Werner Arber Nobel Foundation Autobiography 1978

I was born on June 3rd, 1929 in Gränichen in the Canton of Aargau, Switzerland, where I went to the public schools until the age of 16. I then entered the gymnasium at the Kantonsschule Aarau where I got a B-type maturity in 1949. From 1949 to 1953 I studied towards the diploma in Natural Sciences at the Swiss Polytechnical School in Zurich. It is in the last year of this study that I made my first contacts with fundamental research, when working on the isolation and characterisation of a new isomer of Cl^{34}, with a halflife of 1.5 seconds.

On the recommendation of my professor in experimental physics, Paul Scherrer, I took an assistantship for electron microscopy at the Biophysics Laboratory at the University of Geneva in November 1953. This laboratory was animated by Eduard Kellenberger and it had two prototype electron microscopes requiring much attention. In spite of spending many hours to keep the microscope "Arthur" in reasonable working condition, I had enough time not only to help developing preparation techniques for biological specimens in view of their observation in the electron microscope, but also to become familiar with fundamental questions of bacteriophage physiology and genetics, which at that time was still a relatively new and unknown field. My first contribution to our journal club concerned Watson and Crick's papers on the structure of DNA.

In the 1950's the Biophysics Laboratory at the University of Geneva was lucky enough to receive each summer for several months the visit of Jean Weigle. He was the former professor of experimental physics at the University of Geneva. After having suffered a heart attack, he had left Geneva to become a researcher at the Department of Biology of the California Institute of Technology in Pasadena. There, he had been converted to a biologist under the influence of Max Delbrück and had chosen to study bacteriophage lambda. This is why the first electron micrographs of phage lambda were made in Geneva. Stimulated by Jean Weigle we soon turned our interests also to other properties of lambda, and the study of defective lambda prophage mutants became the topic of my doctoral thesis.

In the summer of 1956, we learned about experiments made by Larry Morse and Esther and Joshua Lederberg on the lambda-mediated transduction (gene transfer from one bacterial strain to another by a bacteriophage serving as vector) of bacterial determinants for galactose fermentation. Since these investigators had encountered defective lysogenic strains among their transductants, we felt that such strains should be included in the collection of lambda prophage mutants under study in our laboratory. Very rapidly, thanks to the stimulating help by Jean Weigle and Grete Kellenberger, this turned out to be extremely fruitful. We could indeed show that lambda-mediated transduction is based on the formation of substitution mutants, which had replaced a part of the phage genes by genes from the bacterial chromosome. This made the so-called lambda-gal phage derivatives so defective that they were not able any longer to propagate as a virus. In fact, one of the at first sight rather frustrating observation was that lysates of lambda-gal, which indeed could still cause the infected host cell to lyse as does wild type phage lambda, did not contain any structural components of lambda (phage particles, heads or tails) discernible in the electron microscope. This was the end of my career as an electron microscopist and in chosing genetic and physiological approaches I became a molecular geneticist.

After my Ph. D. exam in the summer of 1958 I had the chance to receive an offer to work at the University of Southern California in Los Angeles with Joe Bertani, a former collaborator of Jean Weigle. Several years before, Bertani had isolated and characterised another bacteriophage of *E. coli,* P1. Phage P1 rapidly had become a very welcome tool of bacterial geneticists, since it gives general transduction, i.e. any particular region of the host chromosome gets at some low frequency wrapped into P1 phage particles if P1 multiplies in a cell, and this enables the geneticists to carry out linkage studies of bacterial genes. While working as a research associate with Bertani, I received P1 at first hand which enabled me to study phage Pl-mediated transduction of monomeric and dimeric lambda prophage genomes as well as of the fertility plasmid F.

In the meantime, my Ph. D. thesis on lambda-gal, although written in French, had been read, or, what is perhaps more essential, understood in its conclusions by many leading microbial geneticists.

This may be the reason why I received offers to spend additional postdoctoral time in several excellent laboratories. On the other hand, I had remained in close contact with Eduard Kellenberger, and he urged me to come back to Geneva in order to lead an investigation on radiation effects on microorganisms. As a compromise, I decided to return to Geneva at the beginning of 1960, but only after having spent several very fruitful weeks at each of the laboratories of Gunther Stent in Berkeley, Joshua Lederberg in Stanford and Salvador Luria at the Massachusetts Institute of Technology, Cambridge.

At the end of the 1950's, a special credit had been voted for by the Swiss Parliament for research in atomic energy, including radiation effects on living organisms. Eduard Kellenberger felt that important contributions to the latter questions could be expected from studies with microorganisms, and he had therefore submitted a research proposal which found approval by the granting agency, the Swiss National Science Foundation. The project could bring insight into the nature of radiation damage to genetic material and its repair mechanisms, as well as of the stimulation of genetic recombination by radiation. These topics had already engaged the attention of Jean Weigle and Grete Kellenberger for a number of years.

