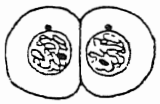

Profile #9
PRISCILLA SCHAFFER, Ph.D.
Professor of Microbiology and Molecular Genetics

BIOGRAPHY

One of America's leading virologists, Dr. Schaffer attributes her very early success to hard work, ambition and a willingness to take risks. Dr. Schaffer is Chief of the Laboratory of Tumor Virus Genetics at the Sidney Farber Cancer Institute, where her major research is concentrated on defining the DNA of the **Herpes Simplex** virus. Dr. Schaffer's commitment to improving medical education began during her early years at Baylor University; as a member of the Admission Committee at Harvard Medical School, she is a strong supporter of women and minority students.

VIDEOTAPE SUMMARY

Professionals Portrayed:

Virologists

Research Scientists — (Ph.D.s) — post-Doctoral Fellows

Laboratory Technicians

Medical Equipment and Procedures Demonstrated:

Tissue Culture Techniques

Electrophoresis of Proteins

Glycoprotein Analysis

Social Concepts Discussed:

The Significance of Mentors in Career Development

The Importance of Collaboration in Scientific Research

The Effects of the Women's Movement on Aspirations and Expectations

Decisions and Factors Affecting Career Advancement

Updating Medical Education

Transcript

Dr. Schaffer: One of the most common questions that I'm asked by the candidates for Harvard Medical School, the females, the women, is "what's it like to be a woman at Harvard?"

Interviewer: The Joint Committee on the Status of Women has created and produced this series on "Women in Medicine" with senior women professors of Harvard Medical School. Today we're talking with Dr. Priscilla Schaffer, Professor of Microbiology and Molecular Genetics.

Dr. Schaffer: I literally fell into a project that has been my life's work. The problem, as you know, involves **Herpes simplex** virus and specifically the genetics of **Herpes simplex** virus and how the virus transforms cells. In fact, we and others have shown that one specific piece of this viral DNA is able to transform cells. So that now we can focus our attention on using this genetic approach on that piece of DNA, and we can say what genes specifically are present in that small piece of DNA which now represents about 15% of the genome, having eliminated 85% of the genome. Indeed, it seems that there are about 7 genes and our current efforts are focusing on identifying the specific functions which each of those genes performs, again during the active infection initially. Then later on, and concurrently actually, we're asking what are the functions of these gene products in transformation? I can say that we know something rather specific about three of those seven genes.

The first gene is the gene for a glycoprotein which is called GAGB and this glycoprotein has been shown to be essential for the penetration of virus particles into cells because the glycoprotein is present on the surfaces of virus particles and if this glycoprotein is defective in some way as in the case of some of our mutants or if it's absent then the virus particles can attach to cells but it won't cut in, it won't penetrate.

The second gene about which we know a fair amount is the gene for the major viral gene binding protein viruses make in cells and this particular protein has the ability to unwind the DNA and perhaps facilitate transcription or DNA replication. So that we know something about what this protein is doing in productively infected cells. The question is, do we find it in transformed cells? The answer is, yes we do. It certainly is in transformed cells and what is its role in transformation? We are not certain, but it is interesting that this protein is found in about 40% of cervical carcinoma biopsy specimens and we have shown that in fact the degree to which this protein is expressed, now I am talking about cells transformed in laboratory, **in vitro**. The more of the protein that is present in those cells, the more cells that have the protein, the more tumorgenic the cells will be in newborn animals. So that there seems to be a correlation between the expression of this protein and tumorgenicity, at least in the laboratory.

And the last gene about which we know something is the gene for viral DNA polymerase, the **Herpes Simplex** virus specifies its own viral DNA polymerase, it doesn't use the polymerase of the cells which many DNA viruses do. Interestingly, Don Cohen in my lab, a post-doc, in collaboration with Jennifer Hall of the University of Arizona have shown that this viral DNA polymerase, interestly, is a mutagenic polymerase. In other words, it is not a very faithful copier of DNA. Others have shown that in addition to the polymerase function, there is an exonuclease function associated with the protein. One could postulate that a potential mechanism of transformation would be if this polymerase found itself in a cell and it is able to, if the nuclease function was able to act on the cellular DNA, for example, and also the protein had unfaithful copying properties. This could possibly be responsible for mutagenesis of cellular DNA. The mechanisms which we propose, and others propose, for the action of the polymerase is called the "hit and run" hypothesis because one only needs, in both the presence and the polymerase, one would have to have the viral DNA present for some time, sufficient time for viral DNA polymerase to be made. The polymerase is made, it acts on the cellular DNA mutagenizing it, some manner of it and then the viral DNA can disappear and the polymerase in fact can disappear. This is in fact consistent with the finding that in **Herpes simplex** virus transformed cells one is often hard put to demonstrate the presence of viral DNA or viral proteins, you can find them early after transformation, the DNA is present, you can find viral proteins yet the cells are transformed. So at least the observation that we can't find DNA in proteins is consistent with this "hit and run" hypothesis and specifically, the people in my laboratory are working on problems associated with the three genes I mentioned.

