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BORIS MAGASANIK

Transcript of an interview
Conducted by

Sondra Schlesinger

In three sessions between

1993 and 1995

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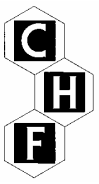

BORIS MAGASANIK

1919 Born in Kharkoff, Russia, on December 19

Education

1941 B.S., biochemistry, City College of New York
1948 Ph.D., biochemistry, Columbia University

Professional Experience

Columbia University
1948-1949 Research Assistant, Department of Biochemistry

Harvard University
1949-1951 Ernst Fellow, bacteriology and immunology
1951-1953 Associate
1951-1956 Markle Scholar
1953-1955 Assistant Professor
1955-1959 Associate Professor

Pasteur Institute, Paris
1959 Guggenheim Fellow

Massachusetts Institute of Technology
1960-1977 Professor, Department of Microbiology
1967-1977 Head, Department of Microbiology
1977-present Jacques Monod Professor of Microbiology

Honors

1993 Waksman Award, National Academy of Science

ABSTRACT

Boris Magasanik begins the interview with a description of his childhood years in Vienna, Austria. Shortly after graduating from the Gymnasium in 1937, Magasanik immigrated to the United States to live with his sister in New York City. It was still possible for Jewish families to leave Austria, and both Magasanik and his parents left the country. He enrolled in City College of New York, where he earned a B.S. in biochemistry in 1941. Hearing of its good reputation for organic chemistry, Magasanik decided to attend graduate school at Pennsylvania State University. While at Penn State, Magasanik was drafted into the U.S. Army to serve in the Second General Hospital. His unit was transferred to Oxford, England, where he remained until the spring of 1944. After his release from military service in 1945, Magasanik went back to New York and continued his graduate education at Columbia University, researching inositols and RNA with Erwin Chargaff. After his postdoctoral work, Magasanik went to Harvard University as the Ernst Fellow in 1949. After joining the faculty at Harvard, Magasanik and his students researched histidine and purine biosynthesis and inositol degradation. When he joined the faculty of Massachusetts Institute of Technology [MIT] in 1960, Magasanik continued his work on inositol degradation, studying enzyme pathways. Later, Magasanik researched histidine degradation in *Salmonella* and *Klebsiella*. In 1967, Magasanik became head of the Department of Biology at MIT, serving in that capacity for ten years. During his years as chairman, Magasanik helped found the Center for Cancer Research. After his chairmanship, he remained active in the department, helping to establish the Whitehead Institute. Magasanik concludes the interview with a discussion of MIT's teaching environment, financial support for research projects, and continuing as an educator after retirement.

INTERVIEWER

Sondra Schlesinger is Professor of Molecular Microbiology at Washington University School of Medicine. She received her Ph.D. in biological chemistry from the University of Michigan and spent three years as a postdoctoral fellow with Professor Boris Magasanik at the Massachusetts Institute of Technology, where she worked on enzyme induction and regulation in bacteria. She joined the faculty at Washington University in 1964, where initially she continued her research in the field of microbial genetics and physiology. In the early 1970s, she began her research work on the structure and replication of animal RNA viruses, which continues to this day. Dr. Schlesinger has over one hundred publications spanning these areas of microbiology. She was President of the American Society for Virology in 1992-1993, at which time she began her present interest and work in the history of virology.

TABLE OF CONTENTS

INTERVIEWEE: Boris Magasanik

INTERVIEWER: Sondra Schlesinger

DATE: Three interview sessions conducted between 1993 and 1995

SCHLESINGER: Let's start at the beginning and tell me both where you were born and a little bit about the first years of your life.

MAGASANIK: I was born in Kharkoff, which is now in the Ukraine, on December 19, 1919. I left there with my parents for Vienna two years later, so obviously I have no recollections of what was then Russia. I grew up in Vienna and went to primary school and Gymnasium in Vienna and graduated from the Gymnasium in 1937.

SCHLESINGER: I think it would be interesting for you to describe some of the influences during the time that you were in school that led you to think about science.

MAGASANIK: The science teaching at the Gymnasium wasn't particularly good and I got interested in chemistry, which I think was only taught for two years, in the sixth or seventh year. But I got intrigued with chemistry, and then perhaps another influence was that my uncle, my father's younger brother, was a chemist and at that time was working in Israel. I didn't know him very well, I just knew him from his very infrequent visits to Vienna. He was an associate of [Chaim] Weizmann. He was working at the Agricultural Research Institute in Rehovot. So getting intrigued with chemistry and having some sort of family connection with chemistry, I think, were the elements that decided me to study chemistry at the University.

SCHLESINGER: Are there any outstanding events that happened during school and before we leave Vienna?

MAGASANIK: My parents were trying to get into Poland because they had property there. Fortunately, they didn't succeed, and so they followed me to New York in the fall of 1938.

SCHLESINGER: What happened after you arrived in New York?

MAGASANIK: In 1938, the occupation by the Germans excluded all Jews from the University. I left Vienna. My sister was married to a physician and they had moved to New York two years previously.

SCHLESINGER: So you went by yourself to New York?

MAGASANIK: I was staying with my sister and I went to City College [of New York]. There was no tuition, and I went back and forth from the evening session to the day session.

SCHLESINGER: When did you learn English?

MAGASANIK: I had some English lessons in Vienna and when I came to New York, I took a few more lessons with the wife of a colleague of my brother-in-law.

SCHLESINGER: City College was where many famous scientists went to school. Did you meet anyone?

MAGASANIK: I had very little contact with other students. City College had an enormous number of required subjects and I got credit for some of the courses that I had studied at the university in Vienna. I had no classmates, so to speak, and I was also working and switching back from night to day sessions so I had relatively little contact with other students. I had some friends then who were acquaintances from Vienna or acquaintances of acquaintances. I really don't think I had much contact with American students.

SCHLESINGER: So there is no particular highlight to point out during your college years?

MAGASANIK: No, not really, other than working at Mount Sinai and some of the courses in chemistry.

SCHLESINGER: And after you graduated in 1941 what happened?

MAGASANIK: I wanted to go to graduate school and went to Penn State because it had a good reputation for organic chemistry and it charged out-of-state graduate students the same low tuition as the in-state students.

SCHLESINGER: Was that the first time you left New York City?

MAGASANIK: Yes, essentially.

SCHLESINGER: Had you begun to feel yourself an American by then?

MAGASANIK: It's very hard to tell. It is, after all, a big country that was built by immigrants. It was a procedure—that you got your first papers that said "I am a citizen," and you more or less felt that what you were going to do was very clear. And in New York, of course, there were so many recent refugees from Austria and Germany.

SCHLESINGER: We have you now at Penn State in 1941. How long were you at Penn State?

MAGASANIK: It was very short; I was at Penn State during Pearl Harbor and immediately all the undergraduate students in chemistry had defense jobs at Penn State. Because I wasn't a citizen, I finished the semester and then about that time I was drafted into the Army. So that by February (1942) I was in the Army.

SCHLESINGER: What did the Army do with you?

MAGASANIK: I didn't exactly understand what was going on because all the others who had come in with me had been sent out, but they kept me since I worked in the hospital and had done chemistry. They were organizing a general hospital. Physicians and nurses came from the civilian hospital, and the Army supplied the enlisted staff. They were organizing such a hospital at a place between Washington and Baltimore. So I was sent there to join the second general hospital, whose staff came from Presbyterian Hospital, and in a few weeks I was promoted to corporal, then staff sergeant, which was appropriate for me as chief technician in the biochemistry lab at the station hospital there. Then our hospital was sent to England in June or July of 1942. Just before we left, the Army noticed I wasn't a citizen after all, but we went before a judge in Baltimore and I became a citizen.

SCHLESINGER: So now you are going off to England?

MAGASANIK: So we were then in England and our hospital was very lucky. Our hospital was stationed in Oxford until about the spring of 1944—in a general hospital in Oxford. For some reason, ours must have had an advantage over another general hospital organized by Harvard Medical School. They were always parallel with us and always in a worse place.

SCHLESINGER: Were there any outstanding experiences during that time—either people who influenced you or how were you being influenced by the events at the time?

MAGASANIK: Well, obviously working in a chemistry lab at a hospital at that point, and among the physicians who were in research and who were very intelligent, interesting physicians—and so in viewing this—half my mind was made up to study biochemistry.

SCHLESINGER: Before we leave here you were also sent to France, is that right?

MAGASANIK: Yes, our hospital then went on to Normandy until Thanksgiving of 1944.

SCHLESINGER: Were you actually in England and Europe for more than three years?

MAGASANIK: Yes, and then we were sent home.

SCHLESINGER: One event in terms of science during the war was the use of penicillin—

MAGASANIK: Yes, I was very close to that because we were stationed in Oxford and our hospital was the first hospital to use penicillin on an experimental basis. It was so valuable that we recovered it from the urine of patients. In fact, the head of our laboratory wanted to do some experiments on the action of penicillin and the results we got were completely wrong, but I published a paper (1).

SCHLESINGER: Was that your first publication?

MAGASANIK: No, it was my second publication. I had one paper on the levels of iodine in blood from work I did at Mount Sinai (2).

SCHLESINGER: When did you get out of the Army?

MAGASANIK: It was in the fall of 1945, I think it was October. Anyhow the semester had already started, that I know, and I was back in New York, where my parents lived. I wanted to continue graduate school—this time in New York. The connection was that my brother-in-law, who was a physician and also did research, and my sister were friendly with Erwin Chargaff and his wife. Erwin Chargaff was an assistant professor of biochemistry at the College of Physicians and Surgeons at Columbia University. And so when I returned, my parents told me that "Chargaff would like to meet you and it might be nice if you went up there to see him." So I still was wearing my uniform when I went up to Columbia to meet Chargaff, and we had a pleasant talk about what he was doing and my experiences. And then he said that I should also meet Professor Clarke—Hans Thatcher Clarke—who was the head of the department. Professor Clarke came to Chargaff's office with another of the senior professors, Professor Miller, and

gave me an impromptu oral exam in organic chemistry. He asked me a few questions, which I answered, upon which Professor Clarke said, "Now you are admitted to the department." I hadn't asked to be admitted—and I was looking forward to having a little bit of free time after being away in the Army for so long. So I said that the semester was already advanced and I would start in February. Professor Clarke said, "Oh no, the biochemistry course only starts in November and just go down to 116th Street and take advanced organic chemistry." I asked: "Well, will they admit me? I mean, the semester has already started." He said, "It doesn't matter, just tell them I said so." So that is exactly what happened. So without any respite, I was now taking courses. Actually, the advanced organic chemistry course was then taught by a young professor who had originally been at Harvard and then went back to Harvard. His name was William [von Eggers] Doering, and it was an absolutely fabulous course. I was very impressed, and I really began to enjoy it immensely. I also started to work at Columbia, and obviously, with Erwin Chargaff. We didn't discuss the question of working with somebody else. In fact, I didn't know anybody else.

