefully marked what the geography was, and picked out the growth in the area of the non-streptomycin plate, matching the place where the colony grew on the streptomycin plate. It was not too difficult to pick out a volume of growth which was about 1 percent of the total growth on the plate. It is hard to get better than that, but a one in a hundred resolution you could do. By theory if you did that you would enrich the frequency of resistance mutants by a factor of a hundred—because JL would have gotten all of the resistant clone that was left, and he would have excluded 99 percent of the sensitive cells which he wasn't picking. That was testable and that worked.

236 That being the case, what JL could then do was to dilute that culture that he knew had a hundred times higher frequency of streptomycin resistance for another plating down to the point where there were only one or two streptomycin resistant clones. He found out where they were, and enriched them by another hundred fold. You do this three or four times and you get a pure culture of streptomycin resistant organisms, and yet the culture had never been exposed to streptomycin—it was only the sibling plate that had done so. They called this sib selection, to match what goes on in other areas of genetics. So here were several things

wrapped up at once. It was a very simple experiment with very simple material which solved a lot of technical problems, and also went very deeply into the issue of the preadaptive occurrence of the mutations. There has been some flurry about this recently, and of course this works for a very narrowly constrained set of occurrences—that is to say mutations that result in resistance or an environmental change which is very abrupt, which is all or none in its killing, like phage resistance or streptomycin resistance. It does not prove that every other adaptive mutation is also pre-occurrent, pre-adaptive, and some people have had the idea that if you take bugs that cannot use lactose, leave them starving but alive in the presence of lactose, that under those conditions you nudge them to want to become lactose positive—they're still alive so their wants might be satisfied, and that you might under those conditions have a new form of environmentally induced mutation. There has been a huge fuss about that for the last several years, and JL would be the first to admit his replica plating experiment does not really bear on those conclusions, but in the end that has turned out to be so full of artifacts that very few people will still concur.

260 Several people have asked JL about his wife Esther's role in this particular experiment. Esther, who was a superb experimentalist, was a co-author on the paper relating to replica plating. Esther received a Ph.D. from the University of Wisconsin. For her dissertation topic she took on something close to R. A. Brink's interest, which was might there be genes affecting mutability in *E. coli*? The system she looked at was reversions from lac - to lac +, which are easily detected because if you grow your *E. coli* on an indicator medium with lactose as the principal but not the only carbon source, the lac - cells that you start with make reasonably constrained colonies, but lac + mutants, that can use a sugar, grow much better and emerge as papillae, literal button-like outgrowths in the colony. You can actually more or less readily count them colony by colony. So strains of different mutability would have different numbers of papillae per colony. She tried finding genetic factors that would influence mutability. In the end, she did not find such factors partly, JL thinks, because they were all imbued with looking at this from the reverse end and they were, in effect, looking for genes that would reduce mutability. So it's rather unlikely that they would get, by further mutation, strains that would be more faithful—less mutable than the wild type—but they did not know any of that at the time. That whole framework of thinking about mutation did not then exist. So Esther actually did find things that had different papillation numbers, but they ended up being either second mutations at the lac locus, which would then take a double mutant, which doesn't happen, to make a papillae, *or* other modifiers of lactose metabolism that so slowed them up that they did not emerge very well. So it ended up giving a negative answer, but it was just ahead of its time. The same system has been used subsequently to identify factors that will in fact enhance mutability, but she did not encounter that.

301 To meet all the formalities, Esther was registered as a student. Brink was listed as her supervisor, but she did her research with JL in his laboratory. After receiving her Ph. D., Esther remained in JL's lab as a research associate through the remainder of their stay in

Madison. Esther served more or less as JL's "chief operating officer" and attended to many of the details in the lab—a function, JL notes, she performed extremely well. JL's lab, which was small, was usually staffed with a research assistant, a couple of lab technicians, and two to three graduate students—somewhere in the vicinity of six to eight people.

312 The discussion turns to some of JL's graduate students. Norton Zinder was JL's first graduate student and was, by all accounts, outstanding. JL found his graduate students basically through word of mouth. In Norton Zinder's case, he had worked a little with Francis Ryan. Zinder turned to JL when he was denied admission to medical school.

321 Larry Morse also served as a graduate student under JL. Morse, who had been working at Oak Ridge, sought out JL. Morse did his work on galactose transduction, and subsequently took a job at the University of Colorado-Denver. He ended up being a dean for research and retired a few years ago. He has continued working on other galactose metabolizing systems, which is more physiological than genetic work.

330 S. G. Bradley was another of JL's graduate students. Bradley worked on looking at recombination in still another microbial group called *Streptomyces*. *Streptomyces* were important in many ways, but especially because they were the source for new antibiotics—starting with Streptomycin and moving on to numerous others. Thus learning about their genetics would be of practical importance. The gist of Bradley's dissertation was proving heterokaryosis, which JL discusses. In the course of the work, JL and Bradley began suspecting that there was some gene silencing going on, in that there were genes being carried along that were not being expressed over many generations. This phenomenon has been noted by others in other *Streptomyces,* and also in other gram positive organisms where cell fusion has taken place and you have mixtures of nuclei in one cell. Even today this is not very well understood. It is one of the reasons JL wants to get back to cell fusion in *E. coli*, where if these phenomena occurred we would be in much better shape doing a detailed genetic analysis of it. JL notes that we are still at a very early stage, comparably speaking, in that we do not know as much about how to handle the genetics of *Streptomyces* or of other gram positives compared to *E. coli*. Bradley continued his research at, JL believes, Old Dominion in Virginia, and also has become a dean. He is at present CEO of a biotech institute in Baltimore.

377 Concerning what research a graduate student of JL works on when he begins his training, JL notes that if a graduate student approached him with a carefully crafted proposal, such as JL presented to Ed Tatum, JL would be most eager to at least negotiate the nature of the research with the student. This has basically never happened. Generally, graduate students need a basic introduction to the area of research. What JL has typically done is present the student with a problem that had been bothering JL or his lab for some time. The student is then assigned to work on that problem until he finds something he finds compelling, or until

he becomes sophisticated enough to present an alternative research proposal. Almost without exception the first happens. Then the student has something he has discovered and can make his own. This is exactly what happened with Norton Zinder. It is a developmental process for the graduate student, in that they start out with an opportunity to learn the field, learn the methodology and get some actual experience doing research under fairly close supervision. Then they become more and more independent as they begin to grab hold of a problem they can make their own. This is what JL strives for. He wants that student to know that he knows more about the problem he is studying than any other person in the world.

390 David Skaar was a post-doc who came from T. M. Sonneborn's laboratory, where he had worked on paramecium research. While in JL's lab, he found an accessory mutability factor in *E. coli*. This was a mutation that enhanced mutability. Skaar also found that if you cultivate *E. coli* in the soft agar and you push it for maximum motility, it drops the F factor on the way. Thus it becomes a very handy way of getting F minus variants. The process is not fully understood, and JL discusses why this might occur. Skaar did some work, also on the F factor, that one could treat cells with periodate, which is an oxidizing agent that goes after polysaccharide.

408 End of side. End of tape.

Tape 5/Side 1

001 JL continues his discussion of David Skaar's research. One of Skaar's findings was that one could inactivate the F+ phenotype—that is, the ability to conjugate with F- cells in *E. coli* by treating them with periodate. What Skaar's research suggested was that there was a carbohydrate marker that is necessary for that interaction. The chemistry of that interaction, JL notes, has not really been followed up in detail and is worth doing. Skaar then went out to Wyoming, but JL has lost touch with him since that time.