Interviewer: What types of problems are the people in your lab working on?

Dr. Schaffer: Yes, Dr. Cohen, a post-doc who has recently been appointed assistant professor in the Department of Pharmacology here at Harvard Medical School, has been working on the polymerase, the properties of polymerase, trying to identify the sites of activity, polymerizing activity and to map it on the viral genome. He is also interested in the fact that the **Herpex Simplex** viral DNA polymerase is a locus, which when mutated can confer resistance to some of the most important anti-herpes drugs.

Dr. Weller, another post-doctoral fellow, is studying the major DNA binding proteins and she is also interested in introducing mutations, new mutations into this piece of DNA hoping to identify any additional genes that may be present. You simply, in this case, isolate the fragment of DNA and mutagenize it in vitro, and there are ways in which we can reintroduce this mutagenized piece of DNA into the normal virus and then ask, "What has our mutation done, and can we identify a new gene for example in that piece of DNA?" So she is interested in nucleic acid biochemistry as well and is involved in cloning and mapping mutations, fine structurally, that we know are present in the morphologic transforming region.

Dr. Saboren is the person who has most recently been involved directly in the transformation studies, that is, attempting to transform cells with ever smaller pieces of DNA to try to identify the minimal piece of DNA that will transform cells. He also looks in cells, that are transformed by the virus, for the presence of these viral proteins, the glycoproteins, GAGB, DNA binding protein, hopefully, ultimately the polymerase, although there is no ready assay in transformed cells for the presence of the polymerase, we hope to be able to develop one.

Dr. Betty Pancake and Dr. Richard Respess, two fellows, are working on the glycoprotein specified by the virus, the reason that we are interested in the glycoproteins is not only because glycoprotein GAGB is involved in transformation, of course we would like to know as much as we can about that glycoprotein, but I mentioned before that the immune response somehow plays a role in maintaining the latent infection. The latency is clearly a problem for us, it is fine for the virus, but we are interested then in knowing how does the immune response play a role in maintaining latency. In order to do this we have to know something about the immune response and we do know that the viral glycoproteins are the major antigens which stimulate the immune response. So these two post docs are involved in identifying the viral glycoproteins that the virus makes. We are now in the process of using mutants which don't make individual glycoproteins. They make everything but this glycoprotein, everything but another glycoprotein. We are asking, what is the nature of immune response to a virus like that, for example; have we impaired the cellular immune response; is there less of a humoral immune response; and can the virus then become latent in an animal which has a certain kind of antibody, or a certain kind of cellular immune response? So these are the kinds of problems that we are working on.

Interviewer: What exactly were the enticements of coming to Sidney Farber?

Dr. Schaffer: There were times, especially later during my stay at Baylor when I felt that I needed to grow and that the place no longer, the lab, at least that lab no longer offered the kinds of things that I wanted for myself, and that was mostly independence and so after six years I decided that "I am going to look for another position." I had an opportunity to work with another very well known herpes virologist but decided against it because I would have, I felt, gone from the shadow of one mountain to the shadow of another and I really wanted to build my own mountain!

Interviewer: How did you go about looking for a new job at this stage?

Dr. Schaffer: Well I, fortunately, I didn't really look for a new job. I was giving a paper in Nuremberg on my studies, the studies of my group, and Jack Strominger, who was then putting together a new group at the Farber asked me if I would be interested in coming to the Sidney Farber and I said yes. So with the financial situation at Baylor and my dissatisfaction with that part of my professional life and this good opportunity, and also I had been asked by Bernard Risman at the University of Chicago whether I would be interested in coming to his laboratory, I felt very strongly that now was the time for me to go. As I have indicated, Dr. Risman is a herpes virologist and he was the mountain whose shadow I wished not to be in, so I came here instead. Of course, the decision was based, well, on the tremendous research opportunities here, marvelous intellectual environment and the fact that one can get good post-docs and graduate students here and in other places it is somewhat more difficult. So there were many opportunities I felt that Harvard offered and also the position here was one of full independence and that was very appealing.

Interviewer: Is it curious to you that there are three women professors in this department?

Dr. Schaffer: I think it is fantastic of course, but again, it doesn't surprise me in that I mentioned before Microbiology has always been very kind to women, very appreciative. I think that other departments at the school should follow the lead of Microbiology and I've heard some pretty sad excuses why there aren't more tenured women in other basic science departments and the clinical departments as well.