Professor Miller—who wasn't using it—lent me his little laboratory because the system at Columbia was that all the graduate students worked in one big laboratory where each student had a bench. And at that moment, there was no free bench, but one would become available because David Sprinson, who was one of Chargaff's students, was very close to finishing his experimental work. I was going to inherit his desk, but in the meantime I could work in the small private laboratory. We tried several things that I didn't enjoy particularly—by which time David Sprinson had finished—which also liberated the only water bath for Warburg manometers in the department, which was standing on part of his desk. Chargaff said, "I have some interest in the oxidation of inositols and so why don't you to do that?" So it really hinged on the fact that I couldn't possibly have done that until the water bath was free. So before that was available this project couldn't be started, it was not possible.

SCHLESINGER: Do you think that many scientific projects are started that way?

MAGASANIK: Well, I don't know. I mean, usually, it's some rather superficial event that leads to it. And Chargaff had very broad interests. In fact, David Sprinson had worked on the bacterial oxidation of L-serine. Chargaff had accumulated some inositol isomers. There was a rather interesting problem—it was an interest of Chargaff at that time before he got involved in nucleic acids and concentrated on that. The point was that much, much earlier, maybe even in the previous century, I am not sure, Monsieur [Gabriel] Bertrand, who was one of the great French biochemists at the Pasteur Institute, had studied the oxidation of polyhydroxy alcohols by Acetobacter suboxydans. Now Acetobacter suboxydans is an economically important organism because it carries out the oxidation of hydroxyl groups, usually only one step to the appropriate keto compound and not beyond it. So for example, Acetobacter is used to convert glycerol to dihydroxyacetone. This is a useful product for making vitamin C. And when, for example, six-carbon polyhydroxy alcohols were used, Bertrand had observed that the compound formed was a monoketone and the position that was oxidized by Acetobacter was always the hydroxyl next to a primary hydroxyl, but only when the next hydroxyl was in cis-position to the one being oxidized. And these rules were formulated as Bertrand's rules. So Chargaff was intrigued about what would happen with inositols because inositols obviously didn't have a primary hydroxyl group. It was already known that Acetobacter oxidized what was then called

meso-inositol and is now called myo-inositol (which is the most important of the nine isomers of inositol) to a monoketone compound by picking out one of these hydroxyls for oxidation. Chargaff had gotten methyl esters of several other naturally-occurring forms of other inositols. In other words, they had the hydroxyl positions arranged differently with regard to the ring. He wanted me to try to oxidize those and to find out whether they would give monoketones, diketones or would be oxidized or not oxidized.

In the case of myo-inositol, the organism did oxidize one hydroxyl that was in cis position to its two neighbors but, in principle, it would have had other choices, so it wasn't quite clear what determined the attack on the particular hydroxyl group. So I started to carry out these experiments and in fact found that of the total of four inositols—two naturally-occurring isomers, and two that were synthesized from the reduction of monoketones derived from myo-inositol— that one was not oxidized at all, one gave a monoketone, and the two naturally-occurring ones that were optically active, as levo- and dextro- inositol, were oxidized to diketones. The results were hard to interpret at that point and I carried out some organic chemistry, making the appropriate derivatives to identify the hydroxyl groups that actually had been oxidized.

Initially, the results didn't seem to make much sense until I happened to see an article by a physical chemist. I can't remember his name now. The article dealt with the stereo chemistry of the cyclohexane ring. It had long been known that the form in which the cyclohexane ring is usually presented, namely as a planar ring, is incorrect and that it exists in a puckered configuration either as a chair form or as a boat form. Thermodynamic measurements had shown that the boat form did not really exist as it had much too low a probability. So that the actual form was the chair form and if you look at the cyclohexane ring in the chair form, you find that six bonds are directed in a ring around the group of carbon atoms. They were then called, and I think they are still called, equatorial and the second bond in each case for each carbon atom is either perpendicular up or perpendicular down, which was then called north polar or south polar. So you have then to look at the cyclohexane ring as a group of six carbon atoms surrounded by bonds in the equatorial plane and by bonds directed up or down, which are now called axial and equatorial bonds. The next statement in that paper was that substituents on the cyclohexane ring can obviously either be axial or equatorial but that the stable form is the one with the smallest number of axial substituents. Since there are two chair forms that are interconvertible, by shifting from one to the other, each axial hydroxyl becomes an equatorial one and vice versa. So if you have a single substituent—in the one case, it would be axial and in the other case, equatorial—that actually the stable form is the equatorial one and when you have more than one substituent, the conformation chosen is the one in which the majority of the substituents are equatorial and the smallest number axial.

Well, once I read this, I immediately looked at my inositol isomers and wrote the formulas no longer in the planar projection, but in the way that showed me the equatorial and axial bonds. I could then write the formula for each inositol so that the bulky hydroxyl groups were always preferentially located in the equatorial position, and then it became immediately clear that only axial hydroxyls were ever oxidized. So now there was a general rule that only an axial hydroxyl could be oxidized and equatorial hydroxyls were not oxidized. Looking further, and analyzing additional compounds and isomers of quercitol that had only five hydroxyl groups, it turned out that a second rule prevailed: that an equatorial hydroxyl had to be located in one direction two places away from the axial hydroxyl that was being oxidized—that was

then the second rule—and further work showed a third rule, which is not as strictly obeyed. It was more a question of how much oxidation there was. I think for another equatorial hydroxyl next to the one that was being oxidized, the other positions didn't matter at all. So we had now the so-called Magasanik–Chargaff rules—so called once the papers were published—that still hold, and occasionally you see papers even at this late date published that mention them. So I was very pleased with the results and it presented a good thesis (3).

SCHLESINGER: How many years were you a student?

MAGASANIK: It went very fast in that I started in the fall of 1945 and I got my degree in the spring of 1948. So I finished in somewhat less than three years.

SCHLESINGER: This was certainly different from what most graduate students do today and I wondered if you wanted to compare a little bit your life as a graduate student, both in terms of social life and scientific life, compared to what you've seen during the time you've been a professor and had your own students.

MAGASANIK: A comparison, though, is difficult because I've always only known well the department I am in, which is unusually big, and most biochemistry departments are at medical schools. So it's hard to generalize that way. One thing that I recalled was the story of how I was admitted. It was a relatively informal process in that the departments were small and the department head, particularly in medical school departments, had considerable power to do as he—and it was hardly ever a she—pleased. Clarke decided how to admit students and how to run the department and what would be appropriate. He was an organic chemist and he strongly stressed organic chemistry in the training of graduate students, which I think was very good. Of course, it is less common now because the field has changed. Clarke still looked at biochemistry as a branch of chemistry and by now other aspects, for example, molecular biology, which has its own "Gestalt", is much more important in biochemistry. So I think Columbia was unusual in that the emphasis was on organic chemistry. In other places where biochemistry was taught, the emphasis was more on nutrition and physiology. Clarke didn't care about physiology, although all graduate students still had to take a physiology course. The emphasis was all organic chemistry and I think it was very good training.

SCHLESINGER: Who were some of the other students at the time you were there?

MAGASANIK: David Sprinson just finished when I started. He then had a very distinguished career at Columbia. I should say that being in Chargaff's laboratory was a little out of the main stream at Columbia because the great influence—although he had died a good number of years earlier—was [Rudolf] Schoenheimer, who introduced the use of isotopes, stable isotopes, into biochemistry. So other faculty members like [David] Rittenberg and [George D.] Stetten worked with stable isotopes and that was essentially in what Columbia was really a pioneer.

SCHLESINGER: But at that time it was heavy isotopes?

MAGASANIK: Yes, N15 and deuterium. And so, many of the other graduate students in the department were working either with Rittenberg or Stetten and were doing isotope experiments that were really quite different from what I was doing. Of the students that I remember, although I haven't had much contact with them, one is Jonathan Wittenburg, who later was on the faculty at Einstein [Albert Einstein College of Medicine]. Norman Radin, who I met recently again, is in Ann Arbor, Michigan. Of the women—Celia Levine was a student of Chargaff. She has just retired after playing quite a role in scientific education in San Diego. But she did not really have a research career of her own. It was always harder for women. Another student was Adele Karp, who became my wife. She was a student of Stetten and got her degree at the same time I did.

SCHLESINGER: And after you got your degree with Chargaff, did you stay in his laboratory?

MAGASANIK: I stayed for another year and Chargaff at that time had started to work on nucleic acids. In fact, the students that came after me, I think, most of them worked on those problems, like David Elson, who died just a few years ago after working for many years at the Weizmann Institute in Israel. And Steve Zamenhoff, who was then at UCLA. By the time I had finished in the laboratory, it was almost entirely being devoted to analytical studies on nucleic acids.

SCHLESINGER: And what did you work on?

MAGASANIK: I worked for that year on the analysis of RNA [ribonucleic acid], improving the methods of analysis by paper chromatography for ribonucleotides and carrying out a study on what we hoped was the structure of RNA by subjecting RNA to hydrolysis with RNase and trying to assess the effects on the sequence of the remaining nucleic acid as the hydrolysis proceeded.

SCHLESINGER: At the time that you were at Columbia was there agreement or lots of discussion about the role of DNA as the genetic material?