018 Aleck Bernstein was a post doc who came to JL's lab with some experience in *Salmonella* serotyping. He did not stay long, but during his stay he assisted in work on serotypic variation in *Salmonella*. He also found something quite curious. As JL noted earlier, there are two phases of flagella—the group and the specific kinds. Bernstein found that quite consistently the one we call group makes its cells agglutinable with acridine dyes, and vice versa. There is some general chemical difference in the structure of the flagellar protein at one end of the locus. There has been a lot more work done on the chemistry of flagellae since then, but JL is not aware if anyone has noticed this particular observation. While in Madison Bernstein met Helen Byers, another graduate student in JL's laboratory, and they married. Bernstein found a job at the University of Wisconsin-Milwaukee, or perhaps Marquette, and remained there for a number of years.

051 Bob Wright was a post doc who came to JL's lab after he had a visit from Professor Sydney Rubbo, who was head of the Bacteriology Department at the University of Melbourne. This would be around 1954. Rubbo had approached JL because he wanted a sabbatical experience. He was a very progressive minded but old line microbiologist who wanted to learn microbial genetics. Getting back to Bob Wright, he was in JL's lab as a graduate student, having been highly recommended by Sydney Rubbo. Wright was a very bright young man deeply committed to science. Rubbo was interested in yeast and Wright had a similar interest. The problem Wright addressed was very early work on what would now be called cytoplasmic hybrids—cybrids—in yeast. There is a stage in yeast conjugation when two cells have formed a conjugation tube and they mix cytoplasm, but where the cells are still very much intact and can be separated. This is a way of getting a clone of one haploid strain of yeast that has been contaminated with the cytoplasm of a completely different strain. You can put genetic markers in the nucleus and you have no trouble at all making sure what happened. JL briefly discusses some other work on petite variants that Wright engaged in. He goes on to note that Wright did crosses where he showed that the inheritance of the normal versus petite variant did not segregate along with the chromosomes, but that did not prove it was in the cytoplasm. If you contaminated the cytoplasm of one yeast clone with the cytoplasm of another, then you restored the normal mitochondrial phenotype. This was pretty much the nature of Wright's work in JL's lab. JL goes on to note that Wright was visiting a friend in the winter of 1956 and was involved in a serious automobile accident that left him significantly impaired. He returned to Australia and later committed suicide.

139 The discussion turns to another of JL's graduate students, Boris Rotman. Rotman was a Chilean who JL thinks might have originally been in chemistry at Wisconsin. He worked with Henry Lardy for awhile at the Enzyme Institute, where he did some brilliant work on measuring enzyme production in single bacterial cells. He turned up again at Stanford, where he was an early member of the Syntex Institute for Molecular Biology. He ended up as a professor at Brown University, which is where he has been ever since.

156 Tom Nelson, who was very much interested in kinetics, was a post doc who had completed his doctoral degree under Francis Ryan. Nelson wanted to do what Dulbrück was chiding JL for not doing, which was to study the kinetic aspects of the yield of recombinance as a function of the concentration of the parental cells, and so forth. The way they went about it, there were no surprises. Nelson first got a job at the University of Wisconsin-Milwaukee, then at Eli Lilly & Company, where he spent most of his professional career working on the development of antibiotic producing strains.

175 The discussion turns to the two leaves JL took while on the Wisconsin faculty. The first leave was in 1950 to go to Berkeley for the summer. Roger Stanier had been the moving figure relating to this. JL had never been to California before, which had become a vital place in microbiology. In retrospect JL thinks that perhaps they were trying JL out for a

possible future move. JL enjoyed the summer, and California, very much. He and Esther lived in the hills and it planted a seed in his mind regarding moving there someday. JL got two research programs underway that summer. One was with Roger Stanier and it showed that ultraviolet light prevented enzyme induction and stopped it dead in its tracks, yet allowed the expression of the set of enzymes he was interested in, which was oxidative metabolism of organic molecule substrates. That made it much easier to do kinetics of the rate of development of new enzymes. The second line of work he engaged in was with maltose metabolism, which was discussed earlier. JL notes that his summer in California coincided with the beginnings of the Korean war and occurred at the height of McCartyism, so a lot was going on at the time.

215 When JL returned from Berkeley, he suggested to the UW administration that it might be interested in hiring Stanier. This came about because in California at the time there had been a lot of reaction about the imposition of the loyalty oath. The oath itself, as JL recalls, was not so awful. What was bad, however, was who it was demanded of. The implication was that if you were a faculty member of the university, you had to redouble your proof that you were loyal to the United States. There were some number of faculty who simply refused to do it. Stanier signed the oath, but said he would resign if other members of the faculty were fired without there being a proper tenure proceeding for it. Other members were fired, and Stanier submitted his resignation to be effective at the end of 1950. Thus JL thought there might be a good chance for Wisconsin to pick up a very notable microbial biochemist. JL believes the problem was resolved by Stanier solving his California problem.

247 In terms of McCarthyism and the University of Wisconsin, JL notes that Joe McCarthy was very shrewd, in that he was very careful about Wisconsin. When he did start picking on Wisconsin is when he started getting into serious trouble. There were, JL recalls, any number of petitions and campaigns and JL stood up for civil liberties, but he took a somewhat maverick position on this matter, in that he thought it was anybody's constitutional privilege to invoke the Fifth Amendment and he did not think it was such a good idea to hide evidence of past relationships with the party. JL believes that if everybody had banded together and acknowledged their membership, McCarthy would have been laughed out of court. That never happened, and JL thinks one of the reasons it did not was because the far left did not want it to happen, and the reason they did not was because they liked nothing better than to keep McCarthyism an issue and something to be feared. During this period the far left and the far right, JL notes, fed off each other. The faculty was critical all along, and JL is sure he signed any number of petitions regarding McCarthyism. Still, JL had some reservations in that he thought Communism was a threat. JL says he was too young to become involved in any far left affiliation, but his instincts were against communism as he did not like authoritarian regimes of any stripe.

301 JL returns to a discussion of his research, focusing on protoplasts, L forms, and penicillin. Penicillin, he notes, has had a checkered history in the past he has been describing. It enters this narrative in a couple of ways, most importantly because of the penicillin method for isolating auxotrophs. This was founded on the empirical observation that non-growing cells were barely affected by penicillin, whereas growing cells were rapidly killed—in fact, they literally dissolve if you try growing them in the presence of this antibiotic. Penicillin has historically probably been the most important antibiotic we have ever had, so trying to understand its mode of action was an interesting challenge. This also comes up in rather fitful efforts to get at the genetics of penicillin resistance. In gram negative bacteria it is rather more complicated; in gram positives you can get sharp increases of resistance fairly readily with mutational changes. With gram negatives, like *E. coli*, there are plasmids that carry penicillinase genes, which are genes for an enzyme that will destroy penicillin. You do not get these by mutation, rather you get these by infection or contamination from plasmid particles. These are the general reasons to be interested in penicillin.

318 JL had been reading some papers by Weibull in which he talked about being able to sustain protoplasts in *Bacillus subtilis*, a gram positive, which had been produced with lysozyme, if you keep them in high osmotic media—that is media with two moleasucrose, or other high solute concentrations. In effect, this balances out the osmotic pressure of the inside of the bacteria, and when its wall has been dissolved it does not pop and lyse. It occurred to JL that the previous observations that penicillin only attacked growing cells and that you got lysis as a result could be tied together if penicillin attacked the wall. This would be of little damage if the cell was static, but a broken wall would be disastrous if the cell was growing and expanding against it. One Saturday afternoon JL thought he would try an analogue of Weibull's experiment of *Bacillus subtilis* with *E. coli*, but more importantly instead of using an enzyme lysozyme, whose action we do know is directed at the cell wall, he would use penicillin instead—and use this as a test as to whether the cell wall is the target. The experiment worked within the first hour. JL went into a much more systematic study of it, published a brief note in the proceedings—that this was an argument that the cell wall growth was the target of penicillin—and this coincided with a couple of other people's work, especially Jack Strominger's.

