Published in final edited form as:

Res Microbiol. 2014 June ; 165(5): 348–350. doi:10.1016/j.resmic.2014.05.015.

Mission Possible: Getting to Yes with François Jacob

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In the late 1980s, my wife Barbara and I traveled to see friends in Paris and then to bicycle in southwestern France. It was shortly after François Jacob had published his memoir “La Statue Intérieure” (1987) (1). I stopped off at the Institut Pasteur to visit François. We talked only briefly about science since he had long since changed his research to fields far removed from my own. I had remained a microbiologist because of my conviction that the power of bacterial genetics could be used to solve a broad array of problems, a conviction initially inspired by the early papers of Jacob and his long-time collaborator, Élie Wollman. François had long since been studying mouse cell differentiation working with multipotent teratocarcinoma cells.

Mainly, I was there to tell François how much I admired his memoir “La Statue Intérieure” (Jacob, 1987) (1). I had already known from his scientific papers and his book “The Possible and the Actual” (2) that his writing could be fluid and compelling. “La Statue Intérieure” revealed a different style, as he lyrically described both his early life, his often hair-raising experiences as a medic with the Free French Army of Charles de Gaulle and his late entry into science. What was next? I was surprised to hear him say that one reason he wrote his memoir was to help him segue into writing a novel. Wow- with all that he had accomplished in his lifetime, was there more to come? A few years later, visiting Paris again, I asked him how the novel was going. François passed over the question quickly, indicating that it wasn’t going to happen. I was hardly disappointed as there was so much he had achieved in so many areas that my personal narrative of how I had been inspired scientifically by him remained as strong as ever.

My narrative begins with a paper on permeases I wrote for a course in graduate school taught at Harvard by Bill Siström and Jim Watson in the late 1950s. Researching this subject led me to papers on permeases from the Institut Pasteur, which in turn inspired me to seek all the microbiological papers from this French research institute. I can still visualize myself, sitting in the library for weeks in Harvard’s Biological Laboratories, devouring papers from the French journals *Annales de l’Institut Pasteur* and *Comptes Rendus Hebdomadaires des Séances de l’Académie des Sciences*. The scientific papers of François Jacob, Élie Wollman,

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George Cohen, Jacques Monod and their coworkers made me more excited about science than I had ever been. And, this was even before the publications that established the concept of repressor control of gene expression.

I was particularly in awe of Jacob and Wollman's accomplishments in understanding the nature of bacteriophage lysogeny and bacterial conjugation. The rapid progress in their studies seemed to me to result from a combination of logic and intuitions based on just a few key experiments. For many years before Jacob joined forces with Monod, he and Wollman did much of the major work in elucidating the mechanism whereby a bacterium can exchange and transfer genetic material to its descendants, a mechanism quite different from the basis of conjugation in humans and other animals. This work provided much of the foundation for doing genetic studies on bacteria that was to become essential to progress in biology in the subsequent decades. The discovery that the sex factor of the bacterium *E. coli* could incorporate genes from the chromosome (e.g. the *F-lac* episome) opened up the field of plasmid biology and cloning. The studies on bacterial lysogeny led to the discovery that bacteriophage genomes can integrate into and, thus, become part of the bacterial chromosome. Stimulated by these findings, researchers proceeded to show that cells infected with certain tumor viruses had their genomes integrated into mammalian chromosomes.

Nearly all of the research accomplished on lysogeny and bacterial conjugation by Jacob and Wollman was published during the period from 1953–1959. Of the actual research papers (as opposed to reviews), close to 90% were written in French and appeared in French journals. A majority of these were 2- to 3-page papers in the *Comptes Rendus*, which while containing only one or two experiments, provided dramatic leaps in the understanding of their subjects. This, all with no additional tables or figures available in supplementary files on the Web (obviously)! These compressed and beautifully written jewels achieved a sharpness of communication that was effective in impacting the scientific community. The extent of their accomplishments shines through in their book "Sexuality and the Genetics of Bacteria" (3), a review of the field which was largely theirs by that time. It was those genetic tools that made it possible subsequently for Jacob, Monod and coworkers to discover how genes are expressed and regulated.

By the time I finished my stint in the library reading the papers from the Institut Pasteur, I knew that I wanted to do postdoctoral work in François Jacob's lab. Up to this point, I thought of myself as a passive person, being carried on to each new stage of my life by whatever seemed to be the "safe" next step to take. In high school, I had been good at mathematics and chemistry, so I would major in a science (chemistry) in college. However, by the time I was a senior in college I was more passionate about literature (particularly French) than science and I thought of taking a year off. I went to discuss the idea with one of my chemistry professors, Paul Bartlett, who told me that a year off in my record would be frowned on if I were later to apply to graduate school in chemistry. That scared me. I went ahead and took the next "safe" step for a person with my background: I entered graduate school in chemistry in the fall of 1957.