MAGASANIK: Well, when Chargaff started his studies on nucleic acids, he was firmly convinced that DNA was the genetic material. He took the experiments of [Oswald Theodore] Avery very seriously and really had no doubt. That's rather interesting, because the concept was not accepted by many biochemists. He started to develop methods for determining the base ratios of nucleic acids by paper chromatography. And the purpose, as far as DNA was concerned, was to show—which Chargaff firmly believed would come out— that if one examined DNA from different organs of the same animal, the base ratios would be the same, whereas the base ratios would be different if one compared DNA from different organisms.

And that's exactly what came out. Chargaff found, for example, some bacterial species had DNA that was very rich in G and others were relatively poor in G and so forth, and of course that is all very well known. But what also came out of these studies, and we talked about it quite a bit, was the so called regularities—the fact that G was always equal to C and A always equal to T. These ratios were duly recorded by Chargaff and published, but they really didn't make any sense. They were not what he had expected because he really wanted to show irregularities. So the appearance of regularities did not really fit into the concept of DNA from different organisms really being a different species. So that is what went on during the year that I stayed at Columbia.

SCHLESINGER: And what year are we now?

MAGASANIK: I stayed from the summer of 1948 to 1949.

SCHLESINGER: At that time was it usual to go on and on for postdoctoral training?

MAGASANIK: Nothing was terribly usual. Rules hadn't really been formed. I don't know whether I had any real expectations. I was in New York. Adele was in New York.

SCHLESINGER: Were you married?

MAGASANIK: No, we were not married at that time. She was working for Stetten, who had been at Harvard in the interval but had returned to New York and was working at the Public Health Research Institute of the City of New York, which was on 14th Street. She was working for Stetten then, if you want to call it pos-tdoctoral work. What I did with Chargaff was essentially post-doctoral work, but basically we just looked at it as a continuation of an academic career. It then happened that Clarke, who was head of the department, came to me to tell me that a position was open at Harvard in the Department of Bacteriology and Immunology and his friend, J. Howard Mueller, who was head of that department, had asked him to recommend a biochemist. Mueller had a higher opinion of the Columbia biochemists than of the Harvard biochemists; that was the reason he came to Clarke. Actually, somebody who had also been from Columbia, Max Bovarnik, had been working there, but was just leaving at the time. That seemed to be an interesting possibility. I think we met Mueller at a meeting in Detroit first and then I came up to Boston, where I gave a seminar. I found out later that Mueller had consulted the graduate students of the department as to whether they thought that I would be a suitable addition to the department. His idea was that, because of his own research interests, it would be a good idea to have somebody in the department who could help out with a knowledge of biochemistry.

SCHLESINGER: And what were his research interests?

MAGASANIK: Well, Mueller was essentially a biochemist, although he didn't admit it. He claimed to be a high-school chemist, which wasn't quite true. Although, he only had had high-school chemistry, so it may be formally true. He had a Ph.D. in pathology, of all things, and was a very remarkable man because he had, while at Columbia College of Physicians and Surgeons as an assistant professor right after the First World War, in the early 1920s, discovered methionine, and he discovered methionine as the growth factor for pneumococci. He had written, then, two papers (4) describing the discovery of methionine as an essential element for the growth of pneumococci and expressed in these papers the idea that by the analysis of complex media that the clinical bacteriologist used to grow bacteria, one would find new unknown substances that had a role beyond just being growth requirements for bacteria and also recognize known substances as playing a more important role in the physiology of all organisms then had been thought, and that, of course, was quite true. So he really initiated this type of chemical study on bacterial nutrition. He then went with [Hans] Zinsser, who was a virologist, to Harvard, because Zinsser was appointed head of the Department of Bacteriology and Immunology at Harvard.

SCHLESINGER: And where did Zinsser come from?

MAGASANIK: Zinsser was from New York and had been at Columbia at that time and had just gotten the offer for the position. Zinsser was interesting. Some people know him as a writer—he wrote Rats, Lice and History, the History of Typhus (5) and he wrote a rather interesting autobiography that's probably not known anymore. It was in the third person and was called As I Remember Him (6). Zinsser was an M.D. and knew what bacteriology was all about. So as the head of the department, he influenced Mueller sufficiently that Mueller gave up his nutritional studies and instead did some chemical studies on antigens. They were actually quite good, but not of major importance.

SCHLESINGER: At Harvard at that time, was Mueller an independent investigator?

MAGASANIK: I don't know how to assess the situation—Mueller came as an assistant professor and was eventually promoted to associate professor. As an assistant professor, I guess he did not have a tenured position and to what extent it was independent is hard to say. It is clear that, just as at Columbia, the department head made the rules, but after ten years, Mueller was clearly independent enough to return to his nutritional studies.

SCHLESINGER: When did Zinsser go to Harvard?

MAGASANIK: It must have been about 1924—1924 or 1925. So Mueller, about ten years later, was in a position to do whatever he wanted to do and returned to nutritional studies. And that he was very aware of it, although he never talked about it, was the fact that his first papers in the early 1920s are studies on bacterial nutrition, numbered, I think, one and two (4). Studies

on bacterial nutrition three and four are in the 1930s. And that was a great pity because at that time other people had gotten interested in bacterial nutrition, notably [Esmond E.] Snell, and although Mueller still did some very important work on bacterial nutrition there were now others who were also involved in making advances. If you read his original papers it is very clear that he knew exactly what to do and he could have gone right on with important work in the 1920s.

SCHLESINGER: When did Mueller take over the department?

MAGASANIK: I don't know exactly when. I know that during the Second World War—so we are now in the early 1940s—Mueller was already head of the department. Apparently it was then a question whether he would become Chairman because the other very eminent scientist in this field who remained at Harvard was [John F.] Enders. He was a great virologist. He also worked with Zinsser and could have been considered the choice for department head, but it was Mueller who was then chosen. But Enders remained at Harvard and worked at Children's Hospital.

SCHLESINGER: When you arrived in that department, who were the other faculty members who were there?

MAGASANIK: At Harvard, then, the large departments had two tenure positions, the small departments, one. Bacteriology by this definition was a large department and the two holders of tenure positions were Mueller as Professor and Monroe Eaton, who had already discovered, then, but continued to work on the so-called Eaton agent, the agent of atypical pneumonia. It was identified as mycoplasma at Harvard. It had first been thought to be a virus. Of the younger people who then became very eminent, there was [Albert H.] Coons, who had developed fluorescent antibodies. These were the ones who remained at Harvard after Mueller died.

SCHLESINGER: Did you have any teaching responsibilities at Harvard?

MAGASANIK: Actually Mueller asked me to help, of all things, to teach an immunology course for graduate students, so I helped with that for a while. I think I stayed a research fellow for two years but then became an associate and started to teach a course for medical students. I taught pretty much from the beginning. I gave the introductory lectures of general microbial physiology and then taught enterics and occasionally anerobic toxin producers.

The department was very interesting because of the personality of Mueller, who was head of the department. I think on the basis of his experience, Mueller had the rule that he would not influence anybody's work at all so that meant that his graduate students had essentially their own problems and worked completely independently. Mueller did his own research with one technician—coming in at six o'clock in the morning and working until about

10:00 p.m. Anybody who was in the department was completely on their own. On the other hand, he was very supportive if he thought the work was very good. As a result, when people came to Harvard essentially to be postdoctoral fellows with Mueller, he would get them to work with someone else in the department. So in that manner a young Scottish microbiologist, Marcus Brooke, ended up working with me. Then a visitor from Japan [Daizo Ushiba] was working with me.

Mueller arranged to have me nominated at Harvard for a Markle Fellowship, which was then a new Markle scholarship. The Markle Foundation decided that there was a need for people at medical schools to continue to do research. They set up a program in which they offered support for five years for people to work independently as junior faculty members in medical schools. The way it worked was that each medical school in the United States and Canada could nominate one candidate each year and provide a program or support for this candidate. The Foundation decided on this as a pet program and I was nominated by Harvard in 1951. I think I became an associate (the lowest faculty position) and a Markle scholar that year.

SCHLESINGER: What was your salary?

MAGASANIK: I remember, vaguely, when I started, I think it was forty-five hundred dollars. This was a reasonable salary for that position. Mueller told me that his salary was ten thousand dollars. So I continued teaching at Harvard and expanded my research due to having obtained first a grant from Harvard and then a grant from the National Institutes of Health [NIH]. That allowed me to pay for a technician and, as I mentioned before, I had postdoctoral fellows.

At that time, Harvard started an experiment in graduate education in the medical sciences. I obtained a grant to set up a laboratory for the first year of graduate study, which combined the efforts of all the departments. The way it worked was that one laboratory was equipped with work places for, I think, approximately twenty students and one member of each of the departments was to spend time teaching these students in the cooperative joint program.

One my first graduate students at Harvard, Fred [C.] Neidhardt, had finished the first year in this program and then came to my laboratory. But this was not the only student of mine. A second student, Helen Bowser [Revel], came directly to the department.

SCHLESINGER: I wanted to ask you a little about how you began your research program at Harvard, whether you brought projects with you or what you began to work on when you came to Harvard.

MAGASANIK: Well, my position, when I first came to Harvard, was actually that of a research fellow. The department had a fellowship, which belonged to the department, and Mueller used that because he felt that since I was coming as a biochemist and had no experience in bacteriology that I should not immediately start as an instructor or faculty member, but have this position, which was actually a research position. On the other hand, Mueller strongly believed that everybody should do their own research. I mean that's the way he did his own work, and so

I was absolutely free to do whatever I wanted to do. And the easiest way to start was to continue some of the studies that I had done at Columbia on the inositols. I first tried, and fortunately quickly saw that wasn't going anywhere, to do a strictly chemical problem since, as I mentioned earlier, oxidation using Acetobacter resulted always in the oxidation of a hydroxyl in an axial position. I wanted to see whether a dehydrogenation catalyzed by platinum would also preferentially bring about oxidation at the same position, and that to an extent was true. Then I felt this was really not an interesting problem and gave up very quickly doing these experiments, but instead decided to find out whether other organisms were capable of oxidizing or metabolizing inositol beyond a single or two oxidative steps and, if the degradation continued, whether the initial attack, by quite a different organism in the case of myo-inositol, would be on the same hydroxyl group, which had been oxidized by Acetobacter. So I discovered that Escherichia coli [E. coli] could not use inositol as a sole source of carbon—in other words, it could not oxidize inositol—but that another organism closely related to E. coli could grow on inositol as the sole carbon source. This organism, which was already a subject of much research, was then called Aerobacter aerogenes, but the genus is now called Klebsiella. So Klebsiella obviously had the ability to degrade the inositol molecule beyond a single oxidative step. So I decided to study the pathway of inositol degradation in what is now called Klebsiella aerogenes and that work turned out to be quite interesting. In fact, it turned out that the initial attack was the same as by Acetobacter; the same hydroxyl was oxidized, but then there were further steps, which led to the opening of the ring.