344 Looking at these globular forms, they seemed to reproduce pretty much by budding—certainly not by the usual form of fission. These were little balloons that would grow and grow, and every now and then there might be an out-pouching of another little balloon. They could be quite large, in that they could be 20-30 microns in diameter, which is immense compared to *E. coli*. Then it struck JL that these were the L forms that others had been talking about—and from there everything just seemed to all come together. These bizarre L-forms were wall defective mutants or wall defective because of external agents, which might be lysozyme. Phage secrete lysozyme and bacteria have their own wall lytic enzymes, so they might be generated under those conditions, or, as JL then found, also by

having mutations that are on the pathway of wall synthesis—and a particular one that requires a wall component called diaminopimelic acid. These mutants would lyse if you tried growing them without diaminopimelic acid, but again if you put them in hypertonic medium—high sucrose medium—they would form these little globules and sustain themselves like the protoplasts or L-forms that JL was getting with penicillin. Everything all came together. So these were not life cycles or gametes or whatever. They were soft forms that had defective walls. JL notes he was called up short on one point, in that when others did more detailed chemical studies on what JL called protoplasts, they found they really did have almost everything that is present in normal walls. They were not devoid of walls; they had greatly weakened walls. So they said let's not call these protoplasts. JL agreed, and they called them spheroplasts. Since then they have been used for various purposes, but mostly to understand what happens in natural history.

368 There are still some strange things about L-forms. You can sometimes find streptococcal infections in joints where the penicillin being administered is not effectively curing the patient and there seems little doubt that the so-called L-form type of growth is what is responsible. Since they do not have enough of a wall to matter, they are not inhibited by penicillin. JL notes one does not always need hypertonic media to preserve them, in that other medium constituents might do it. This line of research helped clear up a mystery that had been befogging bacteriology for a long time. There is still a lot we do not know about them. To this day JL is trying to use them to make cells fuse. He conducted these experiments in 1956, '57 and '58 with Jackie St. Clair serving as his technical assistant. He has recently come back to this problem and says there must be a way to make this work!

383 Spheroplasts are sometimes more amenable to transformation with DNA, so there have been some genetic uses of this category of things, but they end up mostly clearing up a curiosity that had been misinterpreted by others and put away.

388 End of side.

Tape 5/Side 2

001 There are two science related issues that were initialized during JL's career at Wisconsin. The first has to do with the mechanism of antibody formation and JL's Fulbright trip to Melbourne, Australia. This took place in August through early November, 1957. JL and his wife, Esther, were both fellows of the Fulbright Foundation. Sydney Rubbo from Melbourne had orchestrated the arrangement. When it came to a choice of where to work, JL thought he could learn the most by going into MacFarlane Burnet's laboratory. Burnet had been a renowned early worker in bacteriaphage. He tends to be overlooked because of Luria and Delbrück but he really did provide, after D'herelle, some of the most important foundations for quantitative studies with bacteriaphage. But he then moved in somewhat similar fashion

into the influenza virus, and he had recently discovered a recombinational mechanism in the flu virus that intrigued JL. For his part, JL wanted to learn more about it and learn how to handle flu, and perhaps pick up some work along those lines when he returned to Madison, particularly if Wisconsin was going to be branching out in other directions with a new department. That was JL's premise for going down there.

038 When JL reached Melbourne, he learned that Burnet was at the tail end of his work on flu. Burnet put JL into a lab and he went through the basic exercises of how one handles flu, how one does a recombination experiment, and a few genetic systems that JL might be able to carry on further—methods of selection for influenza variants, for example. But the fact is Burnet was turning his attention to antibody formation, and had just reformulated a proposal that had been floated by Niels Jerne—we are talking about Burnet, a future Nobel prize winner and Jerne, another future Nobel winner—so this was leading edge stuff. That had reopened the question, very closely related to what JL had been talking about earlier in connection with induced resistance in bacteria: How does an antigen induce the formation of a new antibody? The prevalent theory, which had been crystallized most sharply by Linus Pauling, is what JL later called an instructionlist model, which is shorthand for saying that the antigen instructs the on-coming would be antibody molecule what shape to adopt.

071 The alternative in principle could be, just as with bacterial variants, that maybe antibody forming cells beforehand are diversifying all over the place, and maybe the only role of the antigen is then to select out what diversity nature had already provided. Oddly enough, in 1954 or 1955, JL had put that hypothesis next to his discussion of enzyme induction, but said no, it isn't going to work for antibody formation because there are too many kinds of antibodies. For selection to be feasible, you have to have no more kinds of antibodies than there are kinds of cells to start with. JL was led to believe that there was an infinity—that for any antigen you care to mention you could always find an antibody. JL says he had not really thought through the numbers on this point. So he walked right up to this wonderful new theory, then turned his back on it. It was Burnet who walked up to it again and did not turn his back on it. The provocation meanwhile was Niels Jerne, who had floated a paper on a selective theory, but it "was wacky" because his unit of selection was a globulin molecule. He said nature provides a wide diversity of globulin molecules. Prefigured beforehand the antigen reacts with this immunoglobulin, and then *somehow* this reproduces itself. JL could not swallow the "somehow," and he wrote to him and told him so. Gerne later told JL he was the only one who had responded to his reprint.

101 It all hinged, basically, on how many kinds of antibodies there are. So JL walked into Burnet's office and Burnet told him about his idea and asked for JL's opinion. JL said he thought about it and decided it was not going to work, because there is an infinity of antibodies and there is not an infinity of cells. At that point Burnet backed up a bit and said Jerne could not be right, because it has to be a self reproducing unit. The only one they were

certain of was the intact cell. Perhaps there were a lot of diversified plasmids, and perhaps every cell has a few thousand of those that would multiply the opportunities, and then the antigen might select one plasmid for further replication—that in principle might work—but there was no particular evidence for it at the time. But JL does not think Burnet was on to that. His intuition was the cell, and when JL challenged this, Burnet said, in effect, "Says who?" about how many antibodies. To which JL, upon reflection, responded by saying that Burnet was, indeed, right.

121 JL said as he stopped to think about it, he was not sure that it had been proven that there were more than about a thousand antibodies all together. To prove it, you would have to have a panel of 1,000 antigens and 1,000 antibodies, and show that each one reacted specifically only with the other one. The fact that you get specific anti-flu when you inoculate with flu, and specific anti-strep when you inoculate with strep, does not prove a point, because until you have tested it one of these anti-streps might be the same as one of those anti-flu. But that thought had not been given in the whole history of immunology. JL thus became an enthusiastic supporter, and the job he did was translate this very good biological intuition, put it into molecular genetic lingo, and retranslate it into terms of what DNA sequences are, what protein sequences are, what the diversification could consist of—and produce what you might call a much sharper version of Burnet's theory.

141 In the meantime a man called Talmadge, from the University of Colorado, was coming up with some similar notions as well. Thus JL notes that he does not claim primary authorship on clonal selection, having looked at it and turned his back on it. However he had given it enough thought, conscious and unconscious, that he very quickly came to a much more precise formulation. JL believes that has been generally recognized. He wrote a paper for *Science Magazine* on genes and antibodies in which he put together a version of the theory of antibody formation that had all the necessary ingredients laid out and allowed the different points he laid out to be supported or attacked one at a time. What misled JL was his belief in Occam's razor, which is the philosophical principal that you do not multiply entities without cause. JL tried making an economical theory of antibody formation using no more different cell types than the data absolutely demanded, and of course they did not have the data then, but the number of cell types is what nature says, not what a philosophical simplicity would say. JL says he now realizes that there are some aspects of evolutionary diversification that defy Occam's razor, that nature sometimes multiplies entities without obvious reason.

