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Tribute to François Jacob (1920-2013)

Chair of Cell Genetics from 1964 to 1991

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Tribute to François Jacob (1920-2013)

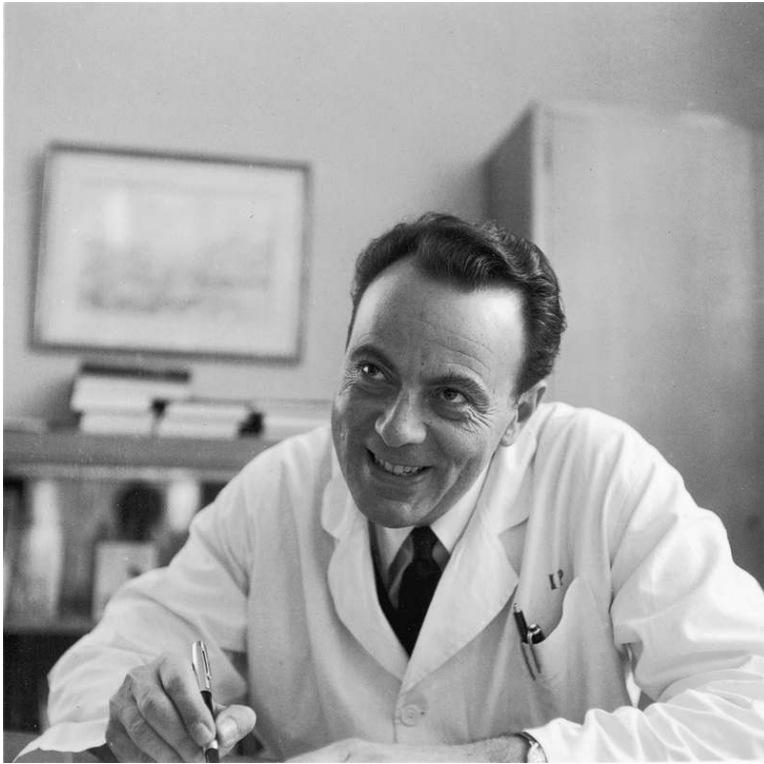
Chair of Cell Genetics from 1964 to 1991

Christine Petit and Philippe Sansonetti

EDITOR'S NOTE

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- ¹ **François Jacob, born in June 1920, was the only son of Simon Jacob and Thérèse Franck, both from Jewish families with strong though surprisingly different beliefs. François Jacob described his father as someone who combined religious practice with radical-socialist opinions, reconciling “a taste for tradition with the taste for revolution”¹.**