SCHLESINGER: What kind of methods did you use at that time?

MAGASANIK: Well, the standard method was to measure oxidation in the Warburg monometer because that gave you immediate information on how many oxygen molecules were taken up before the oxidation stopped. In addition, the methodology of the little manometers was developed to such an extent that you could use it to measure anaerobic breakdown by measuring carbon dioxide formation and acid production. Acid production was, for example, measured by doing the experiment—these were all intact cell experiments and what was used was called resting cells, that is you grew up a cell population, then collected the cells by centrifugation, washed them, and placed them in a manometer. For example, if you wanted to study fermentation, you would produce anaerobic conditions by flushing the manometer with an appropriate mixture either of nitrogen or a mixture of nitrogen and carbon dioxide depending on the experiment you wanted to do. And you could measure evolution of carbon dioxide simply by doing the experiments in phosphate buffer and measure the increase in pressure in the manometer and then determine by other means whether the gas produced was carbon dioxide or hydrogen, which could be done by finding out how much of the extra gas produced could be absorbed by alkali. The manometers were designed so that you could do these experiments very easily and you could measure acid production by carrying out these experiments in bicarbonate buffer and, in this case, the acid would bring about the release of carbon dioxide, which again you measured by increasing pressure and so on. So it was really a very versatile and useful instrument. Then you could carry out anaerobic or aerobic metabolism in the vessel and then analyze the content of vessels for other compounds that could have accumulated. So essentially you looked at the end products of the pathway and then you could use various inhibitors to block different steps of the pathway that were known from studies on glycolysis to block steps in the pathway and then find out what accumulated.

The interest in inositol degradation was that inositol served as a general carbon source in the same way as glucose and, of course, the pathway of glucose metabolism was by then known. The interesting question was: at what point would the degradative pathway of inositol merge with the pathway of glycolysis? So that was quite interesting simply from the biochemical point of view and eventually years later we did these experiments with isolated enzymes and worked out this pathway, but that was much later. What I also found then very intriguing was that in this organism (Klebsiella), cells that had been grown in the absence of inositol were not capable of immediately oxidizing or fermenting inositol, but acquired this ability in the Warburg vessel if you shook them long enough. In other words, there was a lag and eventually they would acquire the ability to metabolize inositol, but cells that had been initially grown on glucose did not have this ability.

SCHLESINGER: Had that been observed in other systems?

[The remainder of the first section is a corrected version and not a direct transcript.]

MAGASANIK: Yes, it was then called adaptive enzyme synthesis and enzymes were classified as either being adaptive or constitutive. It was known that the enzymes of glucose metabolism were constitutive because if you grew the cells on whatever carbon source—let us say inositol—and then placed the washed cells in a Warburg vessel and gave them glucose, they would oxidize the glucose immediately. So glucose degradation was constitutive; inositol degradation was adaptive.

About the same time—and actually as a parallel project because it had to do with particular strains of bacteria that could or could not utilize glycerol—Marcus Brooke was studying glycerol metabolism and I also got very intrigued by the fact that by degradation of inositol required adaptation, as it was then called. It was not yet called induction. So the enzymes were inducible. And one of the questions that had not been solved was whether induction was new protein synthesis. Now I had also collaborated with one of Mueller's graduate students, Ed [H. Edwin] Umbarger—and that is a typical example of how Mueller operated. Mueller became very interested in amino acid-requiring bacteria for the analysis of components from the medium required for toxin production of the tetanus bacillus. Mueller wanted to identify the essential components and realized that a good way of measuring them was to use bacterial mutants, which were blocked in the biosynthesis of appropriate amino acids. So he sent Ed Umbarger to the laboratory of Bernie [Bernard D.] Davis in New York to learn how to make amino acid-requiring mutants and to work with them and to do essentially whatever he wanted to do with them. And Ed chose to study isoleucine and valine using the appropriate mutants. I helped Ed with the necessary biochemistry, so I was quite aware of the use of amino acid requirements and decided to determine whether amino acids were necessary to form the inducible enzymes. The requirement for amino acids indicated that protein synthesis was involved. Some of these experiments were done by Daizo Ushiba, a more senior Japanese postdoc who had come to work with Mueller. He had also isolated a pyrimidine-requiring mutant. It appeared that the slant on which the mutant was kept was put in the refrigerator and looked peculiar. As a good microbiologist, he looked at the slant under the microscope and

noticed there were crystals. So we took the culture filtrate and put it in the refrigerator and the compound crystallized out. It was orotic acid, so it became very interesting that the substance of the blocked reaction accumulated. In this case it didn't help us all that much because orotic acid had already been identified as an intermediate in pyrimidine biosynthesis.

[END OF SESSION ONE]

MAGASANIK: When I got the position at the Department of Bacteriology, Adele got a position in the Microbiology Department in the School of Public Health with John Snyder, who was the head of the department. She was to work on typhus and what it involved was infecting eggs with ricketsia—because the ricketsia couldn't be grown any other way—and then to get preparations of the ricketsia and study their metabolism. Unfortunately, due to an error of a technician who created an aerosol of infected egg yolk, she was infected with typhus, which was a very dangerous condition. Fortunately, there was enough—I think it was aureomycin, which was not then commercially available. It was provided by Max Finland; that really saved her life. She was quite ill with typhus. After she recovered she continued to work at the School of Public Health and then later changed and got a position in Farber's [Dana-Farber Cancer Institute] laboratory in the Jimmy Fund, which was formally the Deptartment of Pathology, to essentially do independent research. She got her own grants and worked for a while on problems related to mine, but quite independently.

As I mentioned before, there were several distinct problems being studied in my laboratory. I will discuss them individually, particularly those that eventually were not continued. One problem was the pathway of inositol degradation. We had made good progress—still at Harvard—in working out the initial steps and identifying the fermentation products and therefore getting the general ideas of the pathway. Eventually, when I moved to MIT [Massachusetts Institute of Technology], we continued this work and identified the individual enzymes in the pathway. There were two graduate students who worked on that problem at MIT—Tom Berman and Alan Anderson. After that, this particular project ended. The other problem that I started at Harvard, which was very interesting, but then later did not continue at MIT, was purine biosynthesis. Originally we had collaborated with people at Sloan-Kettering [Memorial Sloan-Kettering Cancer Center]—because we didn't have the ability to work with radioactive isotopes—to do C14 experiments. Eventually we got the equipment and did the work ourselves and were able to show that there was in fact an irreversible pathway that led from inosinic acid via xanthylic acid to guanylic acid and that guanine-requiring mutants lacked either the first step of the pathway or the second one.

There was one rather amusing incident associated with this. Marcus Brooke had worked on this problem and initially, we had shown with mutants the accumulation of xanthosine, and therefore felt we had good evidence that this was the pathway, although we had not yet been able to isolate the enzymes or show the enzymatic reactions. At that time, there was a meeting of the bacteriological societies in San Francisco and we—Adele and I—drove to that. Marcus Brooke went to that, too, and presented this work. Arthur Kornberg had just become a professor at Washington University in St. Louis and had now decided to be a microbiologist because he was head of the microbiology department and he was at that meeting. Mark had done a very nice job presenting this work, showing that the guanine-requiring mutant accumulated or

excreted xanthosine. Obviously it can make the purine ring and so there is presumably a block in between the two purines (xanthosine and guanosine). Kornberg came to me and said, "I can't understand how you can say such things. Have you shown the enzymes?" I apologized and said that we were trying to and we would do it but didn't it make some sense to think that if a mutant excreted xanthosine and required guanine that a xanthosine derivative was on the pathway; and Kornberg said, "No."

So this work, and in particular the studies with radioactive precursors, also gave the rather surprising result that in the mutant blocked between IMP [inosine monophosphate] and GMP [guanosine monophosphate] guanine could still serve as a source of adenine. Radioactive guanine was still incorporated into adenine. On the other hand, there were mutants that indicated that the normal pathway went from IMP to AMP [adenosine monophosphate], so that said rather definitely that there had to be a way back from GMP to IMP that did not involve XMP [xanthosine monophosphate]. Eventually, when Jacob Mager from Israel worked in my laboratory, I tried to convince him that there had to be an enzyme that would reduce GMP to IMP, and he finally agreed there had to be and found the enzyme. So there is a little cycle in which IMP goes to GMP and GMP goes directly back to IMP via GMP reductase. So, in principle, it's a cycle, but since the first step—IMP to GMP—is inhibited by GMP, and AMP or ATP [adenosine triphosphate] inhibits the reaction from GMP directly to IMP because then it is not needed so it never actually works as a cycle but it could be one.