178 JL notes that he did one little bit of experimental work while he was in Australia with Gus Nossal, who was a young post-doc Burnet had assigned JL to work with. JL says he brought the *Salmonella* motility lore along with him, in this case turning it around and using the bacteria of known composition to diagnose what kind of antibody a single plasma cell was making. One of the postulates of the clonal selection theory would be that the antibody

present in the serum is the aggregate of what all of the immune cells are pouring into it—but that a single host cell is only making one kind of antibody. Another cell might be making a different antibody, JL notes, so in the serum is the mixture, but cell by cell they ought to be segregated out. They tested this hypothesis in rats by taking two different *Salmonella* strains, immunizing rats against them, taking out plasma cells from those immunized rats, putting them into little droplets of fluid, and then injecting into those same droplets either *Salmonella* 1or *Salmonella* 2. Most of the cells did not react to either, which was no surprise. The ones that did react, either reacted with 1 or with 2—but not with both. That was support for the clonal selection story. It did not really prove it, because they were not clones of cells—they did not know how to do that in those days—instead they were only looking at cells as they finally arrived at the end of their differentiation. The work only started while JL was there. Gus Nossal finished it up. They exchanged a lot of notes and papers, finally publishing it as a note in *Nature*. This was JL's one and only published report in experimental immunology. Nossal followed up on the work and indeed built his career on it. Nossal succeeded Burnet as director of the Institute, but not until after JL had tried to recruit him at Stanford. What happened was Nossal had come to Stanford for a year or two, but Burnet lured him back by promising him the directorship when he retired. Now retired, Nossal ranks as Australia's outstanding biomedical scientist. He currently serves as president of the Australian Academy of Sciences, which he is trying to build into an important policy forming organization.

224 Another interest of JL's has to do with NASA. This includes the space program, the search for life on other planets, and the like. This came about as another outcome both of how history was unfolding, and of JL's trip to Australia—or rather his trip home from Australia. On October 6, 1957, while JL was still in Melbourne, the Soviet Union launched Sputnik. It created a sensation in Australia, because due to the orbiting pattern of Sputnik people living in Australia were able to view it on its first night. It was right there, so there was a lot of talk about its implications. A month later, on his way home, JL stopped in Calcutta where he had been invited by J. B. S. Haldane to spend a week. Haldane, who had helped JL develop the background for the statistical analysis of JL's data on linkage mapping, was at the Indian Statistical Institute. JL knew he was a confirmed communist, even though he had broken with the party over Lysenko. JL could believe he was a radical alternativist. Haldane had left England earlier in 1957 under the slogan that he wanted to leave a country under American occupation, but the real fact of the matter is the professorial appointment he had been hoping to get did not materialize, and he had alternative arrangements in India.

260 JL and his wife Esther were met at the airport in Calcutta and brought into town. There were several parades in progress, because it was the night of an eclipse. They soon arrived at a palace, the Indian Statistical Institute, which was where Haldane was living. As they prepared for dinner, Haldane remarked that this was the 40th anniversary of the October Revolution. At dinner Haldane was gloating about the Soviet success with Sputnik, and he

commented that maybe even more spectacular things would happen later that evening. He then remarked, in jest, "what if they planted a red star on the moon?" The discussion then turned to whether or not you would be able to see a thermonuclear device if it was exploded on the moon, and they determined that indeed you would be able to. At a point in the conversation they both began wondering what the world was coming to, in that this competition between the superpowers might end up in a destructive exhibition just to show who is first. It left JL with a determination to try and see what was happening when it came to putting science in the space program. He realized that the reaction to Sputnik ought to be to produce good, solid science, and not just phoney demonstrations. JL notes that he checked later, and indeed there was a project to plant a star on the moon.

309 JL started a science policy campaign, which was his first political campaign. He wrote a couple of memoranda pointing out the opportunities that space exploration held for biological inquiry, and deploring the possibility that there would be missions planned either for the moon or the planets without thought to contamination—be it radioactive, physical, chemical, or biological—and that some scientific study committees should be formed to explore those possibilities and recommend a sensible program to the president. This caught on and got to Detlef Bronk, who was the head of the National Academy of Sciences and later president of Rockefeller University. It got to Fred Seitz, who was chairman of the policy committee at the National Academy and was Bronk's successor as president of Rockefeller University. Both Bronk and Seitz dealt with it very seriously. JL notes that in 1957 he had just been elected a member of the National Academy, which gave him the standing to raise this kind of issue. The committees were set up and JL was asked to join some of them. JL promoted planetary quarantine as the first step. This became institutionalized, and JL was subsequently challenged to do something constructive as well as critical. Thus he was basically offered a chance to enter into preparing experimental missions for NASA, which occurred later during his transition from Wisconsin to Stanford, and it helped him set up a very significant instrumentation laboratory at Stanford with NASA funding. For twenty years JL was closely tied into it, and ended up being on the Viking Lander bio-instrument team. JL saw his job as trying to see that sensible experiments were being designed and planned with sensible objectives. At one point he wrote a letter to Vice-President Johnson, who was then chairing the National Space Council, relating to our sending a manned mission to the moon. JL noted that we should show how much smarter we were, both policy wise and technically wise, by sending automated devices to Mars. The drumbeats, however, were to send man into space, which, of course, is what ended up happening.

351 In terms of his interest in, and article concerning, moondust, JL notes that it seemed likely the moon would be a much earlier target—which indeed it was. JL was invited to attend a symposium organized by AAAS early in 1958, where he met Dr. Dean Cowie, who was a biophysicist at the Carnegie Institution. They discussed what one might find on the moon. JL was not as concerned about contaminating the moon, which he viewed as self-sterilizing,

as he was Mars. He thought the moon might have preserved primitive infall—that is everything that comes in as meteorites and comets and gets burned up in the earth's atmosphere. JL says that neither he nor Cowie were thinking too clearly about what would happen next, which was that somehow this would end up on the moon intact. The flaw is that the moon has been reworked by successive collisions—by new craters, new meteors—so its surface is much more weathered by meteoritic impact than is the earth's, which is weathered by the atmosphere but has not had as much damage done to it by infall. There were people besides JL who were calculating that there might be a very fine dust on the surface of the moon that was as much as a kilometer deep, and that there was a danger that any vessel landing on the moon would go "clunk" and be smothered through this very loose alluvium. Some of the premises were right, and the innovation as it relates to life is that maybe life did not begin on earth, in the sense that organic matter is being manufactured throughout the universe on a very large scale, and the precursors for the origin of life might in fact be in the comets and meteorites and things of that sort. That is what JL was discussing in his article about moondust, or meteoritic in fall. It is worth looking into, but you are not going to see much organic matter at this stage because of succeeding impacts volatilizing most of what was there before. There may be some, he notes, but there may be even less than is on the earth. This is the beginning of the story which took place while JL was at Wisconsin.

387 End of side. End of tape. End of interview session.

Third Interview Session (October 1, 1998): Tapes 6-7

Tape 6/Side 1

001 The session begins with a discussion of JL's relationship in Madison with Carl Sagan. JL believes he met Carl Sagan through Lynn Sagan, who was a graduate student in the Zoology Department working with Walter Plaut on her dissertation. At some point JL met Carl Sagan socially, probably in 1957. When the time came for JL to put together a committee to start exploring the issues of planetary quarantine and the establishment of a biological basis for investigations using spacecraft, it occurred to him that despite his youth there were few astronomers who could speak biology as well as Sagan. JL essentially introduced Sagan, who was doing his doctoral work with Kuiper at the University of Chicago, to NASA. JL describes Sagan as bright, articulate, eager and energetic, as someone capable of imaginative and critical judgments. Sagan proved helpful in getting JL's committee underway and provided authentic astronomical verisimilitude to the other kinds of things they were arguing about. There were not that many astronomers interested in planetary astronomy in those days, being drawn instead to the study of stars and galaxies and the like. Besides, there was not much information available at the time about planets. More was known, relatively speaking, about the composition of the sun and stars. JL continued seeing a good deal of

Sagan after his move to Stanford in February of 1959. During all of 1958 JL was very busy with the academy-based committees on space travel, with Carl Sagan playing an active role as well.