My inspiration to obtain a place in the Jacob lab, which occurred late in my graduate career, became a mission that would take four years to achieve. My first shot at it arose when

François visited Boston to give a talk at Harvard Medical School and I asked to meet with him. After a pleasant discussion, François made it clear that I did not have enough background in genetics to join his group. He suggested that I seek a postdoctoral position in Arthur Pardee's lab at the University of California, Berkeley to get more experience. Art had recently returned from a sabbatical year in Jacques Monod's lab, joining the extraordinary collaboration of Monod and Jacob. There he did the experiments that appeared in the famous PaJaMo papers, first, the usual short report in *Comptes Rendus* (4) and then a longer paper in the *Journal of Molecular Biology* (5). The PaJaMo papers along with subsequent papers from Jacob, Monod and their colleagues would provide several of the most important founding principles for the field of Molecular Biology.

After nearly two years (1961–1962) of postdoctoral work with Art, I felt I was now well-experienced in the field of gene regulation, doing genetic experiments with the *lac* operon and even collaborating with Jacob's lab on the regulation of the enzymes involved in pyrimidine biosynthesis. It was time to re-apply to François for a position as a postdoctoral fellow in his lab. Foiled again: he responded in a nice letter but said that his lab was full for the following year.

I was not going to give up on my mission. I decided to spend my third postdoctoral year in London, doing research in the laboratory of Bill Hayes. Bill, pretty much on his own, had made several of the important early findings about bacterial conjugation and had published a joint review of progress in understanding conjugation with Jacob and Wollman (6). Here, not only would I be in a lab that was focusing on bacterial genetics and, in particular, on conjugation, but also, I would be much closer to Paris. Once settled in London, I contacted François yet again and asked if I could talk with him in Paris about spending my last postdoctoral year in his laboratory. He responded that I could visit and discuss the possibility. This sounded more positive.

But, after arriving in Paris, there was one last and unexpected barrier that I came to imagine would interfere with a “yes” response from François. The night before going to the Pasteur I delighted in eating a classical French meal and the next morning took a Metro train to the stop Pasteur. However, on the train, I noticed a very strong smell of garlic. So strong that I moved to another place in the car to avoid whichever neighbor of mine it was who had “garlic breath.” In the new place, I again smelled garlic and again I moved, but the smell stayed with ME. I then became convinced that it was I who had garlic breath and if I appeared at an interview in this “state,” I was sure to offend and lose my third chance. Should I go back to my room and brush my teeth again and be late for the interview? My imagined crisis, I was soon to learn, was due to my ignorance of French cuisine and to my upbringing in the United States where “garlic breath” could be a reason for failing a job interview. However, clearly in France this was not an issue; garlic was a staple of French cuisine. Despite not having brushed my teeth, I arrived at the interview on time and “I got the job.”

My year in Paris, 1964–5, was a successful one both scientifically and culturally. I talked with François and his student François Cuzin about using a technique they had developed for moving the Lac operon to different positions on the *E. coli* chromosome to approach

some questions about DNA replication (7). This eventually led to a fruitful collaboration with Ethan Signer, another postdoctoral fellow in Jacob's lab. While we were not being directed by François in our work, he followed it with great interest, particularly when we were able to obtain transducing phages for the Lac operon (8). However, the days of research on the Lac operon were waning at the Pasteur. Essentially all of the work that provided the material for the major papers on the Operon theory and messenger RNA had already been published with an impact that revolutionized biology. Jacob was collaborating with Sydney Brenner on the replicon theory of DNA replication, presenting a model still a touchstone for those studying cell division and the mechanics of passing on chromosomes to daughter cells (9). Some of the best interactions were at lunchtime when we all (students and postdoctoral fellows) sat down for lunch and discussion at the long table in the library with the three soon-to-be Nobel Prize winners, Jacob, Monod and André Lwoff sitting in the center.

In the years since I returned from my postdoctoral year at the Pasteur to my position at Harvard Medical School I progressively learned that I had much more in common with François Jacob than I imagined. Jacob had often discussed in his writings the social context and social impact of genetics. A number of articles in *Le Monde* (one translated into English for the *New York Times*), an extensive interview in the *Nouvel Observateur* and chapters in some of his books dealt critically with such issues as eugenics, sperm banks and racist theories emanating from scientific sources.

Jacob, in his books and elsewhere, presented views of science less positivist than that championed, for instance, by Jacques Monod (10). Jacob characterized science as follows: "Science cannot answer all questions. It can, however, give some indications, exclude certain hypotheses. Engaging in the pursuit of science may help us make fewer mistakes. It's a sort of gamble." (11) He described a component of scientific discovery as a "night science, a stumbling, wandering exploration of the natural world that relies on intuition as much as it does on the cold, orderly logic of day science." (12). His concerns about the social impact of genetics and his responses to the frequent mystification of the scientific process were very close to mine.

In fact, Francois's portrayal of the doing of science fit exactly into the picture of the content and style of the work of Jacob and his colleagues that had catalyzed my mission to the Pasteur.

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