At the same time, studies of other mutants showed that histidine reduced the purine requirement. We demonstrated that the mutants were blocked between amino imidazole carboxylic ribotide and IMP and began to get evidence that in some way the purine ring was involved in histidine biosynthesis. After some false starts, we were able to show that there was a reaction that allowed ATP, in the presence of phosphoribosylpyrophosphate, to be converted to an intermediate and provided imidazole glycerol phosphate, which is on the pathway to histidine, and converted the rest of the purine ring back to amino imidazole carboxamide ribotide. So there was a purine cycle involved in the biosynthesis of histidine. This was one thing that I was particularly pleased with because it was one of those rare occasions—which is always very gratifying in science. I particularly remember how we couldn't understand our results at first and how by sudden illumination and one straightforward experiment the whole problem could be solved. We had evidence using the radioactively-labeled purine ring that one of the carbons—it was carbon two of the purine ring—would show up in histidine. So that was the result we knew. We originally thought of some other complications that had to do with adenine being inhibitory under certain conditions and we thought that this carbon came from guanine. Finally we convinced ourselves by working with mutants and radioactive labels that the carbon of the purine ring came from adenine. And then we didn't quite know how to tackle it biochemically. Harris Moyed was a postdoc with me and we read in a report something that struck us as being very bizarre. Somebody had reported that by incubating ribose phosphate and glycine with ATP and ammonia—in other words, providing many of what were recognized building blocks in purine biosynthesis—it was possible to synthesize amino imidazole carboxamide ribonucleotide. However, it appeared unlikely that crude extracts could carry out all these steps effectively and all the work was done in a mutant that was supposedly blocked in this pathway. It was extremely puzzling, so we decided to take a look at that. So Harris Moyed set up the experiments, and lo and behold, it was correct. We knew it couldn't be because it was a mutant that was blocked in the pathway. But nevertheless amino imidazole carboxamide ribonucleotide was formed when you incubated ribose phosphate, ATP and ammonia. So that

was extraordinarily bizarre. And then it turned out by experiments of Harris Moyed that if you didn't add ammonia, but if after incubation of just phosphoribosylphosphate and ATP you subjected the mixture to fairly mild acid, you would also get amino imidazole carboxamide ribonucleotide. So it was clearly not de novo synthesis and the only possible source of it could be the ATP that was added. We were completely puzzled why incubation of ATP with phosphoribosylpyrophosphate should suddenly produce something that readily hydrolyzed to amino imidazole carboximide ribonucleotide. Why would ribose phosphate pull carbon-2 out of the ATP?

I remember that, for some reason, I was walking in Cambridge, near the Bio Labs, and I suddenly realized what was going on. After all, we were interested in histidine biosynthesis. So the probability was that this compound was on the way to histidine, since we already knew that this missing carbon of the purine ring turned up in cells in histidine. So I said we would do a very simple experiment. We will keep ammonia in and if ammonia and ribose phosphate were there and you need the additional carbon from the purine ring and maybe a nitrogen, then the product of the reaction other than amino imidazole carboxamide ribonucleotide should be imidazole glycerol phosphate. So we simply did the incubation and found imidazole glycerol phosphate, and it was the solution. So that was very gratifying because we had discovered the first step of histidine biosynthesis. It was very nice because it showed that there was a purine cycle involved in the biosynthesis of histidine. We then did some additional work, including some work with N15 that then showed quite convincingly that this cycle existed. There was a rather interesting thesis by Alex [Alexandra E.] Shedlovsky [Dove] arising from the instability of some of the enzymes involved (7). We did not continue that work. Bruce Ames, who was studying histidine biosynthesis then, really became much more involved in analyzing these reactions. Essentially, after publication of the paper on the cycle and Alex's papers, we did not continue working on histidine or purine biosynthesis (8).

The other problem became very interesting because of the results of the glucose effect. The finding that histidine was destroyed when glucose was not present in the growth medium led us now to study, on the one hand, the pathway of histidine degradation. Another graduate student, Helen Bowser, worked on that problem and worked out the steps of histidine degradation in Aerobacter aerogenes. Fred Neidhardt worked on the induction and the effect of glucose on the induction of the histidine-degrading enzymes. He did the most interesting experiment—that has kept us going ever since—which was asking Klebsiella what it could do when provided in the medium with glucose and with histidine as the only nitrogen source. If glucose prevented the formation of the histidine-degrading enzymes, the organisms wouldn't grow. If, on the other hand, glucose would not block the induction of the enzymes under these conditions, the organisms would grow, and that turned out to be the case. So this led us then to formulate a hypothesis of the glucose effect, which was based, as it turned out eventually, on false premises, but is in principle, on the physiological level, still a perfectly valid hypothesis.

The way we reasoned was that the synthesis of the histidine-degrading enzymes would not be blocked by glucose alone but would be blocked by glucose plus ammonia. As far as the cell was concerned, the products of histidine degradation were carbon building blocks and energy as well as nitrogen, because ammonia was one of the end products of histidine degradation. So the fact that the induction of enzymes occurred when a poor carbon source other than glucose was present suggested that it was the overproduction of catabolic products arising from glucose that was responsible for the repression. If you lifted that by providing

nothing but histidine, or histidine plus a poor carbon source, that made sense. We said the other end product of degradation is ammonia. As far as the cell is concerned, as long as you provide all the end products, namely energy and ammonia, the enzyme synthesis does not take place and there is repression, but if you leave one or the other out then the enzymes can be formed. So we looked at the entire effect as feed back repression. And we explained the fact that in the cells growing on glucose-histidine, addition of inositol still did not allow the induction of the inositol-degrading enzymes because the only end products of the inositol-degrading enzymes were energy. Energy and building blocks that, of course, as long as glucose was there all these products were being provided so there would be repression. Eventually it turned out that the reason that the cells produced the histidine-degrading enzymes in the presence of glucose in the absence of ammonia was a totally different one. It became clear with later work on nitrogen regulation. But the hypothesis that the glucose effect, which was then called catabolite repression, was due to excess production of the end products of glucose metabolism, which could also be obtained from degradation of these other carbon sources, still holds pretty well.

We did a number of controls—for example we did the obvious thing of showing that glucose did not work by keeping inositol out of the cell and other things like that, but with [Jacques Lucien] Monod's hypothesis of induction being due to a repressor and the beginning of molecular models, you couldn't even think in these terms. Until Monod presented this hypothesis, nobody had visualized a molecular mechanism. In many ways, it was Monod's discovery and the PaJaMo (Pardee, Jacob, Monod) experiments that led to the concept of mRNA, and without mRNA one could not even begin to think about molecular control mechanisms. Although Monod had come up with the repression model—I guess 1958 was the PaJaMo experiment—it took a number of years after that before we clearly understood—that was the early 1960s—what messenger RNA was and how transcription was being regulated.

SCHLESINGER: Did you have any questions or doubts about some of these models?

MAGASANIK: No, I think that we accepted both of them, both the repression and the concept of mRNA. In fact, after Fred Neidhardt finished his thesis, he went to France as a postdoctoral fellow and then came back and continued to work with me, but on a different problem, mainly the relation of protein synthesis to a level of total RNA, which was ribosomal RNA. These results provided very good evidence that the rate of protein synthesis was always directly tied to the amount of ribosomes in the cell and that there was a control mechanism, which saw to it that the cell had just the right amount of ribosomes relative to the rate of protein synthesis.

SCHLESINGER: When did you meet Monod?

MAGASANIK: I had met Monod on his visits to Boston. I think it was 1958 that Monod was invited to give the Dunham Lectures at Harvard Medical School. Bernie Davis was the head of the department and he asked me to act as host. So I saw quite a bit of him in Boston at that time. Then I took a sabbatical in the second part of 1959 and we went to Paris and I chose to work in Monod's laboratory. I worked on a problem that Monod suggested. It was at the time when there were reports that you could make spheroplasts and damage the spheroplasts and get

synthesis of beta-galactosidase in the system. Monod didn't believe it, but he wanted me to try to do experiments of this sort and see whether there was anything to it and so I worked on that.

Adele worked with me on that. That is the only time we worked together. My impression was that it was not a useful system and that the results were meaningless. I was only in Paris from about February until September. So it was not a long period. But what had also interested me in Paris was this strange phenomenon of the lifting of the catabolite repression in the case of histidase. It was clear at that time, particularly in view of Monod's results, that if I wanted to study such a problem I would need a system where I could do genetics, which up to then I hadn't done other than just to isolate mutants. There was no good system for transfer of genetic material in Klebsiella, so if I wanted to study the regulation of the histidine-degrading enzymes, using a genetic approach Klebsiella was out of the question. But the same enzymes also existed in Salmonella typhimurium and there was a good system of transduction in Salmonella. So what we wanted to do in Paris was to see whether we could get started with Salmonella and see if we could study histidine degradation there. Now, it turned out that not all strains of Salmonella degraded histidine, and the strain that was usually used in genetic experiments, which was the LT2 strain, did not grow on histidine as a nitrogen source. But François Jacob found us other related strains that did, and he also found transducing phage for these strains when we were in Paris. So that was great because we now had organisms that would degrade histidine by the same pathways as in Klebsiella and where a genetic system was available. The only trouble was that Salmonella did not show the phenomenon that Klebsiella showed. When Salmonella were given glucose with no nitrogen source, they simply did not grow. So the particular problem that we were really interested in we could not study in Salmonella, but nevertheless we could use Salmonella to just get some information on the genetic organization of the histidine-degrading enzymes.

While I was in Paris and just before I left for Paris on sabbatical, Salvador Luria, who had joined MIT about a year earlier, had brought up the question of whether I would not leave Harvard and join MIT. Now I have to go back and say something about Harvard in those days. In the medical school, the big departments (like biochemistry and bacteriology) had two tenure positions; the small departments, like pharmacology, had one tenure position. So that once you were at Harvard, the outlook for getting tenure was essentially zero. Nevertheless, when Bernie Davis came to Harvard, he wanted to get me a tenure position and I asked him to delay it one year, but I did get tenure at Harvard—an additional position. Nevertheless, I was very tempted to leave for MIT for a variety of reasons. One of them was that Adele was not that happy being alone at Sidney Farber's Institute at the Jimmy Fund. We had worked together in Paris and she wanted to work with me. And the other reason was there were some tensions at Harvard. Although I got along with Bernie Davis rather well, other people were frightened and intimidated by him, particularly the younger faculty members, and I was in the middle.

I had enormous respect for Salva Luria and I was at that time very friendly with Cy and Jeanna Levinthal. Cy worked at MIT, so there was a great temptation to join Cy and Salva at MIT, where there were plans to change the direction of the department. So while in Paris, I went back to talk to the people at MIT. When I came back, the decision was made that I would move across the river to MIT.

I came back to Harvard in the fall of 1959 and it was already decided that I was going to move to MIT and was formally to start in my position at MIT in January. In reality, I moved in

the summer of 1960 and we got new labs fixed up. This was before Building 56 had been built at MIT; it was still Building 16. The set of labs, at one point, had been teaching laboratories and they were redone properly, so they were very nice laboratories next to Luria's laboratories.