087 The discussion moves to James Watson, the co-discoverer of the structure of DNA with Francis Crick. During JL's years in Madison, Watson occasionally attended meetings of the so called Midwest phage group Leo Szilard had organized. The group had two purposes: one was Szilard's own education; and the other was a means of getting together people who were at the cutting edge of this work, who those days were mostly in the Midwest. The group included Luria, Sonneborn, Spiegelman, Novick and Szilard in Chicago, Benzer at Purdue, and the Madison group. Various group members met from time to time in Chicago or Madison or some other city in the Midwest. Watson showed up at a couple of these meetings as one of Lurie's graduate students. JL describes Watson as a very "lanky fellow"—then even more than now. He had just changed his interest. As an undergraduate at the University of Chicago, JL believes him as an avid bird watcher primarily interested in birds. His work with Luria altered his direction, pointing him toward canonical phage work. After completing his degree, Watson at some point tied up with Bill Hayes and did a paper on mapping genes in *E. coli*. Since JL had reported on this at the Cold Spring Harbor Symposium of 1951, a crisis had developed in trying to understand the chromosome structure in *E. coli*. There was no question about linkage—up to a certain point you could draw a linear map, after which it collapsed. Using the methods of analysis available at the time, the only way JL could formally represent the data was for the map to branch, because there were two or three different things that appeared to be linked to some common point, but were not closely linked to one another. These just did not fit linear mapping at all. Some people thought JL was proposing a branched chromosome, which was not correct.

136 Watson and Hayes did their own analysis using mostly existing data. They came out with an alternative theory stating there were three separate chromosomes in *E. coli*. JL did not think that was justified. He had data suggesting there was linkage between markers they had put on separate chromosomes—even if he could not put them on a linear map. That was a passing item, soon superseded by the work of Jacob and Wollman, showing what was wrong was not the question of linearity in the chromosome, but the fact that you were not getting the entire genome into a fusion cell "all in one go,"and different fragments of varying size were entering.

151 JL had no idea Watson was going to work on the structure of DNA. He did not think Watson himself knew he was going to work on the structure of DNA. Watson's original fellowship abroad was to work with Herman Kalckar in Copenhagen, but as Watson has described, Kalckar was preoccupied with his courtship of Barbara Wright. Watson describes how he then moved to Cambridge and the rest, as they say, is history. As far as the chemistry of DNA, the previous node of studies on that point appears in the 1951 Cold Spring Harbor

Symposium. At that Symposium there were extensive allusions to the work of Gulland, Chargaff, and others. None of those people were doing x-ray structures, as far as JL can recall. They were doing analytical work to try and get a little more detail on the precise space composition—and especially from the work of Chargaff it eventually became evident that there was not an exact one to one to one ratio of the four nucleotides, and that deviations from that meant that there was a rather more complex structure than the tetranucleotide that Phebus Levine had been arguing for.

177 These were very active years, but JL was not connected to Watson in the years he was abroad and he does not recall precisely when he heard of the structure, although he believes there was some inkling of it in the days immediately preceding its publication in *Nature*. JL was not aware of the race at the time, nor was he aware of who was in it. He thinks it uncanny how thoroughly and how profoundly Watson and Crick not only did the structure, but how they understood how to couple the physical structure that they elucidated with what this meant for the biological mechanism of replication. That, JL believes, is the really brilliant part of their paper—a totally accurate forecast of how complementarity of DNA sequences was going to work out for the mechanism of information transfer of replication. The only thing they got wrong, according to JL, was they thought that somehow DNA all by itself would have this self replicating capability. It was Arthur Kornberg's lot to have the inspiration to study the enzymatic machinery by which DNA was replicated. There is no mention of such enzymatic machinery in the Watson-Crick paper. But in a way maybe the nucleotide chemists have had the last laugh because it now turns out that if not DNA, RNA has enzymatic activity as well as its informational one. This has not been demonstrated for DNA, but it was not such a bizarre thought after all to think that it might have both catalytic activity and be the information store. Again, it has not been substantiated yet for DNA, but it has for RNA.

211 The discussion turns to computers. JL notes that his first introduction to computers was in 1941, when there was a card sequence controlled calculator installed in the American Institute Science Laboratory at 310 5th. Avenue, in the shadow of the Empire State Building. This laboratory was the forerunner of what later became the Westinghouse Science Talent Search, but in 1941 it was the program that provided facilities to high school students who wanted to do bonafide research at a time when high school labs were less equipped to do that than at they are at present. By examination, JL won what might be called a scholarship permitting him to work at this laboratory. While his own project was in cyto-chemistry—the chemical identification of cellular constituents by specific staining reactions under the microscope—there were some other students who were starting to experiment with these various machines. These were not very elaborate computers. They were relay driven and involved punch cards. Basically the only memory they had were the intermediate cards, so if you wanted to calculate a square root, for example, you could put in a number, program it to do that, and probably burn up several cards to get the results. But it was the first

intellectual robot JL had ever seen. He was quite intrigued by its analogy to living organisms, and he from that moment on followed the development of computers, though mostly from afar and from the press.

241 When JL came to Wisconsin, he found there was a Numerical Analysis Laboratory, which was run by Fred Grunenberger. JL did not have any immediate use for the lab, but be thought he should familiarize himself with robots at that stage of their development. This took place around 1952. He took Grunenberger's course, and it was there he learned about plug board programming. JL understood the importance of what he was learning, but was not doing the kind of statistical work that Jim Crow and others were doing, so computers had no practical use for him at the time. In addition, the machines of the time were pretty rigid and did not yet have compilers, programming languages, and the like. It was not until he arrived at Stanford and took a FORTRAN course that he began working more seriously with computers.

260 The discussion moves from JL's research at Wisconsin to his teaching. It was expected of JL, and he says he would have been disappointed if it had not been, that he give a course on the genetics of microorganisms. JL suspects it was among the early courses of its kind in the country. The course was cross-listed with microbiology and was offered as an advanced undergraduate course. For a textbook JL used a compilation of papers of recent work, which he reprinted and bound into a red covered book, which was put together by the University of Wisconsin Press. Using that kind of material was in itself an innovation, but in a rapidly developing field there was not time to wait for the publication of a textbook. The technique proved successful, and the use of the red book was emulated by others on campus. JL briefly discusses some of the topics covered in class. Until the mid-1950s, one could in a single course teach everything that had been published in the field. JL notes that he almost certainly gave at least an annual lecture in the standard genetics course, and from time to time he lectured in other courses, such as microbiology.

306 The discussion turns to the early development of what eventually was to become the Department of Medical Genetics. JL begins by noting that his own work was in the genetics of microorganisms, and while he was very much concerned about the further reaches of genetics and its implications for medicine, that was not going to be a first order of consequence in his own investigations. Nevertheless, he was strongly committed to medicine and medically oriented research. He had gone past the midway mark in his studies as a medical student, and had faced a difficult dilemma in deciding whether to continue working for his M.D. It would have very much been JL's preference to have continued his research work in a more medical environment. Still, his research with Ryan at Columbia had not been in a medical environment, nor had his work at Yale—although he had been a frequent visitor to the medical library and knew several people in the medical school. At the time, there was not that much interest in genetics by medical schools generally. There was

nothing going on at Columbia at the time, for example; nor can he think of any genetics at Yale at that point in time. But there were matters of locating genetic factors in the human, of genetic counseling, of tracing pedigrees, and the like. The field was burgeoning.

