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Jean Francois Daniel Nicolas. François Jacob: daring thought, daring action. Tribute to François Jacob - January 27, 2015., Co-organized by the Pasteur Institute and the Academy of Sciences; Institut Pasteur; Académie des Sciences, [Paris], Jan 2015, Paris (France), France. <hal-04531594>

HAL Id: hal-04531594

<https://hal.science/hal-04531594v1>

Submitted on 3 Apr 2024

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**Tribute to François Jacob - January 27, 2015 Co-organized by the
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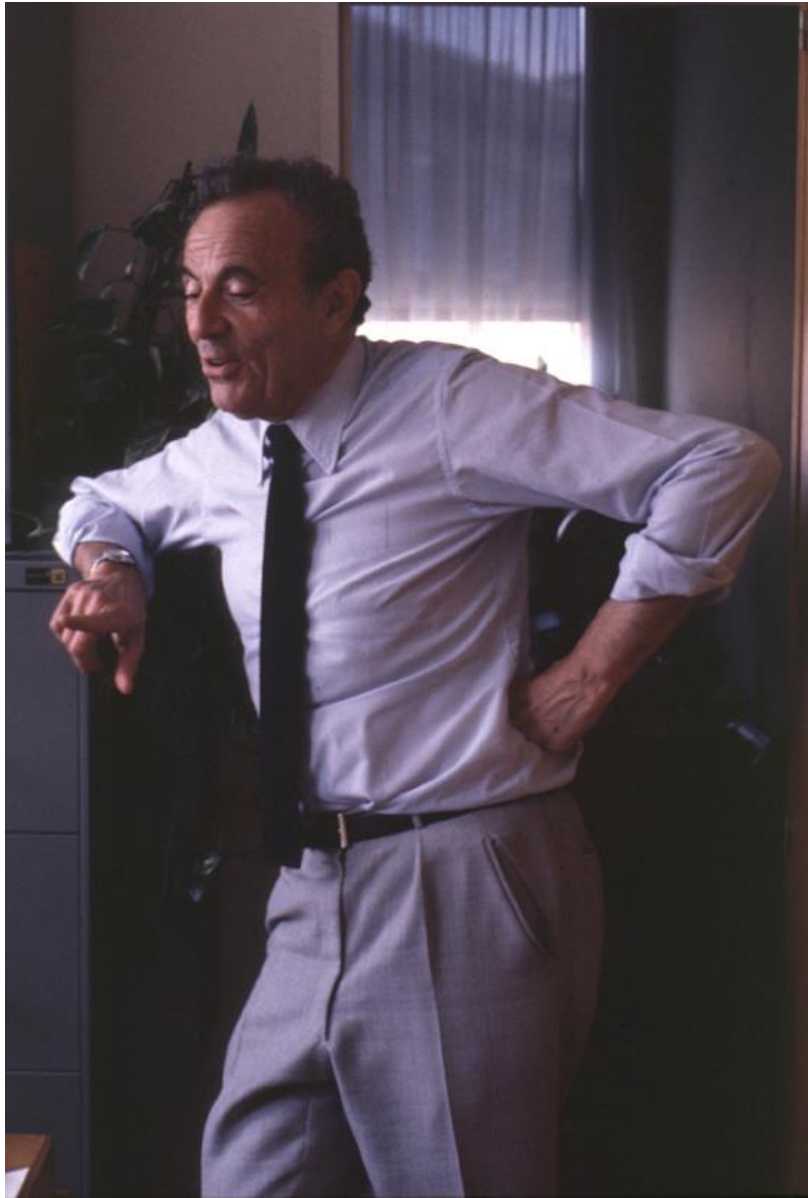
François Jacob: daring thought, daring action
Jean-François Nicolas

Summary

The immense contribution of François Jacob to bacterial genetics and molecular biology, where he stood as one of the founding fathers alongside Francis Crick, Sydney Brenner, Jacques Monod, and a few others, is widely acknowledged. However, it may have overshadowed his impact on developmental biology. In this tribute, I propose that without his choice of teratocarcinoma as a model for studying cell differentiation, which drew about a dozen laboratories worldwide into its orbit, the history of developmental biology and mammalian genetics would have taken a completely different trajectory.

Tribute to François Jacob - January 27, 2015
**Co-organized by the Pasteur Institute and the Academy of
Sciences**

"François Jacob: daring thought, daring action"
Jean-François Nicolas



History is marked by individuals who speak directly to its narrative.
François Jacob is one such figure
(Photo JR Rubenstein, personal collection)

On this day of tribute to François Jacob, it is a great honor for me to share with you some reflections—far from any epistemological endeavor—on his contribution to developmental biology¹.