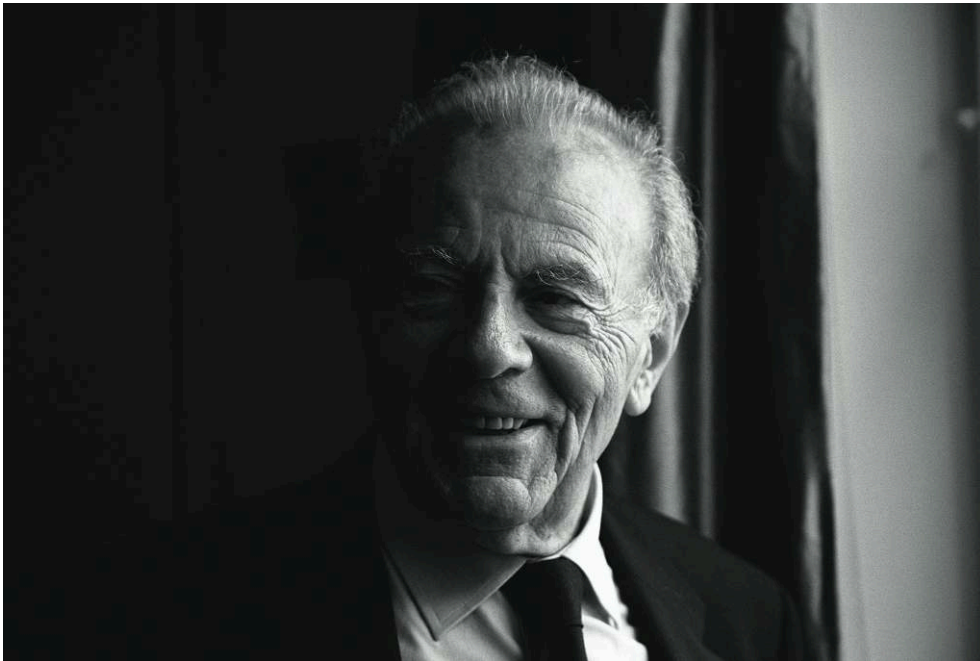
© Institut Pasteur 1965

- 2 His mother, agnostic, even atheist, was politically far more conservative. François grew up with the affection and tenderness of this woman, who died in June 1940, “in time”, he wrote, “not to experience the horror, ... the flight from the yellow star”². But “his ideal, his model”, in his own words, was his maternal grandfather in Dijon, Albert Franck, for whom he claimed to have “some sort of adoration”³. Albert Franck, “the general”, as François Jacob called him, was the first Jew to reach the rank of lieutenant general. He made François Jacob both see that “the sky was empty” and understand that “there was an Earth to fill”⁴. As a child, François Jacob looked up to him to build himself “a coherent representation of the world”. His school years at the Lycée Carnot in Paris left him with a memory of the Republican school as an institution concerned not so much with teaching as with “subduing the youth, standardizing it, making them all fit the same mould”⁵. After his baccalaureate, drawn to surgery, he started studying medicine but his studies were soon interrupted by the war.
- 3 When François Jacob turned 20 on 17 June 1940, he was on the road fleeing Paris with three of his friends. That was when, travelling towards the South West of France, he heard Pétain announce the armistice, which the General had asked for – “with honour and dignity” – in the words of his communiqué⁶. François Jacob refused submission outright. Determined to fight, he headed to Saint-Jean-de-Luz and the next day left for England with a friend. There, with a few thousand men, Free France was formed. Their strategy was to enter the war by relying on the African colonies. François Jacob asked to be appointed to the artillery; he was made to join the health service. On 1 September 1940 he left for Dakar, then continued on to Brazzaville, Libreville, and then to Fort-Archambault, where he was appointed to the Senegalese infantry regiment. From there he was sent to Mao, a large isolated town North of Lake Chad, to serve as a doctor – a sanction for refusing an appointment that would have removed him from the combat

units. It was only in the summer of 1942 that he was allowed to join the troops heading towards Libya: Fort-Lamy, then the desert crossing to Fezzan and Tripoli – “a trek to the ends of the earth” for three thousand men “in an impossible desert”, he wrote⁷. Finally, he was sent to the South of Tunisia, where he endured days of uncertainty and nightmares in Ksar Rhilane, decisive days for the course of the war. His first combats were in Djebel Matleb, then in Djebel Garci, where he was wounded in May 1943. In April 1944 he left Casablanca for England. On 1 August, he landed in Normandy, on Utah Beach. Eight days later he was severely injured during an air raid. He was evacuated to Cherbourg and then to the Val de Grâce hospital in Paris where he spent six months, and later had to be hospitalized again.