335 An important factor was that JL got to know Jim Neel rather well. Neel had gotten his Ph.D. with Curt Stern at Rochester, had been a visitor at Columbia, then had made the very bold decision that he was going to go into human genetics and get an M.D. JL remembers others thinking Neel crazy because what could you do in human genetics? But Neel persevered and he proved—famously—that he was right. He worked out the genetics of sickle cell disease, noting that it was a classic recessive mutation. That was part of the background in JL's thinking about how one instills more genetics into medical research and into medical education. In spite of what R. A. Brink said in a letter to JL in 1946, that there was no obstacle to genetics becoming a factor in medical research, neither was there much enthusiasm concerning it. Van Potter and a few others around the McArdle Cancer Lab would have certainly listened to these matters. JL had posited a genetic somatic mutation theory for the origin of cancer while he was a medical student in 1946, and they could have—may have had—several conversations around that. But nothing was happening in that area, and besides JL was extremely busy with his own research.

360 The possibility of going further in that direction appeared with John Z. Bowers' arrival as dean of the Medical School in 1955. It so happened JL had met Bowers at a dinner in Curt Stern's home in Berkeley in 1950, during his summer teaching sabbatical. Stern had left Rochester and accepted a position as a professor of biology and genetics at Berkeley. Stern would have known Bowers from Bowers's connection with the Atomic Energy Commission (AEC). For a few years prior to 1950, Bowers had served as director of the Division of Biology and Medicine at the AEC. In that position he oversaw research on the effects of atomic radiation in animals, and also the program investigating the consequences of Hiroshima at the Atomic Bomb Casualty Commission. JL had known Stern since he was a medical student at Columbia in the 1940s.

379 Bowers was about to assume his position as dean of the medical school at the University of Utah when JL met him that night at Curt Stern's house. JL challenged him at the dinner table about what he was going to do about genetics in his new role, and he received an encouraging response. JL does not recall having any further contact with Bowers before his arrival at Wisconsin, nor did JL play any role in his selection as dean. As soon as JL heard he was coming, he contacted him immediately and repeated the challenge he had made at dinner that night five years earlier. When asked by JL to do something combining medical school and genetics into a program at UW, Bowers said: "Let's try it." Bowers asked JL to put together a proposal, which he did. Eventually this led to forming a program which provided the opportunity to teach genetics in the medical curriculum. The program needed to start there because up to that point no genetics was being taught in the medical

school—which was typical of the times. They may have had a course in embryology and human development as a subsidiary to the gross anatomy course, and within that framework there may be two or three lectures on Mendelian genetics or something to that effect, but one must remember that there was not that much to teach in that area.

408 End of side.

Tape 6/Side 2

001 The discussion moves to Curt Stern's book, *The Principles of Human Genetics*. Although 99 percent of Stern's research was in *Drosophila* genetics, he was the next generation after Muller, Morgan and Sturtevant. Stern had a deep interest in human genetics. He taught it not in the medical school, but as a course in the biology curriculum at Berkeley. His book was basically the only text available. The history of the teaching of genetics in medical schools, JL notes, has yet to be written. It did exist as a subsidiary topic, and JL thinks the first major teaching program—and he does not think it was elevated to the departmental level—was initiated by Jim Neel when he went to the University of Michigan. But even there it had a secondary role in the teaching of medical students. The typical pattern, JL recalls from his own experience as a student, was that a few lectures in the genetics of Mendelian ratios and the like were given as part of an embryology course. Then there would have been examples like hair color and a few of the classical recessive mutations. One of the first of those to be understood was sickle cell disease, a hemoglobin disorder, and the genetics of that was only first worked out by Jim Neel, as mentioned earlier. This research and some of the research in the area which follows on its heels, and which JL describes briefly, constitutes what might be called the beginning of molecular genetics—that is to say of the understanding of a disease syndrome of genetic origin in molecular terms.

068 Thus the field was just beginning at a research level, but it was taught only incidentally in the schools. Still, there were questions of radiation injury and of chemical mutagenesis that one needed to be concerned about. One of the things that held back the teaching of the subject in a medical context, JL postulates, was the cloud of eugenics, and in turn the cloud of abuses in the Nazi regime. At the time, there was a debate going on, with Muller being one of the centerpieces, about the extent to which one should encourage selectivity in human reproduction in ways analogous to how we breed race horses or better strains of corn and the like. There were obviously so many ethical no-nos in that general arena that one could see how it might be regarded as a very touchy subject. At any rate JL does not recall ever being required to lecture to the medical students at Wisconsin.

092 What JL did was propose the establishment of what was first a program and then a department of medical genetics in order to instill better appreciation of the numerous developments occurring in the field, such as the discovery of the structure of DNA, which

JL and others could readily see was going to overtake many aspects of research in medicine, as it was already beginning to in agriculture. Newton Morton was hired to staff the early medical genetics program. Morton, a former graduate student of Jim Crow's, was very skilled in population genetics and provided a good starting point for a human genetics program. JL notes that had it been up to him, he would have brought in someone with a microbiological background, while still others might have preferred a more molecular orientation.

110 Naming the new program brought about some interesting questions. Since there already was a genetics department, it would have been confusing to have a separate department of genetics in the Medical School. The department was thus named the Department of Medical Genetics, which brought about some misgivings on JL's part, because he viewed it as a basic science department housed in a medical school. It was a convenience to put "medical" in the title, but JL was concerned that it might be too confining a term—because it would not have left a place for JL, for example, or for the more molecular aspects of it. JL objected to the term "human genetics" for the same reason, in that this was just a part of the field. What eventually happened, of course, was that the two programs joined together in an across-school initiative.

134 When he was first starting the programs, Bowers faced a lot of conservatism from the people in the Medical School. He did not exactly encounter a lot of enthusiasm on the Ag side, either. There were several turf issues and a lot of split votes on many of the committees, although there was a slow approval of these concepts as it worked its way through the Medical School and the rest of the University administration. Relating to financial support, there was reasonable promise of substantial support from the Rockefeller Foundation, however there was no assurance that the Foundation's funding would extend beyond five years. The question Bowers and the others faced time and again was even if they got funding for five years, what funding guarantee did they have after that point? JL believes that if the top levels of administration had shown more foresight about where the program was going, and how indispensable it was going to be, they would have understood that this was something that would have to be furthered. It was pretty slow going, JL notes, to get that degree of formal approval, even with the promise of short term funding from outside sources.

161 This more or less dragged on through 1956-57. John Bowers showed a lot of dynamism—perhaps even too much. Maybe, JL notes, he tried pushing things through faster than the medical community was ready to accept. JL had some friends in the medical community, people like Phil Cohen and Van Potter, who were certainly enthusiastic about it. The microbiologists were, JL thinks, mostly uncomprehending. Paul Clark probably had some positive vision in this direction, but he had long since retired as chairman.

180 In the meantime other things were happening in JL's life. He had ambitions and aspirations that he is sure were connected with some degree of exasperation that things did not happen promptly and enthusiastically—that it took all the push Bowers and JL could offer to move them at all. As far as other members of the Ag Genetics Department were concerned, JL is sure Jim Crow was very enthusiastic. Brink and Irwin, however, may have been a little perturbed that JL was so distracted by organizational issues. They may have felt, and quite rightly, that this was going to compete in time and energy with JL's own basic research. He thinks that in their hearts they might have preferred he stick to pure lab work, but they also understood the realities of what was happening to genetics in the wider world. Though Brink and Irwin supported JL, they did not provide aggressive support, perhaps because they foresaw there would be many problems in getting it to happen. There was less than enthusiasm on the part of other members of the Ag Genetics Department. They were not going to get in the way, but they were not going to push it, either. This is reflected in many of the split votes in the various committees. JL thinks there was less than great vision, even at the funding level, in relation to starting and supporting the program.

