Francois Jacob (1920-2013) [1]

By: Racine, Valerie Keywords: bricolage [2]

François Jacob studied bacteria and bacteriophages at the Institut Pasteur in Paris, France, in the second half of the twentieth century. In 1965, Jacob won the Nobel Prize in Physiology or Medicine[3] with André M. Lwoff and Jacques L. Monod for their work on the genetic control of enzyme synthesis. Jacob studied how genes [4] control and regulate metabolic enzymes in the bacterium *Escherichia coli* [5] (*E. coli*) and in lysogenic bacterial systems. He contributed to theories of transcriptional gene regulation [6], the operon model, and the distinction between structural and regulatory genes [4]. Jacob also introduced the concept of *bricolage* (tinkering) in evolutionary biology.

Jacob was born on 17 June 1920 in Nancy, France. He was the only child of Thérèse Franck and Simon Jacob, a businessman. At the age of three, Jacob and his family moved to Paris, where he attended primary and secondary school at the Lycée Carnot in Paris from 1927 to 1937. His mother and his maternal grandfather, a decorated general whom Jacob later said he admired, were both secular Jews, but Jacob said that he became an atheist after his bar mitzvah. He later noted that he did not enjoy his time in school as he felt continually stressed by his peers' competitive attitudes. After his graduation from the Lycée, Jacob studied medicine at the Université de Paris Pierre et Marie Curie in Paris, France. He said that he was inspired to become a surgeon after observing the remarkable precision of a surgery performed by one of his uncle's friends.

Jacob had completed two years in medical school when, in June 1940, he left France to join the Free French Forces in England. The Free French Forces were a collection of military units organized by Charles de Gaulle in London, England, intended to liberate France from German occupation during World War II. The Forces participated in many campaigns during the World War II, including some in North Africa and in the Middle East, as well as the invasion of Normandy in 1944. Jacob's departure from France coincided with the death of his mother, who died on 2 June 1940 from Hodgkin's disease. Jacob claimed that his mother's death and the impending German occupation of France marked the end of his childhood and the beginning of his adult life.

During World War II, Jacob served in North Africa, including Libya and Tunisia, as a medical officer in the Forces. In August 1944, Jacob was wounded in Normandy during his return to France. Jacob received the highest military award in France, called *Croix de la Libération*, for his service. However, because of his wartime injuries, Jacob would no longer be a surgeon. Nonetheless, he completed his medical studies and submitted a doctoral thesis in medicine in 1947, focused on the effectiveness of the antibiotic Tyrothricin. In the same year, Jacob married Lysiane Bloch, a pianist, with whom he would have four children.

The following three years were a difficult time, according to Jacob. No longer having surgery as a career option, Jacob was uncertain about his next pursuits. He took a position at the Cabanel Center, a former gunpowder factory converted into an antibiotics factory after the war. Jacob said that this was a futile project, as the large vats in the factory used to manufacture gunpowder were never suited to produce viable [7] antibiotics as the vats had never been sterilized.

Instead of continuing to work in the antibiotics industry, Jacob sought to move into a research setting. After he requested to work in Lwoff's laboratory at the Institut Pasteur in Paris, Jacob attained a research position in that laboratory in 1950. Four years later, he defended his doctorate degree in science on lysogenic bacteria at the Sorbonne in Paris. In 1956, he became laboratory director and was later selected as head of the Department of Cell Genetics in 1960. In 1964, Jacob became pofessor at the Collège de France in Paris.

Jacob collaborated with Élie L. Wollman beginning in 1954, a partnership that resulted in their 1961 publication *La Sexualité des Bactéries* (Sexuality and the Genetics of Bacteria). The work presented their study on the genetic mechanisms and properties of lysogenic bacteria, which are bacteria that carry a viral genome [8] within their own genomes.

During the 1950s, while Jacob and Wollman researched in Lwoff's laboratory on the viral properties in *E. coli* bacteria, down the hall Monod's group studied the properties of metabolic enzymes, or enzymes that catalyse specific reactions in the cell, with the same species of bacteria. In the summer of 1958, Jacob noted an analogy connecting the two mechanisms studied at the opposite ends of the institute. Both groups had constructed mechanistic models of gene expression guiding the synthesis of particular structural proteins, and in both models there existed an adjacent regulatory gene modulating the activity. In 1959, Jacob and Monod published "Gènes de structure et gènes de regulation [6] dans la biosynthèse des proteins" (Structural Genes and Regulatory Genes in the Biosynthesis of Proteins), in which they distinguished structural genes [4] from regulatory genes [4]. Jacob's student, Michel Morange, later argued that this distinction created a conceptual hierarchy among genes [4], which enabled researchers to categorize genes [4] and genetic elements according to the different functional roles they play in the cell.