One of the most common questions that I am asked by the candidates for Harvard Medical School, the females, is, "what is it like to be a woman at Harvard," and I think that this is a rather serious problem. I think that perhaps it is less serious for the younger people, the women who are with each other in classes, than it is for a young assistant professor, for example, or an associate professor, because the higher you get the more isolated you are, that's part of the deal. I can't say that I feel terribly isolated in a sense that my male colleagues are my good friends and so forth. That's fine, but there are problems that are unique to women and I think that it would be in numerous instances I can think of, times when I would like to have been able to speak with a female colleague of the same faculty rank and I look around and I say, you know there just isn't anyone.

Interviewer: You have, in a sense, made it to the top at a relatively young age. What are the costs of success?

Dr. Schaffer: Well, I don't know that there have been any, let's just say I have no regrets. I don't think I have paid anything that I have second thoughts about. The cost has not been that great; I think the benefits are greater than the costs. I think some of the disadvantages of which I am aware are probably social in that I haven't taken the time to enjoy life socially as much as some other people might have, some other women might have. Family, that is something that perhaps I would have considered.

Interviewer: Did you make a conscious decision not to have a family in deference to your science.

Dr. Schaffer: Actually I did. This was in college, graduate school. I don't think that it can't be done, I think it can be done. I just know myself, that I am very ambitious, or certainly was then, and that in order to have a family and to give to children the quantity and quality of attention that I think they need, that I wasn't willing to make that commitment and that was actually a conscious decision.

Interviewer: You were involved in the Admissions Committee at which time you had contact with prospective students, which encouraged you to be interested in curriculum. Do you have any comments about the curriculum?

Dr. Schaffer: Well, yes I have some rather strong feelings about the curriculum. I was also involved in the curriculum matters at Baylor and also at Cornell even as a graduate student. I have taught medical students for a long time and I am somewhat concerned that curriculum reform here has revolved more around the desire and the needs of department chairmen than around those of the medical students themselves. I know that this is a question which many prospective students ask when they come here, they, of course, have heard that there is some reshuffling of the curriculum going on. I know that the faculty, many of them, are not pleased with the situation and of course we know now that there is a move afoot to rethink the whole curriculum concept here at the school. I think it is great.

biochemistry. Physiological chemistry; biological chemistry; the chemistry of living organisms and of the changes occurring therein.

biopsy. The process of removing tissue from living patients for diagnostic examination.

cancer. A general term frequently used to indicate any of various types of malignant neoplasms, most of which invade surrounding tissues, may metastasize to several sites, and are likely to recur after attempted removal and to cause death of the patient unless adequately treated.

cellular immune response. The cell-mediated mechanism whereby tissue previously sensitized to an antigen tends to resist infection; **or** the response of that mechanism that produces the initial sensitization to an antigen.

cervical carcinoma. A malignant neoplasm derived from epithelial tissue in the uterine cervix.

chloroplast. A plant cell inclusion body containing chlorophyll; occurs in cells of leaves and young stems.

chromosome. One of the bodies (normally totally 46 in humans) in the cell nucleus that is the bearer of genes; it has the form of a delicate chromatin filament during interphase, contracts to form a compact cylinder segmented into two arms by the centromere during metaphase and anaphase stages of cell division, and is capable of reproducing its physical and chemical structure through successive cell divisions.

cytogeneticist. A specialist in cytogenetics, the branch of genetics concerned with the structure and function of the cell, especially the chromosomes.

DNA. Abbreviation for dioxyribonucleic acid.

DNA methylation. The addition of a methyl group to DNA.

DNA polymerase. Enzyymes (transferases) transferring nucleotide residues (nucleotidyls) from nucleoside di- or tri-phosphates into dimer or polymer forms.

DNA replication. The process by which DNA in chromsomes replicates or produces exact copies of itself.

enzyme. A protein, secreted by cells, that acts as a catalyst to induce chemical changes in other substances, itself remaining apparently unchanged by the process.

exonuclease. A nuclease that releases one nucleotide at a time, serially, beginning at one end of a polynucleotide (nucleic acid).

gene. The functional unit of heredity. Each gene occupies a specific place or locus on a chromosome, is capable of reproducing itself exactly at each cell division, and is capable of directing the formation of an enzyme or other protein.

genome. The genes in the complete set of chromosomes derived from one parent, the haploid number of chromosomes.