A number of people who had been working with me at Harvard—postdocs and graduate students—came over to MIT: Jocko Roth, Bernie Weinstein and Dave Kennell, all of whom had been at Harvard, and Betty McFall, who then a year later left for England on a fellowship and then returned to MIT. A technician and scientific coworker, Patricia Lund, from Oxford, from Krebs' laboratory, also came to MIT. Alex Shedlovsky had finished her degree, but continued to work and Harriet [Kaufman] Meiss and Don Nierlich, who were finishing their dissertations at MIT, although they got their degrees from Harvard. So the move was very smooth for me. Nothing could have been easier than waiting for the labs to be completely set up and then just carrying over some of the equipment and starting again. MIT, of course, was a very different environment and presented its own challenges as far as the teaching and the general organization of the department was concerned.

SCHLESINGER: Why don't you talk about some of the research directions that you continued at MIT?

MAGASANIK: Well, at MIT at that time, what turned out to be a major line of research was Harriet Meiss' work that continued what we had done in Paris. She was working with Salmonella and trying to do the genetics and the biochemistry on histidine degradation in Salmonella. Later, a postdoc from Illinois, Winston Brill continued this work. The other line was the work with Klebsiella. Patricia Lund had been working on this and then Sondra Schlesinger joined the laboratories as a research fellow and continued to work on histidine degradation. A postdoc from Italy, Piero Scotto, joined that group. As I mentioned before, we were no longer working on purine or histidine biosynthesis. We were mainly working on histidine degradation in both Salmonella and Klebsiella. Other graduate students, first Tom Berman and then Alan Anderson continued the enzymology of inositol degradation. So these were the important problems at that point.

Another graduate student, Lee Hartwell, joined the lab and then we started on a new problem, which was really suggested by Cy Levinthal's work at MIT. Cy found that in B. subtilis, actinomycin D could be used to block synthesis of mRNA. Cy had done some very interesting studies showing that the mRNA decayed very rapidly after actinomycin D had been added. This was done first by labeling the RNA and then determining which fraction and at what rate the radioactive molecules decayed after the addition of actinomycin D. We attempted to do the same type of experiment with enzyme induction. Still sticking with histidine, what Lee Hartwell worked on was to induce the histidine-degrading enzymes in B. subtilis (now a third organism) by the addition of histidine. He added actinomycin D at different intervals and determined how much histidase would be formed relative to the time at which the actinomycin D had been added after the induction had begun. Then he also determined how much histidase was formed after the addition of chloramphenicol. This would determine, after protein synthesis had been stopped, how much enzyme accumulated simply by the proper folding of pre-existing molecules. That gave extremely interesting results because it showed that upon induction, the synthesis of mRNA started immediately but there was a lag period before any enzyme activity

could be found. Eventually, it turned out this lag was due to the time required for the actual transcription of the genes. His work was then laterextended to beta galactosidase in our laboratory by Ray Kaempfer and also in other laboratories.

There was another project carried out by a Japanese postdoc, Dai Nakada. Dai was interested in studying ribosomal RNA synthesis and the fate of the RNA after the addition of actinomycin D.

The work on histidine degradation in Klebsiella that Sondra was doing was to use non-metabolizable analogs as inducers of histidase. This derived from Monod's work using nonmetabolizable analogs of lactose as inducers of beta-galactosidase. And the work with histidine analogs had very interesting results because they showed that histidine itself was not the inducer of the system, but rather the product of histidine, urocanic acid, was the actual inducer. It was possible to induce the system with an analog of urocanic acid—imidazole proprionic acid. And, in fact, mutants that lacked the enzyme urocanase and were unable to degrade urocanic acid had constitutive levels of histidase. The mutants led us to conclude that only urocanic acid, not histidine, was able to induce the histidine degrading enzymes in Klebsiella.

[END OF SESSION TWO]

SCHLESINGER: Let's begin today with your move to MIT and your career at MIT, which began in 1960.

MAGASANIK: Let me talk first about the research. One of the problems that I was still working on at Harvard was, as I told you last time, purine biosynthesis, particularly the interconversion of the purine nucleotides and the role of purine biosynthesis in the synthesis of histidine. This work was not continued at MIT. On the other hand, the other problem that had started at Harvard, which was the degradation of histidine in Klebsiella aerogenes, was continued and led to relatively important results. As a byproduct of this work was Sondra Schlesinger's discovery that L-methyl histidine served, in an indirect way, as an inducer of the histidine-degrading enzymes and did it by causing overproduction of histidine due to the derepression of the histidine biosynthetic enzymes. This was an important result because she was further able to show that L-methyl histidine acted by inhibiting the transfer of histidine to tRNA and this finding suggested that the actual regulator of the synthesis of the histidine biosynthetic enzymes was histidinyl tRNA rather than histidine itself. This eventually, many years later, led to the discovery that certain enzymes of amino acid biosynthesis—among them those for histidine and tryptophan—were regulated by attenuation, which was of course the discovery of [Charles] Yanofsky. We also did some work on catabolite repression of b-galactosidase, which was of moderate interest and led to some problems that have not yet been solved. But my major interest was a project that had been started by Fred Neidhardt at Harvard, namely to understand the regulation of the enzymes of histidine degradation by ammonia. There it had been shown that in Klebsiella aerogenes growth on glucose-histidine in the absence of ammonia allowed the expression of the histidine degrading enzymes to be activated. It was clear that we had to study this problem at the genetic level, but since there was no genetics

available in Klebsiella, we turned to Salmonella typhimurium. In Salmonella typhimurium you could do good genetics and our studies of the system led to the recognition that the enzymes of histidine degradation in Salmonella are set up as two operons that are closely linked and that the repressor, which negatively regulates the expression of these two operons, is itself a member of one of the two operons—the first example of autoregulation, as it is called now. Nevertheless, Salmonella typhimurium did not show the phenomenon that had really interested us. Namely, in contrast to Klebsiella aerogenes, Salmonella typhimurium was unable to grow on glucose-histidine. In other words, lack of ammonia in Salmonella typhimurium did not activate the formation of the histidine degrading enzymes and it was only in approximately 1970 when strains of Klebsiella aerogenes became available in which transduction by phage could be used that we returned to this problem and now studied it in Klebsiella.

This work in Klebsiella then led very quickly to the realization that the enzyme glutamine synthetase played a major role in this regulation, and that the formation of glutamine synthetase, that is, the expression of its structural gene glnA, was itself regulated in response to the availability of ammonia. We got, in this matter, a clue to the phenomenon of nitrogen regulation, which is quite distinct from catabolite repression, which is regulation in response to the availability of an energy source. Most of our work since this period has been on that problem. Initially we worked on Klebsiella. Then we found that the genes for histidine degradation which served as indicator of the process, could be transferred to Escherichia coli so the work shifted to Escherichia coli, which was more conveniently handled and where better genetic systems were available. And as the new technologies developed—like cloning, sequencing of the genes, identifying the regulatory proteins, we could push these studies further and further. We had extended this work already a number of years ago into a study of nitrogen regulation in Saccharomyces cerevisiae, and that is the work that is still going on in my laboratory. At the moment we have a rather good understanding of the phenomenon of nitrogen regulation in enteric bacteria at the molecular level. In yeast, the work is still more physiological and genetic, but we have isolated some of the regulatory proteins and hope to bring this work closer to the molecular level.

SCHLESINGER: In general, do you have an impression of which of the studies in your lab may have made the most important contribution?

MAGASANIK: If I look back and somehow try to summarize all the studies I have been engaged in, probably the most important ones were the work on the interrelation of purine biosynthesis and histidine biosynthesis, the recognition of catabolite repression as a physiological phenomenon in bacteria, and then, now for a long time, the work on nitrogen regulation, which had important results in that it revealed for the first time—by discoveries simultaneously made in Sydney Kustu's laboratory and my laboratory—of a new sigma factor that was responsible for the transcription of some nitrogen regulated genes in response to availability of nitrogen. In addition, we found that the promoters that use sigma 54 RNA polymerase are regulated from distant sites. In other words, they behaved like eukaryotic enhancers that had already been recognized. This work also led to the identification of the molecular mechanism of so-called two-component systems, in which it could be shown that the product of one gene, a kinase, acts by bringing about the phosphorylation of the product of another gene, a response regulator, in response to changes in the environment. This is quite a

general phenomenon, but we were the first to show that the mechanism was phosphorylation and that it involved a histidine residue on the kinase and an aspartate residue on the response regulator.

SCHLESINGER: In addition to your research at MIT, you played an important role in the department. Do you want to discuss some of those activities?

MAGASANIK: I want to go back to the time when I moved to MIT. It was a very exciting period in that just before that, a complete change in the department had occurred with a new direction toward molecular biology. The person that was closest to me was Salvador Luria, who was a very eminent microbiologist who soon after was honored with the Nobel Prize. Salva also had a very clear view of the direction in which he wished the department to move, particularly microbiological research and teaching. He saw at a very early point that the department should also have faculty members who studied mammalian cells in tissue culture so that it broadened, in a sense, the definition of microbiology, although this then became cell biology. And it was also a period where Cyrus Levinthal who had very definite ideas, and very progressive views on the teaching of modern biology, was a member of the department. And so many innovations in the teaching and organization of the department occurred at that time. I participated in that, becoming—I don't remember the year exactly, probably 1963, about three years after coming to MIT—responsible for the graduate program in the department, and becoming in 1967 head of the department, which was because the position had been vacated by Professor Sizer, who had become Dean of the Graduate School. At that time it was decided to make the department headship a temporary position, so my term was to run five years. Actually, I served a second term afterwards, so my total service as department head was from 1967 to 1977. And I particularly had the cooperation of Gene [M.] Brown, one of my colleagues in biochemistry, which was part of the department, of course. That was important at MIT, then, that all areas of biology were within the Department of Biology, without any particular distinction of field.