- 4 As a “glorious casualty”, as he called himself⁸, another desert crossing awaited him. The consequences of his injuries put an end to his hopes of becoming a surgeon. What was he to do? Finish his medical studies “as fast as possible”, he wrote⁹. Certainly, but then what? He was adrift, caught in bitterness, loneliness and doubts about himself and his future. In 1947, during a stint at the Cabanel centre created by the army to produce antibiotics, he wrote a medical thesis on one of them, tyrothricin. The centre subsequently closed and the years went by. François Jacob gradually developed an interest for research in biology. He sensed a “promise of effervescence to come”, “at the interface between genetics, bacteriology and chemistry”¹⁰. He contacted the few research centres likely to host him, to no avail. As a last resort, he turned to the head of the Institut Pasteur, Prof. Tréfouël, who welcomed him and offered him a research grant. He just had to find a laboratory that would host him. François Jacob’s mind was made up, and nothing could change it: he wanted to join the laboratory headed by André Lwoff, where Jacques Monod was already working. André Lwoff’s successive refusals did nothing to shake his determination. François Jacob insisted, and André Lwoff eventually accepted him into his laboratory. He wrote of François Jacob’s recruitment that while his “preparation for research was [...] certainly classical”, “energy, decisiveness, the spirit of sacrifice and enterprise, the refusal of defeat, and tenacity are vital qualities for a researcher”¹¹. André Lwoff’s sudden change of mind was due to the discovery he had just made. After years of effort, he had successfully induced a prophage in lysogenic bacteria. A field of research was opened, and ... a new PhD student was welcome! After receiving scientific training from the Grand Cours of the Institut Pasteur and two science degrees, François Jacob was finally ready to start working. This was October 1950. Fifteen years later he opened his Nobel speech with these words: “I was fortunate to arrive at the right place at the right time. At the right place because, there in the attics of the Institut Pasteur, a new discipline was emerging in an atmosphere of enthusiasm, lucid critique, non-conformism and friendship. At the right time because biology was thriving, it was changing its ways of thinking, discovering new and simple material in microorganisms, and moving towards physics and chemistry. It was a rare moment when ignorance could become a virtue”. André Lwoff embraced the Darwinian and Mendelian theories, unlike many French biologists, who were more inclined towards heterodoxy. As for microbiology, it had still not been established in the higher education of Pasteur’s land. François Jacob started with a rigorous and systematic study of lysogenic bacteria. His focus was twofold: defining the conditions of induction of the production of the viruses, bacteriophages, which they host in the form of proviruses, called prophages; and understanding the latter’s nature and properties, as well as the basis of the immunity that their presence conferred on the lysogenic bacteria. He thus clarified the lysogeny phenomenon, the fickle nature of

which even had scientists doubting its existence for a while. He turned it into a much broader subject of study (the nature of the relations between bacteria and their viruses), and sought to extend his conclusions to the viruses of complex plant and animal organisms. His unitary vision of life forms, which guided all his reflection, could already be found in the monograph *Les bactéries lysogènes et la notion de provirus* [Lysogenic Bacteria and the Provirus Concept], a compilation of his PhD work, published in 1954. In the preface to this work, André Lwoff highlighted his “exceptional predisposition for research”; “Within two weeks, we knew we had recruited someone great” said his colleague Georges Cohen. “A good pal”, he added, “who liked to get on with people”. He was curious about the work carried out by the researchers around him, particularly Jacques Monod, and soon began collaborating with several colleagues.



François Jacob in 2012

- 5 From 1953, he started working with Elie Wollman, in a rare relationship of trust and friendship. Together, they studied bacterial conjugation, and very soon understood that this phenomenon was related to that of the phage cycle. Genetic material, the F factor, determines the mating type of the *Escherichia coli* bacterium. But this factor exists under two forms: one is free, and the other integrated into the bacterial chromosome. François Jacob and Elie Wollman discovered that this phenomenon could be used to map bacteria's genes. Their order and distance on the bacterial chromosome could be deduced from the oriented transfer of the chromosome, at a constant speed, from a male donor bacterium to a female recipient bacterium, operated from one of the extremities of the integrated F factor. All the genetic criteria transferred from one bacterium to the other were linked: the bacterial chromosome was therefore circular. Elie Wollman flew off to the United States.
- 6 François Jacob's collaboration with Jacques Monod, which he later called “the great collaboration”, began in 1958¹². Jacques was ten years his senior. Agnès Ullmann, a contemporary witness, commented on the “total complementarity between them: François mastered genetics, Jacques biochemistry ... Jacques Monod confided a lot, François Jacob little. They addressed each other with the formal “vous”. François Jacob