Herpes simplex virus. The pathogen of **herpes simplex** in people causing acute stomatitis, especially in children, and so-called fever blisters, usually on the lips and external nares.

humoral immune response. The antibody-producing mechanism of response to an antigen associated with the extracellular fluids of the body: blood and lymph; in contradistinction to **cellular** immune response, as originally proposed in Metchnikoff's phagocytic theory.

leukemia. Disease of progressive proliferation of abnormal leukocytes found in hemopoietic tissues, other organs, and usually in the blood in increased numbers.

locus. A place; usually, a specific site.

methyl group. A group of the radical, $--CH_3$, present in a variety of compounds.

morphology. The science which deals with the configuration or the structure of animals and plants.

mutagenesis. The production of a mutation.

mutant. An individual possessing one or more genes that have undergone mutation, that is, a change in the character of a gene that is perpetuated in subsequent divisions of the cell in which it occurs.

protein. Macromolecules consisting of long sequences of alpha-amino acids in peptide linkage. Protein is three-fourths of the dry weight of most cell matter, and various proteins are involved in structure, hormones, enzymes, muscle contraction, immunological responses, and other essential life functions.

recombinant DNA. DNA produced by recombination or crossing-over between two homologous chromosomes; associated with the increased production of proteins — for example, interferon.

tumorgenecity. The quality of causing or producing tumors.

Dr. Priscilla Schaffer
General Questions

1. How does Dr. Schaffer answer those who ask "What is it like to be a woman at Harvard?" Why does she see this as "a rather serious problem"?

2. What conscious decisions did Dr. Schaffer make about a family? When? Why?

3. What personality traits does Dr. Schaffer reveal? How were they helpful in establishing a successful career in scientific research?

4. What does the interview show about running a research laboratory?

5. Why did Dr. Schaffer come to Sidney Farber Cancer Institute?

6. What does Dr. Schaffer mean when she says "I really wanted to build my own mountain"?

7. What factors did she consider when she decided to look for a new position? Why did she feel that "now was the time for me to go"?

8. Why do women in medicine have to deal with isolation in their careers? How can this isolation be overcome? Who is responsible for bringing about this change? Why?

9. What do people mean when they say "my life's work"? Do you see yourself as having a single "life's work" or as having a number of jobs or careers? What social and economic factors influence these answers?

10. What responsibility do industry, private foundations, and individuals have to support basic and applied medical research?

11. What were some of the trade-offs that Dr. Schaffer had to make, as she rose through the medical school ranks? Do you feel that these were reasonable trade-offs?

Dr. Priscilla Schaffer
Science Questions

1. The research interest of Dr. Schaffer involves the molecular genetics of **Herpes simplex** virus. What is the key question asked by Dr. Schaffer, as it concerns the interaction of virus with host cell?

2. Dr. Schaffer and her medical team have isolated a section of viral DNA which represents about 15% of the viral genetic information. It appears that this "bit" of DNA consists of about 7 genes. What are the reasons for determining the products of these genes?

3. What was the relationship that was established between the quantity of viral gene binding protein and the degree of tumorgenecity in animal cells?

4. What is meant by the proposed mechanism known as the "hit and run" hypothesis?

5. Why is it so difficult to establish a cause and effect relationship between viral interaction with host cells into tumor cells?

6. It has been identified that the gene for DNA polymerase is a locus, that when mutated can confer resistance to some of the most important anti-Herpes drugs. What is the significance of this relationship?

7. What is a potential result of a mutation of the gene that codes for DNA polymerase in **Herpes simplex**?

8. The host's immune response appears to play a negative role, as it relates to the herpes simplex virus. What is this relationship? What is the significance of this relationship?

9. What are the major viral antigens which stimulate the host's immune response?

10. Dr. Schaffer's work with **Herpes simplex** is in basic research. However, why is this basic research of interest to the public? How do public interests influence trends and funding in basic research?

11. What do you see as real dilemmas in trying to link a specific virus to cancer? Why are correlation studies that demonstrate the presence of a virus within a host cell somewhat misleading?

12. How important is the sharing of information between separate lab teams investigating the same topic? Do you feel that it is common practice without a second thought? Might there be reasons why a particular lab team might not share acquired information? If so, what would these instances be?

13. It has been established that certain gene loci can mutate. These mutations can confer resistance to some of the most important anti-herpes drugs. What is the significance of this type of mutation? Why does this create a problem with the treatment of diseases caused by the **Herpes simplex** group?

Dr. Priscilla Schaffer
Social Studies Questions

1. Dr. Huang decided on having a child and still maintaining the same level of her career. Dr. Schaffer opted for not having a family because one could not maintain the intensity of a demanding career and still give the child the quantity and quality of attention. How do you feel about the dilemma of integrating a demanding career in academic medicine with raising a family?

2. How does Dr. Schaffer's career challenge stereotypes? Explain.

3. Ideally, at what level should the federal and state governments fund basic and applied medical research? Where would you place funding of medical research on a list of national priorities? What would be the long and short range effects if government funding for medical research was increased?