216 Along these lines, there had been discussions about hiring people for the newly formed department. After Newton Morton, JL looked to Kimball Atwood, who, at the time, was doing some very interesting studies in mutagenesis in the human using red cell phenotypes as a measure. Atwood found ways in which one could measure the frequency of odd ball erythrocytes that had a different antigenic composition from the main population, and he attempted to validate that as a measure of mutations occurring during production of red cells. Atwood published a number of papers on that, and JL thinks his work in this area has been regarded as a very useful tool. He would then want to correlate it with exposure to radiation, exposure to chemicals, and so on. He had a solid base for that research and he was someone JL had a close personal history with, in fact Atwood and JL had roomed together in New York City when they had both been medical students, Atwood at NYU and JL at Columbia. At some point Atwood married and his wife moved in with them, since housing was extremely difficult to find at the time. JL notes that "there is nothing lonelier than being the third man in an arrangement like that." He subsequently found separate quarters a few months later.

247 Atwood had done brilliant work in a number of areas and JL was eager to have him as a member of the department. He was not notable for answering his mail in a timely fashion, however, or being particularly prompt. This came to the floor at Wisconsin as well in relation to the launching of the new department. Bowers and JL agreed to organize a symposium that might help define the field of genetics in a medical context. Again, JL notes, it seems absurd that one would have to do this, but the field of medical genetics simply did not exist at that time. The symposium was scheduled for April 7-10, 1958. Several notables in the field were scheduled to appear, including Atwood. Atwood appeared and

gave a paper but never turned in a manuscript, thus the publication relating to the symposium does not refer to Atwood.

264 Prior to the symposium, there had been considerable discussion about Atwood's possible appointment to the department. There had been a decision to postpone a decision until after the symposium, in order to see what kind of impression Atwood made. Other events overtook the process before that materialized, however. In other words JL made the decision to leave Wisconsin, putting the question of any other appointments on hold.

269 In December of 1956, Tatum announced he was leaving Stanford and taking a position at Rockefeller University. JL was visiting in California at the time and had some discussions with Stanford officials about the possibility of his being considered to succeed Tatum. JL very promptly made an inquiry as to what his connection to the medical school might be, and received a pretty negative reply. There were plans afoot to establish a new school on the main campus, moving the Stanford medical school, which was associated with a hospital in San Francisco, to the Palo Alto campus. JL would have been delighted to hear that the new medical school was going to embrace genetics, but he did not. The dean of the medical school, however, gave him no encouragement, saying only that he would be happy to have JL teach some courses if he was established in the biology department. That pretty much discouraged JL from considering Stanford. It must be remembered that Stanford was not that great a power base at that time in science or biology. Tatum was no longer there, Beadle had left, and JL did not know what else was going on in biology to make it attractive. Berkeley seemed a much more exciting place. As soon as word got to Berkeley that JL had been talking with Stanford, he started hearing from them about whether he might consider a Berkeley appointment. Early in 1957, JL started conversations with the genetics department at Berkeley, which was housed in the School of Humanities and Science. During that same time, the UC-Davis campus was being organized and consideration was given to locating the genetics department there. That did not appeal to JL, nor to a number of the existing members of the department. It had to do at least in part with ag school connections. At any rate, matters moved forward regarding a position at Berkeley, and while Berkeley did not have a medical school it did have a school of public health, which was loosely affiliated with the medical school in San Francisco. There was also a rich intellectual environment at Berkeley, even without a medical school.

312 In the summer of 1957, JL was on sabbatical for several months in Melbourne. In late 1957 he picked up the threads again, and Berkeley began to look more and more attractive. There were several issues about laboratory space, but they were satisfactorily resolved. There was also a question raised about a position for his wife Esther relating to nepotism which appeared to be on its way to getting resolved. He also liked the idea of being near San Francisco and sharing in the intellectual life of Berkeley, besides which he was exasperated that things were not moving that well in Madison. However his Berkeley hopes were dashed

rather suddenly when, in spite of having been approved at every stage of the game on the Berkeley campus, JL received an astonished letter from Jenkins, the head of the genetics department, saying that the president of the California system had vetoed JL's hiring. No explanation was given regarding the action. Meanwhile more had been happening at Stanford, in that the acting dean from before had been replaced by Bob Alway, who had been head of pediatrics. Alway was to oversee the building of the medical school and its move from San Francisco. Not only was Alway sympathetic to the idea of genetics in medicine, but Stanford was just about to recruit Arthur Kornberg, and then they began thinking of a package deal: if Kornberg was recruited, would JL come? JL says he did not need a lot of arm twisting on that score.

349 One of the things JL sorely lacked at Wisconsin was a base of interest, knowledge, and on-going programs in nucleic acid chemistry, and Kornberg represented the top of the pack. JL had met him a few times before and they got along extremely well. Still, JL felt committed to Berkeley and did not feel he could explore the Stanford option much further. It was at that point in time that the president of the University of California System vetoed JL's hiring, thus freeing him of that commitment. Within two months, JL had a firm "yes" from Stanford. JL then wrote President Elvehjem a letter indicating his intentions.

364 Relating to the UW, JL did not keep his intentions secret but neither did he push matters very hard, choosing not to get into "a bargaining game." He did not have a firm promise from UW regarding the additional positions he was asking for. Along that line, he was not able to make an offer to Atwood. JL is sure that if he had really wanted to stay at Wisconsin he could have pushed that process along, but he was not about to play any games. Once he decided his preferences, he presented his conclusions.

377 Going back a little, in 1950 the University of Chicago had offered JL a position. At the time he had close relations with Novick and Szilard, who were building up a biophysics unit at the University of Chicago. They inquired about JL's interest and, while there were many aspects of the University of Chicago that were very appealing, JL and his wife had been in Madison only a few years where they had been treated warmly and well, and he just did not see moving at that point in his career.

388 In approximately 1955 there were movements made in two different places to hire JL. He gave some lectures in Denver and Ted Puck started a move to see about a genetics program in their medical school. What was appealing was that Puck was one of the founders of somatic cell genetics, which is where you put human cells into tissue culture and do genetic experiments with those cultures.

399 The issue of facilities was an important consideration in helping drive JL to explore other job opportunities. They were very primitive when JL arrived at UW and remained so, though

there was a renovation. In the same vein, Hillary Koprovsky was reorganizing the Wistar Institute at the University of Pennsylvania and made a similar bid for JL's services around that period of time. The offer was generous in terms of facilities. JL notes he could see things moving in other institutions, whereas at UW things appeared to be stuck. Nevertheless it was Stanford that came out on top in the end.

410 End of side. End of tape.

Tape 7/Side 1

001 Stanford came out on top because it had everything going for it. It demonstrated a real understanding of the program JL wanted to develop, it had a very progressive attitude, it had an attitude about medical education which was very research oriented, and at the same time there were interdisciplinary connections with the rest of the school. This combination that the climate draws the people draws the money was evident in the rebuilding of the science base at Stanford. It was the beginning of Silicon Valley and, not too many years after that, biotechnology alley, in terms of being at the very focus of exciting developments in every field.

038 What followed during his years at Stanford exceeded JL's expectations, especially the interdisciplinary base. He had a chance to work in everything from computer science to international security and arms control. His main disappointment about Stanford, oddly enough, was in the medical school. While it built an extraordinary basic science division, with people like Arthur Kornberg, the interdigitation of the basic science with the clinical programs was more disappointing. JL notes part of the reason may have been that at Stanford the sheer financial flow and power of the clinical programs ended up dominating the direction of the school. While there was certainly a high quality of research in those programs, it did not really match the full aspirations of what had been looked for earlier in the ideals of the school. This is a problem that will beset many academic medical centers in that as the funding base for the continued operation of the school chases the patients, chases the dollars, and provides a political base for the continued development of the organization, the basic sciences, in its connection with the clinical programs, tends to lose out. JL notes that still there is little reason to complain, since the basic science component benefitted from what by contemporary standards will seem like unlimited amounts of federal funding, this being the burgeoning years of the NIH. That part JL had no complaints about. It was the integration of it with clinical activity that fell behind, or at least did not meet JL's expectations.