One of the first experiments after my return to Geneva was to render *E. coli* B and its radiation resistant strain B/r sensitive to phage lambda. The first step to accomplish this was easy thanks to a hint received from Esther Lederberg to look for cotransduction of the $Ma1^+$ and $lambda^S$ characters. However, the strains thus obtained still did not allow an efficient propagation of lambda. Very rapidly I realized that this was due to host-controlled modification, a phenomenon described for lambda and *E. coli* strains seven years earlier by Joe Bertani and Jean Weigle. However, I was not satisfied to know how to overcome this barrier. I was also anxious to know how the restriction of phage growth and the adaptation of lambda to the new host strain worked. When I started investigations on the mechanisms of host-controlled modification, I did not of course imagine that this sidetrack would keep my interest for many years. Otherwise I might not have felt justified to engage in this work because of its lack of direct relevance to radiation research. However, a lucky coincidence rapidly dissipated these concerns. At the same time, Grete Kellenberger had looked at the fate of DNA from irradiated phage lambda upon infection of host bacteria: part of it was rapidly degraded after injection into the host. And so was the DNA from unirradiated phage lambda used to measure adsorption and DNA injection into restrictive bacterial strains! This phenomenon became the topic of Daisy Dussoix's doctoral thesis, who very carefully not only studied the DNA degradation of phage that was not properly modified, but who also tried to detect parallels between the fate of unmodified DNA in restrictive conditions and of irradiated DNA in normal host cells.

Within about one year of study, it had become clear that strain-specific restriction and modification directly affected the DNA, without however causing mutations. It soon also became obvious that restriction and modification were properties of the bacterial strains and acted not only on infecting bacteriophage DNA, but also on cellular DNA as manifested in conjugation experiments. These findings were reported by myself and Daisy Dussoix for the first time to the scientific community during the First International Biophysics Congress held in Stockholm in the summer of 1961. In a more extended version I presented them in 1962 to the Science Faculty of the University of Geneva as my work of habilitation as privatdocent. This work earned me in the same year the Plantamour-Prévost prize of the University of Geneva.

At a time before the Swiss Universities received direct financial help from the federal government, the Swiss National Science Foundation awarded "personal grants" to qualified researchers to allow them to guide projects of fundamental research at a Swiss University. I was lucky to benefit from such a support form 1965 to 1970. These years were devoted to hard work to consolidate the preliminary data and the concepts resulting from them, and to extend the acquired notions, in particular with regard to the mechanisms of modification by nucleotide methylation, with regard to the genetic control of restriction and modification and with regard to the enzymology and molecular mechanisms of these reactions.

This work would not have been possible without a very fruitful help by a large number of collaborators in my own laboratory and of colleagues working on related topics in their own laboratories. I was extremely lucky to receive in my laboratory in the basement of the Physics Institute of the University of Geneva a number of first class graduate students, postdoctoral fellows and senior scientists. It is virtually impossible to list them all in this context, but my warmest collective thanks go to all of them. In 1964 Bill Wood laid out a solid basis for the genetics of the restiction and modification systems *Eco*K and *Eco*B. Later, Stuart Linn, profiting from his fruitful contacts with Bob Yuan and Matt Meselson, who worked in the USA on the enzymology of *Eco*K restriction, set the basis for in vitro studies with *Eco*B restriction and modification activities. These studies culminated in the final proof that modification in *E. coli* B and K is brought about by nucleotide methylation. This concept had found its first experimental evidence during my two months' visit in 1963 with Gunther Stent at the University of California in Berkeley. Several years later Urs Kühnlein, a Ph. D student, and John Smith, working for various lengths of time with us, succeeded in careful in vivo and in vitro measurements on methylation to validate and extend the earlier conclusions. Their experiments also brought important conclusions with regard to the concept of the sites of recognition on the DNA for the restriction and modification enzymes.

As an illustration that my work has not always been easy and accompanied by success, I would like to refer to my long, fruitless and thus largely unpublished attempts to find experimental evidence for the diversification of restriction and modification systems in the course of evolution. Systems *Eco*K and *Eco*B form a closely related family as judged from genetic and functional studies. Another family is formed by restriction and modification systems *Eco*P1 and *Eco*P15. One could expect that mutations affecting the part of the enzymes responsible for recognition of the specificity site on the DNA might result in new members of the family, recognizing new specificity sites on DNA. We have in vain spent much time in search for such evolutionary changes both after mutagenization and after recombination between two members of the same family of the above mentioned systems. That the basic idea for this search was good was recently shown by Len Bullas, Charles Colson and Aline van Pel (J. Gen. Microbiol. 95, 166- 172, 1976) who encountered such a new system in their work with *Salmonella* recombinants.