was an early riser, Jacques Monod not so much. Both whistled very well, Brahms or Mozart for François, Bach for Jacques: we knew who was walking in the corridor ... No shadow was ever cast on their immense scientific connivance. They were constantly provoking each other and, with almost unimaginable excitement, always expressed the irrepressible need to compare their ideas several times a day. They shared the implacable desire to understand and the fear of mistakes ... They were so different and yet so similar” – “resistant from the outside, resistant from the inside”, with the mutual incomprehension to which these two forms of engagement led.

- 7 Together, they designed the “PaJaMo” experiment: “Pa” for Pardee, a US researcher on a sabbatical, “Ja” for Jacob, and “Mo” for Monod. Soon renamed “PY JA MA”, it was to become one of the most famous experiments in biology. The aim was to analyze the respective roles of the gene products of the *Escherichia coli* bacterium’s lactose degradation system, using the mapping by conjugation tool that had been developed and the numerous mutants isolated for each of these genes. Jacques Monod’s interest in the lactose system was owed to its inducible nature, actually common to several bacterial enzymatic synthesis systems. The lactose degradation enzyme, beta-galactosidase, is not found in bacteria, but is rapidly expressed after adding lactose to the culture medium. For a long time, Jacques Monod had sought to understand this induction mechanism. The heuristic power of the PY JA MA experiment, both remarkably well constructed and beautifully aesthetic, was considerable. Its results overturned established ideas by explaining an enzyme induction through a mechanism founded on repression: a cytoplasmic material coded by a gene that was independent from that of beta-galactosidase inhibited the latter’s expression, and this repressor was itself inhibited by the lactose. This was a striking discovery, which revealed the existence of two types of gene, one coding structural proteins like beta-galactosidase, and the other controlling the expression of the former. Moreover, this experiment revealed the existence of an operator region upstream from the genes thus regulated, to which the repressor had to attach. During this whole period, François Jacob proved to be “an incredible strategist in the design of experiments”, as François Gros put it. At a remarkable speed and with reliable judgment, he would gather the necessary tools and define the experimental conditions to test the hypotheses formulated.
- 8 A wave of intuitions and discoveries ensued. In late July 1958, François Jacob was at the cinema, watching “a movie of no great interest. The shadows moved about onscreen”, when suddenly, “it was as though a line of fire cut through the darkness”, it was “the glare of evidence”, in his own words¹³: the two experimental models he was studying, lysogeny and the lactose system, follow the same molecular mechanism. A gene synthesizes a repressor, which blocks the expression of other genes. This was a dazzling and genius intuition, which was later expressed through the elegant metaphor of “night science” and its companion “day science”¹⁴, the workshop of possibility in the case of the former and the sifting of rationality in the latter. François Jacob never tired of playing on words. His imagination was fuelled by the power of verbal evocation and meaning, which he expressed metaphorically. By placing subjects of reflection at a distance, by changing their meaning, metaphors afforded the biologist’s striking intuition the conditions for the elaboration of new possibilities.
- 9 François Jacob easily convinced Jacques Monod of this obvious fact, which he had discovered while preparing the Harvey Lecture he had to deliver in September of that year. However, the interpretation of the two systems was halted by a missing piece, an

unstable intermediary between DNA and protein synthesis, a cytoplasmic substance called “X”. During a meeting between François Jacob, Sydney Brenner and Francis Crick, the latter two concluded that this substance X could only be an RNA. Sydney Brenner and François Jacob demonstrated this independently in Matthew Meselson’s laboratory, as did François Gros and Walter Gilbert in Jim Watson’s laboratory. This RNA becomes messenger. The model was thus complete: regulator genes that synthesized a still enigmatic repressor, structure genes, an operator site to which the repressor attached, mRNA, an operon, etc. This whole molecular orchestration was completed on Christmas eve 1960, only ten years after François Jacob had entered André Lwoff’s laboratory.