101 In May, 1958, JL had the Berkeley job pulled out from under him. On July 19, 1958, he wrote President Elvehjem that he was leaving UW for a job at Stanford. A few months later, in October, 1958, JL was notified he had won the Nobel prize. What followed was an

extremely busy time, one that found JL and his wife busy selling their house, making living arrangements at Stanford, and preparing goodbyes for their friends in Madison. So it came as quite a shock when he received a telephone call from a reporter asking about his reactions to having won the Nobel prize. At first JL thought it a joke, since he had no expectation he was even being considered for the prize. It ended up being a standoff with the reporter. JL was concerned that this could generate a difficult situation, because if the rumor spread any further, and if he met his friends, who would be effusive in their congratulations, how was he going to deal with them the next day when they discovered it was a joke? JL wanted to spare them and himself the embarrassment of that event.

138 JL confided in one of his friends and went into hiding until be had a clear understanding of what was actually happening. The situation quickly became embarrassing and awkward. First of all it was painful severing the bonds he had established in Madison. People like Brink, Irwin and Crow, much to JL's relief, took the news of his leaving with more grace than he had expected. Then to have the Nobel prize come in just at that point was bitter-sweet, in that while winning the prize has many benefits for the host institution, announcing one's departure at the moment one secures the prize magnifies the rebuff. JL even seriously considered not accepting the prize. He expressed concerns to friends about whether all the fuss over the prize was helpful to science and whether it elicited inappropriate competitiveness in some areas. There was also the problem that so much scientific work was interconnected that one was bound to leave out people when one makes an award. Although ambivalent about accepting the award, he understood there were virtues as well. At an even deeper level turning it down would have been a slap in the face of Ed Tatum. Besides, if he had turned it down it would have ended in even more notoriety—which is exactly what he was trying to avoid. So JL decided to accept the award. Winning it when he did made things bitter-sweet at UW, but it also left Stanford in an awkward position, for he was winning the prize for work he had done elsewhere.

205 For awhile his wife Esther was so busy preparing for the move that she seriously considered not making the trip to Sweden for the awarding of the prize. JL found an acceptable route to deferring for six months the lecture he was required to give in Sweden. This gave him time to settle in at Stanford and have time to prepare the lecture.

227 Once in Sweden, there was an entire week of festivities. The whole country is involved in Nobel week, which is a week of celebration. There were banquets and affairs of one sort or other almost continuously. All of the other Nobelists gave their talks that week, so JL attended several of these presentations. Besides the academic meetings there was the formal ceremony, which was held in the beautiful structure of the town hall. At the formal presentation, the king of Sweden presented the awards. There was a certain amount of socialization among the laureates, and JL was happy to meet the Russian physicist Igor Tamm, who was outspoken and who, because of his age, told JL he was not worried about

being punished for being outspoken. This was also the year Boris Pasternak won the prize but was not allowed to attend.

285 Beadle and Tatum were JL's co-laureates. The prize for medicine and physiology was divided into two parts, with JL receiving one part and Beadle and Tatum sharing the other part. The Beadle-Tatum award was for their joint work on *Neurospora*, and while Tatum had been JL's collaborator this was an acknowledgment of the fact that the work had really been done at JL's own initiative and that he had done 95 percent of the laboratory work. JL was very proud and honored to be in their company. Those were people who had preceded him by ten or fifteen years in their own scientific development, and JL had "stood on their shoulders" for the work he had done. JL had never doubted that they would eventually receive the Nobel prize, but he never thought that issue would come around to him—especially since he was only 33 at the time. He thought he had been a good enough scientist and if he worked another 20 years he might have an accumulated body of work that would qualify him for it.

316 In his Madison press conference following his winning the award, JL made a point of naming several people who had been instrumental to his winning the award. The names he mentioned were: Bradley, Cavalli, Phil Edwards, Morse, Stocker, Wright, Zinder and Iino. All except Phil Edwards have been discussed earlier in this interview. Phil Edwards was the leader of the Center for Disease Control in Atlanta which provided the raw material with which JL had done his studies on the immunogenetics of *Salmonella*. JL had visited him for a couple of weeks in 1953.

330 In terms of the effect the Nobel prize had on his career, JL said he did not need it, since his career was going fine. It probably added a little bit to prestige, and it probably did not hurt Stanford in raising funds to support the work he was engaged in. JL notes it probably gave him a standing outside of the immediate scientific area he would not have had otherwise. There is a certain certification of authority that goes along with the prize. When a Nobel winner talks about scientific topics in public—sometimes quite inappropriately—it is credited with likely being true. The Nobel prize probably drew attention to JL in policy quarters so that he would be consulted or drawn upon in ways he might not otherwise have been. There is also a certain responsibility associated with winning such an award that one must not abuse. JL notes he does not think the Nobel prize does much for individual scientists in that if it goes to the right people they don't need it, and if it goes to the wrong people, it is inappropriate.

361 The cash, JL notes, has gotten to be a significant factor. At present, the prize is worth over a million dollars. JL's share of the prize in 1958 was $21,000. One other factor about winning the prize is he is forever introduced as "Joshua Lederberg, the Nobel prize winner."

This is an impediment he constantly has to work around. He sees it as a source of distancing from people, as being dehumanizing.

374 End of side.

Tape 7/Side 2

001 The discussion turns to JL's return trips to Madison after having departed for Stanford. Harry Waisman was a renowned figure in the history of medical pediatrics at Wisconsin whom JL had gotten to know pretty well. Waisman was interested in genetic disease and he played an important role in the development of PKU screening for newborns in Wisconsin, and a number of related matters. JL consulted with him, and they may have been fellow members of a president's panel on mental retardation that President Kennedy's family had initiated early in his administration.

030 JL was happy to be asked to receive an honorary degree in 1967. On his trip to Madison to receive the degree, JL relates how he and his luggage became separated because the travel agency had neglected to inform him that he would be departing from a different terminal in Rome. As a result JL's bags went on to the next destination, which was Tel Aviv, and JL did not. It just so happens that coincided with the start of the Six Day War, and the flight JL missed was the last commercial flight into Israel. He ended up heading back to the states *sans* luggage, but managed to buy a new suit of clothes before arriving in Madison to accept his honorary degree.

064 JL was asked if he had any closing comments he wanted to make about his career at the University of Wisconsin. His comments follow. "It was a wonderful experience for me. It was a different world. The University's roots had been in agriculture as a life style—a closeness to the earth—a very important set of values that are connected with that, which I was glad to have an opportunity to experience. It was also a wonderful liberal tradition, a very tolerant one, that Wisconsin had been famous for. And of course there was a severe blot on it with the Joe McCarthy days, but I think totally repudiated by the state as well. The University was the jewel of the state, was regarded as such. The legislature was proud of it—and it's always been amazing that the state of Wisconsin, which I think ranks twenty-fourth in income ... has still had one of the highest ranking of the public institutions of learning in the country. And I think that tradition has been maintained. The quality of friendships that we had, not only the very close and very intimate ones but almost everybody else—I'd feel that whenever I come back to Madison that you can count on an amiability and a friendliness and a courtesy that's really very, very hard to find anywhere else in the country at this time. Now you know Madison has become heavily urbanized since fifty years ago, and become probably more like the rest of the country in many regards, but I think it still has an edge on these kinds of qualities. It's a somewhat quieter

life then, say, New York or San Francisco, but it still has no lack of cultural amenities—you just don't have twenty or thirty to choose and pick amongst, if you're talking about theater or music. But what there is, is very good and you don't have to work hard to have the advantage of it. The climate we'll leave to another situation. But it's the people that really are so wonderful. It's the people who are drawn there, the people that stay there, the people whose own ethos is conditioned by the environment that they find, and who in turn condition that environment themselves. So I have just an enormous fondness and admiration for every level of life there. I certainly learned a lot, grew a lot—in the human as well as the professional side of my life—and it would have been very sad indeed if I had never been there."

124 End of side. End of tape. End of interview sessions.

END