In 1965 I was promoted extraordinary professor for molecular genetics at the University of Geneva. Not only did I always enjoy a continued contact with the students, but I also considered teaching as a welcome obligation to keep my scientific interests wide. Although we had a few excellent students in our laboratories, the teaching of molecular genetics at the University of Geneva in the 1960's suffered a bit from a lack of interest by the young generation.

This might have been related to a more general lack of public interest for this field, which was perhaps due to the economic structure of the city of Geneva and its environments. These, at that time perhaps more subconscious concerns, might have helped me to accept in 1968 an offer for a professorship at the University of Basel, since I felt that more general interest would be given to molecular genetics in this city with a long tradition of biomedical research at its industries.

I started my new appointment at the University of Basel in October 1971 after having spent one year as a visiting Miller Research Professor at the Department of Molecular Biology of the University of California in Berkeley. In Basel, I was one of the first persons to work in the newly constructed Biozentrum, which houses several University Departments, in particular those of Biophysics, Biochemistry, Microbiology, Structural Biology, Cell Biology and Pharmacology. This diversity within the same house largely contributes to fruitful collaborative projects and it helps to keep horizons broad both in research and teaching. Additional contributions to this goal come from contacts with other nearby University Institutes as well as with the private research Institutions in the city.

Since my coming to Basel, I devoted relatively little of my time to further studies on restriction and modification mechanisms. Not that I have lost my interest in them. On the contrary, I was fortunate to be able to set up a junior group which under the leadership of Bob Yuan and more recently of Tom Bickle, became rapidly quite independent, and it continues to be very successful in its investigations on the more detailed aspects of the molecular mechanisms of restriction and modification. This allowed me to turn my main interests back to other mechanisms affecting either positively or negatively the exchange of genetic material. For a number of years Nick Gschwind, a Ph. D. student, and Dorothea Scandella, a postdoctoral fellow, explored two other mechanisms found in some *E. coli* strains or mutants and affecting more specifically than restriction and modification systems particular steps in the propagation of bacteriophage lambda.

For the last several years I have turned my principal interests to the intriguing activities of insertion elements and transposons, which by their actions on genetic rearrangements, seem to be the main driving forces of evolution in microorganisms. Because of their independence on extended nucleotide homologies these forces bring about exchange of largely unrelated genetic materials. Our postdoctoral workers Katsutoshi Mise, Shigeru Iida and Jürg Meyer brought important contributions to the understanding of these phenomena, mainly by the use of the bacteriophage P1 genome as a natural vector of transposable elements. But general knowledge on this to my mind extremely important field is still very scarce and deserves continued attention.

Solid notions on naturally occurring genetic exchange between organisms that are not directly related will also form a good basis for a scientific evaluation of conjectural risks of in vitro recombinant DNA research. Since this research largely makes use of restriction enzymes, although it in no way fully depends on them, I consider it a personal obligation to contribute to the best of my abilities to the solution of questions which arose in the scientific and public debate on this research in the last few years. I see two ways to reach this goal. The first is scientific and tends as just stated to better understand what nature does in its nonhomologous genetic exchange. The second is rather political and it consists in actions to stimulate continued awareness of responsibility to work with a maximum of care in all scientific investigations, which should, however, be allowed to be done under optimal academic freedom.

A curriculum vitae would be incomplete without reference to my private life. I am fortunate to have found a continued support and steady encouragement by my family, in particular by my parents, and, since we became married in 1966, by my wife Antonia. In response to their interest and understanding for my scientific activities, I have tried to give them my personal affection needed for a harmonious life. Our two daughters Silvia and Caroline were born in 1968 and in 1974, respectively. When Silvia learned that I had been honored by the Nobelprize she not only wanted to know what this is, but also why I was chosen as a Laureate. After explaining her in simple terms the basic concepts of the mechanisms of restriction enzymes, she, after some reflection, reexpressed this message in her own terms by a tale, which in the meantime has found wide diffusion around the world. It might thus be justified to finish this curriculum vitae by its reproduction:

"The tale of the king and his servants

When I come to the laboratory of my father, I usually see some plates lying on the tables. These plates contain colonies of bacteria. These colonies remind me of a city with many inhabitants. In each bacterium there is a king. He is very long, but skinny. The king has many servants. These are thick and short, almost like balls. My father calls the king DNA, and the servants enzymes. The king is like a book, in which everything is noted on the work to be done by the servants. For us human beings these instructions of the king are a mystery.

My father has discovered a servant who serves as a pair of scissors. If a foreign king invades a bacterium, this servant can cut him in small fragments, but he does not do any harm to his own king.

Clever people use the servant with the scissors to find out the secrets of the kings. To do so, they collect many servants with scissors and put them onto a king, so that the king is cut into pieces. With the resulting little pieces it is much easier to investigate the secrets. For this reason my father received the Nobel Prize for the discovery of the servant with the scissors".