- 10 Seven years after the structure of DNA had been revealed, this discovery was a real conceptual breakthrough, which moreover was unforeseen. It was to enrich all of biology, both in its ways of thinking and in its methods, through the development of molecular biology. The article presenting the model indicated the expected scope of these advances. It ended by suggesting that the concept be extended to mammals, arguing that regulatory genes were behind cellular differentiation, that they allowed the genome to express only part of its potentialities, and that they could also explain the cell disorders of carcinogenesis.
- 11 In December 1965, the Physiology or Medicine Nobel Prize was awarded to François Jacob, André Lwoff and Jacques Monod, “for their discoveries concerning genetic control of enzyme and virus synthesis”. Six months earlier, François Jacob had become a professor at the Collège de France, where he held the Chair of Cell Genetics. For quarter of a century, his critical mind enlightened the work of biology “in the making”. His lectures were the fruit of long preparation in the loft of his Mouans-Sarthoux house near Nice. All of them were written out in full.
- 12 François Jacob pursued his research in the microbial field until the late 1960s. He studied the replication of episomes, particularly of the F factor, and that of the phage lambda, as well as the division of the bacterial cell. He became increasingly interested in cell membranes, which were now central to his reflection. The Jacques-François duo began to drift apart, with neither of them showing much enthusiasm about the other’s work. According to their colleagues, “François Jacob did not like *Le hasard et la nécessité* [Chance and Necessity]”, written by Jacques Monod. “He did not share the vision of Judeo-Christianity developed therein, and the idea that science alone could define ethics”. As for Jacques Monod, he was hardly interested in François Jacob’s *La logique du vivant: une histoire de l’hérédité* [The Logic of Life: A History of Heredity]. They nevertheless continued to find common ground in certain social and political issues.
- 13 At the turn of the 1970s, many pioneers of molecular biology were drawn to the study of higher organisms. Once again, François Jacob sensed a budding field of research, that of early embryonic development. Convinced that the principles of the functioning of the bacterial genome must apply to higher organisms and account for their development and for their cell differentiation, he gave up his precious collection of hundreds of bacterial *Escherichia coli* mutants. He hesitated over the animal model to study, fully aware of just how critical that choice was. For a moment he considered the nematode, but Sydney Brenner beat him to it. Finally, he opted for the mouse, a model which, in his eyes, combined many advantages. Teratocarcinoma cell lines, germ-line tumours capable of differentiating themselves into a variety of cell types, could be cultivated. They offered the possibility of identifying markers of various stages of the

differentiation process, the relevance of which could then be tested in mice embryos; they allowed for a bio-chemical approach.