And this period from 1967 to 1977 was generally a period of great expansion at the universities. It was at that time that the number of students tended to increase due to changes in the population birth rate, the baby boom reached the universities, funds were relatively readily available, and the University was very interested in enhancing the involvement in biology. So it was a very good period to be head of the department. It was during this period, I think, that the size of the department almost doubled. I would have to look at the figures, I don't remember them anymore. And many people who joined the department when I was head of the department are still with us, which is a very pleasing record if you consider that our policy was, for a large part, to hire people at the assistant-professor level without tenure, with the expectation that we could judge the quality of our faculty members so well that we had a high expectation that these people would eventually obtain tenure positions at our institution, and that is in fact what happened to a large extent. So these were rather interesting years. I continued my research during that time, which was quite possible when you're a department head particularly since Gene Brown was First Executive Officer, as it was called, and then Associate Head. So I had very excellent help, and Gene is a particularly good administrator, so that I could continue my research during that period.

Now, this period, as you might work out from the dates, also included the period of political unrest due to the war in Vietnam and general student unrest, which was handled very well by the MIT administration, where it did not come to the unpleasant confrontations that characterized the events at Harvard and Columbia. So that was a rather good period to be department head for somebody whose heart was more in research than in administration because I noticed at that point that I took administration seriously but it didn't break my heart if something didn't work out. I felt much more worried about the progress of research—I was much more involved in that. So after 1977, when I relinquished this position, Gene Brown became my successor and his successors since then have had to deal with worse problems, or rather less-pleasant problems, in that conditions are not as favorable as they were in the late 1960s and early 1970s.

SCHLESINGER: I wanted to ask you about any particular difficult decisions you had to make as chairman?

MAGASANIK: Well, the usual decisions that had to do with people. So in other words, decisions on hiring somebody or granting tenure, recommending somebody for tenure, were always very serious. Fortunately, we were lucky, and most of our decisions to promote people to tenure were positive ones.

SCHLESINGER: Were there any highlights of this period that you remember in terms of your administration.

MAGASANIK: One of the very important events that took place during that time was the establishment of the Center for Cancer Research. And that was Salva Luria's idea, which I supported, and it has been an outstanding success. It allowed us to have a very good research institute, or rather "center," as it is called at MIT, because obviously you can't have an institute at the Massachusetts Institute of Technology. And we worked it out very well and almost all the credit belongs to Salva. Particularly in the arrangement that although these people were brought in to carry out specific research on cancer, they had full standing as members of the faculty and participated in teaching approximately as much as all other faculty members. So it was an interesting period of setting this up and hiring the people, which again allowed an expansion of the department and the negotiations with the administration to make that a successful enterprise and it has become a very successful enterprise.

SCHLESINGER: Did you have much interaction as an advisor to any of the national committees or any of the national organizations?

MAGASANIK: I was never that interested in outside activities, so I had relatively little to do with them. Although, I served on study sections and I was elected to National Academy [of Science] in 1969. And I served on some committees of the National Academy but, by and large, I've had very little involvement in scientific matters outside of MIT.

SCHLESINGER: After you were no longer chairman, did you maintain an active administrative role in the department or were there other issues that you were involved with?

MAGASANIK: Well, the only major issue that came up—I forget the exact year but that was certainly in the 1980s—was the question of the establishment of the Whitehead Institute. Gene Brown was then head of the department, and I still remember that I hadn't heard much about the whole idea that there would be a research institute associated with MIT for which David Baltimore had been chosen as the director. So that when that was presented at a departmental meeting, simply as a fact that the administration was in favor of it and it was going to happen, I was very much opposed to the idea of not thinking about it in some detail and working out the detailed relationship. So I opposed it at that faculty meeting, not in principle, but just feeling that there were many issues that were raised by the idea to do something that had never been done before in quite that form, and to have an institute that was independently financed yet associated with MIT where the senior scientists would all have faculty positions at MIT. This could not just be done by fiat, but had to be thought over, and the exact conditions of the association had to be established. So as the result of my opposition and that of other members of the department, a departmental committee was set up, of which I was chairman, to make suggestions about how, in the view of the department, the association should be structured. Francis Low, a physicist, was then Provost and responsible for working out the relationship as far as the Institute was concerned. After the departmental committee had done its work, I was then a member of the committee, which was composed of people representing the Whitehead Institute-to-be: a lawyer who was a close associate of Mr. Whitehead, David Baltimore, of course, the Provost, and myself as representative of the department. And in the end I was very pleased that, by and large, the association that was worked out was based on the recommendations that our departmental committee had made, and it has worked extremely well to really everybody's pleasure over the years.

SCHLESINGER: Do you want to discuss some of the issues that caused the department to be so upset, some of the pros and cons?

MAGASANIK: The main problem that arose immediately was the question of what the duties of the faculty members at the Whitehead Institute were to be, relative to the teaching obligations and the departmental obligations of other members of the department, and what control there would be about salary, about working conditions, and about promotions. Was Whitehead to act completely independently or in what way was it going to follow the rules existing at MIT? This had to be looked at. Another very important issue was the question of support for graduate students. In our department, we had a training grant and we had always supported all the first year students on the training grants or other funds so that they were not obliged to anybody. That support continued for several more years. I think originally it was unlimited, now I think it is for a total period of three years while they are doing the research for their dissertation with a member of the department. So that immediately raised a problem: if additional department members were to be added by the establishment of the Whitehead Institute, we had to increase the number of graduate students. Where would the funds come from? And who would be

responsible for supporting the students who went to Whitehead? And this all had to be worked out and we drew up extremely good rules, which have worked very well, over the whole period of the existence of the Whitehead Institute. For example, as far as students are concerned, Whitehead promised, as part of the agreement, to support first-year students, in a number proportional to the number of faculty members at the Whitehead Institute, without any commitment. Students are still free to choose to work with anybody at Whitehead or in the department. So they might get more students than they had supported in the first year or fewer students. And that has worked out perfectly well. They had to promise to support all students after the first year who would choose to work at Whitehead. In other words, they could not count on the training grants of the department for the support of the students because it would have strained us much too much to do that. It was decided that the same rules for appointments and for tenure, and in principle for salaries, obtained both at Whitehead and in the department, although the money for salaries at Whitehead came from Whitehead funds and not from the departmental funds.

SCHLESINGER: And you seem to think that everything had worked very well? Do you think you are expressing the opinion of all the departments?

MAGASANIK: I can't say that. As far as I know, certainly the people who played relatively important roles in the activities of the department seemed to be very pleased with the result and certainly support Whitehead. It has been a relation with very little strain and that certainly was found by all the department heads that have dealt with Whitehead since it was established. Another agreement was made that Whitehead would provide a very large, I don't remember the exact amount, but several million dollars as an endowment to support biology at MIT. Basically in view of the fact that they were taking advantage of the already existing biological strength at the Institute, and MIT made the quid pro quo that formally established a chair, a Whitehead institute chair—a professorship in the department, which was a perfectly agreeable arrangement. And as far as new appointments are concerned, it has worked extremely well in that search committees for faculty positions at the Whitehead always have members both from the department and from Whitehead. And similarly we have used people from Whitehead for search committees for positions in the department and the people at Whitehead have played a very strong role in teaching. Nobody has shirked on the grounds that they really are not paid by the Institute to teach—it has never come up. So all in all, I find that the relation has worked extremely well. There has probably been a bit of jealously because they had a new building and therefore better facilities than we have, but that should be equalized now when we are getting a new building for the department.

SCHLESINGER: You mentioned teaching, Boris. I wonder whether we could discuss a little bit about your role in teaching and how you view your role as a teacher. When you discuss that, I would like to hear some comments about teaching, in terms of giving lectures—whether that is something you feel is useful—and your view on teaching your students and postdocs on a more individual basis.

MAGASANIK: Well, one of the reasons I preferred to leave Harvard Med School and come to MIT was my interest in teaching, which is taken much more seriously at a university and particularly at MIT. So the mix, as far as teaching was concerned, became a completely different one. At Harvard Medical School it was medical students and graduate students, and teaching medical students has the advantage that you deal with usually highly-selected, therefore, very good students. It has the disadvantage that they are under a great deal of pressure to do many different things and they have a very hard time in really getting involved in the particular things that interest faculty members of the pre-clinical departments. The interest is different at MIT because, here, it's teaching undergraduates and graduate students. As far as graduate students are concerned, the difference is not that great. We do certainly much more teaching than at the medical school and I have always enjoyed that. I've taught both undergraduate lecture courses and graduate courses and, of course, I've had a good number of graduate students working on their thesis research in my laboratory; that's a form of teaching. I enjoy lecturing and think, although I can work well in small groups, I'm probably a little bit less good in leading discussions to draw students out. As far as teaching is concerned, I taught for many years now, first jointly with Salva Luria and more recently with Graham Walker, an undergraduate course in microbial physiology, which has biochemistry as a prerequisite so it is usually taken by juniors and seniors, which has always been very gratifying. I taught for a number of years. When we decided to offer the introductory biochemistry course in both semesters, the portion on intermediary metabolism in the biochemistry course, I taught for a number of years, together mostly with Leonard Guarente, a graduate course in the regulation of gene expression in procaryotes and yeast. At the moment I have just finished teaching the microbial physiology course this year and I've begun to plan the teaching of a version of the introductory biology course that will be taught for the first time a year from this spring. That is because the MIT faculty has made introductory biology a general Institute requirement.

SCHLESINGER: Do you have any comments about that. Is it a good idea or not so good?

MAGASANIK: It had been in the air for quite awhile and was never strongly pushed by our department, mostly because it is a very serious obligation. It has a number of problems. For example, so far, the general Institute science requirements, that is, those subjects all students at MIT have to take—and generally take in the freshman year—have been two semesters of physics, two of mathematics, and one semester of chemistry. One version of it is taught by the Chemistry Department and one version, which is somewhat different, is taught in the School of Engineering by the Department of Material Science. As for as the students in engineering, which are now the largest group at MIT, they clearly view physics and mathematics as real requirements in that their engineering subjects are based on these fields. They feel somewhat more of two minds about chemistry, which I think obviously is needed by the chemical engineers and by the material science people, but is looked at with a certain amount of disfavor by the electrical engineers.