In 1961, Jacob and Monod published "Genetic Regulatory Mechanisms in the Synthesis of Proteins," and through their discovery of enzyme induction [9] in *E. coli*, they introduced a logic of gene regulation [6] and expression. Jacob and Monod investigated how these bacteria trigger the production of the enzymes that can metabolize different sugars, such as the complex sugar lactose. *E. coli* produce the enzyme, beta-galactosidase (β-gal), required to break down lactose, only when lactose is present in their environment.

Jacob and Monod discovered that a protein, which they called lac repressor, binds to the gene that produces the required metabolic enzyme and suppresses the gene's transcription and translation when lactose is not present in the environment. When lactose is present, the lac repressor protein detaches from the gene, and the gene's transcription and translation are activated to produce the metabolic enzyme, β-gal. Jacob and Monod concluded that these regulatory proteins act as on/off switches in gene expression, controlling cell physiology at different times and under different environmental conditions during the cell's life cycle. Jacob and Monod named this kind of structural-regulatory gene an operon, and they hypothesized that this kind of ensemble represents a fundamental mechanism that would be discovered in the cells of all living beings. They won the Nobel Prize in 1965 for this discovery.

Jacob continued to work on gene regulation [6] in the 1960s and 1970s, and in 1977 he published "Evolution and Tinkering." In this essay, Jacob argued that the process of evolution [10] by natural selection [11] is more akin to *bricolage* (tinkering) than to engineering, an analogy he said was most apparent at the molecular level where the diversity and the underlying unity of life are most evident. Jacob argued that the action of selection does not operate in the same manner as an engineer accomplishes his designs. An engineer begins with a preconceived plan, or a blueprint, and proceeds by choosing or designing the required parts with the end product or function in mind. A tinkerer, like natural selection [11], must rely on the structurally and functionally imperfect parts of the world to reconfigure viable [7] systems into novel ones. The tinkerer's parts, as opposed to the engineer's materials, have no pre-defined function. Moreover, the tinkerer can and often does find appropriate existing structures to add to other ones. For example, Jacob noted, the human brain is the result of an imperfect patchwork of a structure controlling visceral or emotional drives, the rhinencephalon, and a structure controlling more sophisticated cognitive abilities, the neo-cortex.

Jacob stressed the consequence of this dis-analogy between engineering and natural selection [11]: evolution [10] does not produce new forms from scratch. Instead, it usually transforms systems by reorganizing their components. Jacob argued that this process has been ubiquitous in evolutionary history, accounting for even major transitions such as the passage from unicellular to multicellular organisms. Thus, the lesson for biologists was to refrain from conceiving of natural selection [11] as an omnipotent, optimizing force, and to pay more attention to the constraints of evolutionary history, including the molecular machinery underlying all of life.

In his autobiography, *La Statue Intérieure* (The Statue Within), published in 1987, as well as in a series of interviews conducted in the early twenty-first century, Jacob reflected on his career as a scientist. He claimed that Erwin Schrödinger's 1944 book *What is Life?* had the most influence on his transition from a student and practitioner of medicine to a scientific researcher in biology. He also mentioned that Julian Huxley [12]'s 1940s work on Charles Darwin [13]'s theory of evolution [10] spurred his later interest in evolution [10]. Moreover, he was influenced by the Lysenko affair in the USSR, in which the soviet director of biological research Trofim Lysenko rejected genetics as it had developed from Gregor Mendel's 1866 theories and forbid any scientists to study Mendelian genetics in the USSR. Jacob said that it irked him that someone in power would manipulate or distort science for political ends.

In addition to his 1965 Nobel Prize, Jacob received the Charles Léopold Mayer prize from the Académie des Sciences in France in 1962, and he was also awarded a seat in the Académie Française in 1996. Jacob became a foreign member of the American Academy of Arts and Science and the American Philosophical Society [14]. He also received honorary degrees from nineteen universities throughout the world. Jacob died on 19 April 2013.

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