- 14 The genetic component crucial to the project was also present: mutant mice affected in their early embryonic development had been described. François Jacob proposed the creation of a mouse institute, an idea that was not well received by his biologist colleagues. The project never materialized but this new scientific objective was nonetheless thrilling. Still, it took François Jacob considerable courage to start again from scratch, with biological material that was totally foreign to him. While challenges never scared this man of tremendous drive and restless impatience for experimental results, the change in the timeframe of the experiments, from the fast pace of bacterial genetics to the slow one of the mouse, was a harsh test. The years from 1970 to 1980 were particularly difficult as the genetic engineering tools to isolate genes were developed for mammals in 1979 only. The model François Jacob proposed to account for development posits a sequence gene expression in stages, the unfolding of which depends on signals originating in the cell membranes. Several interesting proteins, including uvomorulin which has since become epithelial cadherin or E-cadherin, were thus discovered. On the other hand, some avenues explored, such as the mouse T complex, proved disappointing.
- 15 In 1984, the first genes regulating early embryonic development were discovered in the drosophila, the homeotic genes that determine the animal's body plan. François Jacob followed close behind these discoveries, and searched for the corresponding genes in mice. The laboratory he headed was a pioneer in gene inactivation in this animal. From the drosophila to the human being, including the mouse, it was discovered that homeotic genes have a collinear organization on the chromosomes, mapped onto that of the segments of the body whose development they control. One could not imagine a clearer demonstration of the conservation of regulatory genes throughout evolution. The fact that these genes had been discovered in the drosophila, which allowed for much faster experiments than in mammals, certainly did not detract from the visionary nature of the experimental approach implemented by François Jacob. In fact, since the eighties, the bulk of the international community's efforts to understand vertebrates' embryonic development have focused on the mouse. As for teratocarcinoma cells, they are similar to stem cells, the study of which has driven a profound revival of biology over the last fifteen years.
- 16 François Jacob enjoyed intimate discussions in groups of two or three. When the group was larger, he often remained silent. While he expected quality conversations, he was perhaps even more demanding when it came to the quality of people. He liked neither flatterers nor over-confident individuals, and could put them back in their place with just a word or gesture of impatience. Conversely, he welcomed some with visible pleasure. Conversations, irrespective of the topic, always started with a question regarding the progress of the other person's research. Eager for new results, he asked questions and suggested correlations with other processes. At any moment, he could exclaim "what you're doing is fantastic!", expressing generous enthusiasm. François Jacob liked to argue. "He looked for people who could put up a fair fight and genuinely needed it", in Michel Morange's words. The conversation then became like a game: he liked to be challenged and, even more so, to be surprised by an idea. The dialogue had a peculiar form. François Jacob would stare at the other person, then utter a few sentences, and suddenly a comment would come up which would shed light on the

debate from an entirely different point of view, as if it had been obvious from the start. In no way did he seek to block the course of the discussion, but conversing with him required a rare presence of mind. He spoke completely freely, unconcerned about whether his words were well received or not, and did not burden himself with any consideration he did not deem useful... he seduced one.

- 17 François Jacob hated dogmatism. According to one of his colleagues, Nadine Peyri  ras, “he never used arguments of authority with his scientific colleagues”. Although they carried out their research freely, according to those who engaged in the study of embryonic development with him in the 1980s, he clearly expected results. Always ready to get excited about a new piece of data, he would rush to the laboratory to assess for himself what could be expected of it. He was meticulous in his scientific writing, and encouraged and accepted all suggestions. Whilst fully endorsing his responsibilities, he was fond neither of commissions nor of “redundant committees”, and had a real aversion to anything pertaining to administration.
- 18 François Jacob rarely spoke about himself, never discussing the pain he still experienced following his war injuries. One day, however, in the atmosphere of freedom of speech that reigned in the 1970s, someone publicly reproached scientific personalities for taking up the front row of the lecture theatre during seminars, to which he bluntly replied: “I need to stretch my leg”.
- 19 François Jacob’s scientific research went hand in hand with epistemological reflection, which he presented in three books: *La Logique du vivant: une histoire de l’h  r  dit  * (1970), *Le Jeu des possibles: essai sur la diversit   du vivant* (1981) [*The Possible and the Actual*, 1982], and *La Souris, la mouche et l’homme* (1997) [*Of Flies, Mice and Men*, 1998]¹⁵. A few elements of this reflection can also be found in his magnificent autobiography: *La Statue int  rieure* (1987) [*The Statue Within: An Autobiography*, 1988]. From *La Logique du vivant* to *Le Jeu des possibles*, François Jacob evolved towards a vision of science that challenged the idea that it could provide comprehensive knowledge of reality. On the other hand, this vision stressed the fact that, just like myth, science fulfils human beings’ irrepressible “need for unity and coherence”¹⁶. We can see here the influence of Claude L  vi-Strauss, whom he held in high regard. François Jacob described science as a construct, like a creation of reality, not its revelation. He applied to it the conclusions of his reflection on evolution. Like evolution, the scientific approach is subject to the range of possibilities, but also to contingency, which, for science, corresponds to its actors’ ways of thinking that are linked to their era. He developed the idea that the unity and diversity of life forms go hand in hand, for, in his own mechanistic metaphorical terms, “evolution proceeds like a bricoleur who, over millions and millions of years, slowly alters his work, constantly making adjustments, cutting this bit off, lengthening that one, finding every opportunity to adjust, transform, and create”¹⁷. In fact, François Jacob saw scientific research itself as bricolage by scientist-bricoleurs. Is this conception a relativist one or, on the contrary, does it tell of an intellectual requirement to identify the limits of knowledge so as to overcome them?
- 20 With short and polished sentences and the right words colliding, François Jacob’s writing was at once precise, full of imagery, alert and powerful. It is hard to believe that, in his own words, he struggled to write. To conclude, we would like to convey the expression of his convictions in a short excerpt from his book *La Statue int  rieure*:
- 21 *Man exudes projects. Oozes plans. Reeks of intention. Does not tolerate contingency. Accepts neither that the evolution of species is random, nor that the history of human beings obeys any*