Now, biology, as far as the engineers are concerned, is really not a requirement in the sense that any of the subjects they are going to take later are based on it, and it is much more a cultural requirement as are the humanities requirements, which are also general Institute requirements that have already existed at MIT for a long time. So what I see as a problem is that we will, for the first time, teach students required to take this subject. It increases our

teaching load enormously. We have given for many years an introductory course in biology, which was taken to a considerable extent also by students who then did not go on in biology. In fact, it was first taught by Cy Levinthal, then by Salvador Luria, and later by Vernon Ingraham. I bring that out mostly in order to show that the policy has always been to have very senior people teaching the most basic course, but up to now it was always taken by people who took it because they were interested. Perhaps the largest number of students was one hundred fifty students. Now we will have to teach between nine hundred to a thousand students and most of them will have to take it whether they want to or not, which will present a somewhat different relationship, which we so far have not experienced. Thus, I have some misgivings about that, but consider it an interesting challenge. It has already been decided that we would give three versions of the introductory course. One in the fall semester and two in the spring semester and they should have—Phil Sharp, the head of the department calls it—somewhat different flavors. Now my impression is that two of the versions, which have already being tried out last year and will be tried out again next year, or rather this year again, don't have very different flavors, but all the courses have in common that they will provide the basic information in biochemistry and genetics and molecular biology. The version I plan to teach, together with Penny Chisholm, a microbiologist in the Department of Civil Engineering who is interested in ecology, will be a version that will be much more heavily based on microorganisms. One can teach the biochemistry and genetics just as well with microorganisms with some departures into higher organisms and with ecology, that is, with emphasis on the particular microbial world that surrounds us, and with discussions on in what way does it effect our lives. So that version will really be somewhat different. So I consider that a very interesting experience and the plan is that I shall probably do it for a number of years, probably two or three years, and one of the younger department members, probably Graham Walker, is going to take that over.

SCHLESINGER: In describing the course that you're planning to give, would you have students read original papers or are you thinking of teaching it from a historical point of view? What is the direction that you will take?

MAGASANIK: Well, I probably won't ask the students to read original papers at this level because they are going to be first-year students. It is extremely hard, it takes a fair amount of training to be able to get the gist out of an original paper. We will definitely use textbooks. Since I like history, I probably will start out with the beginnings of microbiology and biochemistry, which is the work of [Louis] Pasteur, and present his role in determining that the chemical changes that occur in fermentation are due to microorganisms and what follows from that, as well as the question of spontaneous generation. But I will probably, after that, proceed more or less in a logical way, taking up biochemistry first and then genetics.

SCHLESINGER: With your interest in history and teaching have you ever thought of writing a textbook?

MAGASANIK: On the history of biology, no.

SCHLESINGER: Or just a general textbook?

MAGASANIK: No, I'm too lazy. That's probably the answer.

SCHLESINGER: Microorganisms, particularly bacterial, like E. coli, played such an important role in the history of molecular biology. I wondered if you had any ideas or thoughts about what the future of this type of research will be?

MAGASANIK: Well, it's quite obvious that most of the research now of greatest interest has shifted to higher eucaryotes, so that the most interesting work one hears presented at seminars and finds published in the best journals like Cell and MCB no longer deals with microorganisms but rather with questions of development, immunology, aspects of virology, so on and so forth. And it's also been my experience that over a rather long time I have had no graduate students come to my laboratory to work on a thesis dealing with procaryotic organisms. The last group of students I had all wanted to work on Saccharomyces cerevisiae, which is, of course, a eucaryote. So it was more fashionable and that's a shift in general in the department, and course in other places. It's probably not a completely happy trend in that there are many problems of simple procaryotes such as E. coli that have not yet been solved and the advantage of working with such an organism is that one can obtain very clear results that really elucidate mechanisms at the molecular level, which it is not always possible to do in the eucaryotes. I noticed that there is now a great deal of work in progress with organisms other than E. coli and particularly, for example with cyanobacteria, which are fairly far out but are of enormous interest in their control mechanisms and control of gene expression. Mechanisms for control of gene expression are being discovered that differ considerably from those found in E. coli. And another problem that is of considerable interest in microbiology is differentiation, for example, spore formation. And then problems, for example in nitrogen fixation, the interaction of procaryotes with plant cells and those of my colleagues that work on these problems attract very good students. So I think the future research in microbiology will probably move away from enteric organisms and deal more with organisms that present new problems that really haven't been studied so far. But certainly in the foreseeable future, microorganisms will not play the central role in molecular biology that they played twenty years ago.

SCHLESINGER: But surprisingly, at least to me, microorganisms have played an increasingly important role as disease causing agents.

MAGASANIK: Well you're right, new bacterial diseases have come up that nobody expected—and new viral diseases. And I should have mentioned, of course, that this is one very important area where research is very new; namely the mechanism by which microorganisms cause disease. When I was at Harvard Medical School, we always talked about the fact that we should, as the faculty of the Bacteriology and Immunology Department in the Medical School, deal with disease-producing organisms and particularly with the mechanism of disease. There was then no possibility to do that. That has now become possible and there is some very

interesting work going on in a number of laboratories on the interaction of bacteria with their host animals. That's, of course, of very great importance.

SCHLESINGER: I was curious to know if you were going to choose a research project to begin today, what area of science—microbiology or other—would you choose?

MAGASANIK: That is extremely hard to tell. I think I'm satisfied with going on in the way in which I have been going.

SCHLESINGER: We started several weeks ago talking about when you were born, which was 1919, which means that you were seventy in 1989. Do you want to talk a little about your retirement or your lack of retirement?

MAGASANIK: Well, according to the rules that I think are about to be changed, the retirement age that is in effect at universities was changed a number of years ago from sixty-five to seventy and of course, what happens then depends on the particular university. In my case and the case of others at MIT, there is a great deal of flexibility, so in practice, it means that rather than having a salary from the Institute, the bulk of my income comes now from the retirement plan, but since it's a very generous one at MIT, I have no complaints on that score. The rest then depends, at MIT, on the department head and on the administration and, in this case—and this was true with other people who have retired—there is no very critical lack of space. If people wish to continue their research, the administration has been perfectly amenable to that. Of course, it depends on obtaining the funds from NIH and NSF [National Science Foundation] and so far I have been able to do that. So, as far as carrying out research is concerned, nothing has really changed and I draw a certain amount of salary from grants, as the other members of the faculty do. As far as teaching is concerned, since I am interested in teaching and like to teach, I offered to teach. So I continue to teach the microbial physiology course that I discussed before and will teach that introductory course in biology. But the difference is, of course, that as long as you are a tenured professor and not retired, you have the obligation to teach and a right to have a place to carry out research, although that is not absolutely guaranteed. After your formal retirement, this depends on the decision of the department head and the administration, which is made from year to year. So in practice, nothing has really changed and as far as things going as they are going, it seems it will be up to me, to a certain extent, to decide when I want to quit.

SCHLESINGER: Is there anything that you don't do now that you're retired, any responsibilities or obligations that you did before?

MAGASANIK: No, as it works out I'm still involved in departmental matters, I serve on committees, so in practice nothing has changed.

SCHLESINGER: Your research has been, really, in very basic microbiology and I wonder if over the years if you've see any changes in terms of the interest in that field and the ability to get funds—not just you yourself, but in the general attitude of the NIH and the NSF to this area of research?

MAGASANIK: As you know, up to now the granting agencies have been very generous and supportive of basic research. There is a problem there; it may become more difficult in the future. The understanding of support of research by federal agencies, which are the major source of our support, is that it will be good for the nation. It is not always clear, particularly not when you read what the role of the National Institutes of Health should actually be, that the accumulation of scientific knowledge, and the interpretation of scientific knowledge, can really be narrowly described as being important for the well-being of the nation. Whereas advanced research, for example, research that leads to a particular treatment of a disease supported by NIH, obviously can be recognized by everybody as deserving public support. So the problem has been that we have come into these years into a more difficult relation as far as government support is concerned. Particularly since our economic situation is not as good as it has been. And so money is in shorter supply. It's very simple. And since, in principle, the federal government is not in the business to support private universities as such, all support that comes from the federal government has to be disguised as being research that will lead to something useful. As far as health is concerned, the restrictions are a little bit smaller in the case of NSF, but of course, NSF provides much less money. And of course, I've never had any support, never asked for support, from the military and there again you can make a case that it has to be useful for destruction but hopefully there will be less money available from that source. But it creates a very definite problem—and that has been in the news—that the support that has been offered, rather loosely, to the universities by the NIH with the understanding that helping the universities, particularly the research universities, which involves the teaching of students who will be the researchers in the next generation, is worthy of support. Now, Congressional committees may ask, and in fact do ask more specifically, whether these funds and particularly the overhead funds that are used for keeping the institution afloat, are really used to provide directly useful information. Obviously it's going to be a quandary and difficult.

[END OF PART THREE]

[END OF INTERVIEW]

NOTES

1. J. C. Turner, F. K. Heath, and B. Magasanik, “Inhibition of urease by penicillin.” *Nature* 152 (1943): 326.

2. S. Silver and B. Magasanik, “The blood iodine in the period after thyroidectomy.” *Journal of Mt. Sinai Hospital* 8 (1942): 1027.

3. Boris Magasanik, “Studies on the stereochemistry of an enzymatic reaction; the oxidation of cyclitols by acetobacter suboxidans” (Ph.D. dissertation, Columbia University, 1949).

4. J. H. Mueller, “Studies on cultural requirements of bacteria I.” *Journal of Bacteriology* 7 (1922): 309-324.

   J. H. Mueller, “A new sulfur-containing amino acid isolated from the hydrolytic products of protein.” *Journal of Biological Chemistry* 56 (1923): 157-169.

5. Hans Zinsser, *Rats, Lice and History* (Boston: Little Brown and Company, 1935).

6. Hans Zinsser, *As I remember Him: the Biography of R. S.* (Boston: Little Brown and Company, 1934).

7. Alexandra E. Shedlovsky, “The Role of Histidine in the Metabolism of Adenine” (Ph.D. dissertation, Radcliffe College, 1961).

8. Boris Magasanik and D. P. Nierlich, “Control by Feedback Repression of the Enzymes of Purine Biosynthesis in Aerobacter Aerogenes.” *Biochimica et Biophysica Acta* 230, no. 2 (1971): 349-361.

INDEX