secret law. Some claim this history is directed by awareness of a goal. Others by blind fatality. But whether humans believe they are aware of a goal or not, whether they consider themselves active or forced to fulfil tasks of which they do not understand the ultimate reason, all want to see history flowing inexorably in a single direction. What humans seek to the point of anguish in their gods, their art, their science, is meaning. They cannot stand emptiness. They pour meaning onto events like salt onto food. They refuse that life takes off again randomly, over the course of events, with noise and fury. They forever want it to be directed, reaching towards a goal, like an arrow¹⁸.

- 22 As though in echo of that work, he concluded *Le Jeu des possibles* with these words: “It is hope that gives meaning to life... hope one day to be able to change the present world into a possible world, which seems better”¹⁹. François Jacob was a “Companion of the Liberation”, the highest distinction of the Second World War, a laureate of the Nobel Prize in Physiology or Medicine, and a member of the Académie française. He made history, that of Free France and that of molecular biology. He filled his life with meaning and enlightened what is perhaps our humanity. He was a tremendous scientist, and a humanist²⁰.

NOTES

1. F. Jacob, *La Statue intérieure*, (1970) Gallimard, 1990, p. 78.
2. *Ibid.*, p. 35.
3. *Ibid.*, p. 56
4. *Ibid.*, p. 82-83.
5. *Ibid.*, p. 118.
6. *Ibid.*, p. 138.
7. *Ibid.*, p. 175
8. *Ibid.*, p. 236.
9. *Ibid.*, p. 269.
10. *Ibid.*, p. 280-281.
11. F. Jacob, *Les Bactéries lysogènes et la notion de provirus*, Masson, 1954 ; preface by André Lwoff, p. V. (
12. F. Jacob, *Travaux scientifiques de François Jacob*, Nadine Peyriéras and Michel Morange (eds), Odile Jacob, 2002, p. 22.
13. *La Statue intérieure*, *ibid.*, p. 398.
14. (14) *Ibid.*, p. 397.
15. F. Jacob, *La Logique du vivant: une histoire de l'hérédité*, Gallimard, 1970 ; *Le Jeu des possibles: essai sur la diversité du vivant*, Fayard, 1981; *La Souris, la mouche et l'homme*, Odile Jacob, 1997. (
16. *Le Jeu des possibles*, *ibid.*, p. 48.
17. *Ibid.*, p. 72.
18. *La Statue intérieure*, *ibid.*, p. 256-257.
19. *Le Jeu des possibles*, *ibid.*, p. 131.

20. This text draws on Georges Cohen, François Gros, Michel Morange, Nadine Peyri  ras and Agn  s Ullmann’s accounts, collected with the help of Mich  le Roa, to whom the authors are very grateful.

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