This contribution did not begin in 1972 when he decided to focus on the early development of mice, but rather earlier, as early as 1961, as evidenced by several articles in which the concepts of the repressor-operator system of the lactose operon [4] were extrapolated to multicellular organisms. The presumed genetic organization in this system was transposed to one of the three problems of development: the differential expression of the genome in the differentiated cells of organisms. This was extensively discussed, for example, in the article "Teleonomic Mechanisms in cellular metabolism, growth and differentiation" [7]. The finest minds immediately delved into the open path. As an example, embryologist C.H. Waddington, as early as 1961, attempted to reinterpret the fundamental concepts of embryology (induction, determination, self-differentiation, competence, regulation, individuation) in light of Jacob and Monod's repressor-operator system.

However, all this remained largely theoretical exercises for a long time—something the Professor appreciated only to a certain extent—and it took a lot of work, especially from the 1980s onwards—after and thanks to the technological revolution of genetic engineering—to adapt bacterial genetic repression systems to eukaryotic genetic activation systems. It required deciphering the functioning of eukaryotic viruses, SV40 and Polyoma, and then that of genes with restricted expression to certain tissues, i.e., the identification of transcription factors (activators and repressors) and their DNA target sequences. This laid the groundwork for the following fundamental

discoveries: the transcription factors involved in development, from which emerged the general network organization of the genome as currently deciphered. Included in these networks are what have been called architectural genes or master genes, these transcription factors that play a key hierarchical role in genetic control during development, as well as network motifs with remarkable emergent properties upon which the entire dynamics of genome expression depends [1]. However, conceptually, there is not much more in all this than in the foundational theoretical models discussed from the lactose operon. François Jacob rebelled daily against "the ease" of following beaten paths. (For me, this echoed Piotr Slonimsky's injunction to his DEA students: "do not do what others can do") and it was in this mindset that he approached the problem of development at the end of the 1960s by defining the new frontier, which was no longer for him that of genome organization.

In November 2012, I met François Jacob again and we discussed what was happening. Several times he asked me, "But Jean-François, what are they going to do now that they are done with the genome?" I had some difficulty with this question, if it was indeed a question. He did not mean that there was nothing left to do, no; François Jacob knew that we were in a period of refinement and exploitation. He was trying to grasp where the new frontier would be and to invent the next step.

In assembling within a unified model three seemingly disparate elements—the teratocarcinoma, mutants of the T/t complex (embryonic lethal mutants) [8], and the analysis of membrane antigens—François Jacob translated his theory of development into action. Although complex, he viewed it as a problem of cell-to-cell exchanges involving their membranes. In this regard, he was insightful; the second ingredient of development lies within signaling pathways. Furthermore, he chose

¹ See also : Jean Francois Daniel Nicolas. François Jacob, or the thirst for novelty. *Research in Microbiology*, 2014, 165 (5), pp.370-374.

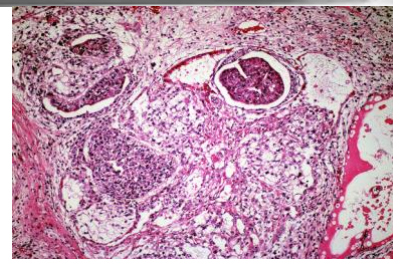
to depart from classical genetic analysis, particularly genetic screens, which were impractical with this model. Instead, he made a wager that nature had already conducted such analyses: the embryonic lethals of the T/t complex were to serve as the genetic arsenal revealing the logic of mouse development. Additionally, the immunological approach employed (isoimmunization) suggested that membrane antigens were specific to development, not utilized by the mature organism. He conceived of development as a series of separate logical operations, with a developmental program inscribed within a specific genetic complex—the T/t complex encoding membrane antigens unique to the embryo. This realm falls within "The Logic of Life"² and embodies a form of finalism (the program).

As soon as he suspected the absence of such development-specific elements, François Jacob abruptly concluded the subject with a staggering shortcut, which, I believe, characterizes him entirely: his hypothesis of evolutionary bricolage in 1977 [3], from which follows the assertion that only makeshift mechanisms exist in development, devoid of logic or program. We enter into contingency, into "Le jeu des possibles"³.

For those pondering the outcomes of research surrounding the T/t complex-surface antigens model, the response would be: molecular tinkering (soon to transcend into cosmic tinkering), definitively demystifying this improbable and wondrous process that is development. Of course, this is not to undervalue the other elements upon which this hypothesis rests, but to underscore the potential role that the experimental endeavors of François Jacob's laboratory during that epoch may have played in challenging the primary hypothesis. The substantial chasm in François Jacob's cogitation between "The Logic of Life", "Le

jeu des possibles" and "Of Flies, Mice, and Men"⁴ deepens from this juncture.

Must we truly emphasize the additional impacts wrought by research on the teratocarcinoma? One might peruse his "Travaux scientifiques," published by Odile Jacob in 2002⁵, wherein François Jacob himself sifted through what he believed should endure from that period.



Roy Stevens : the inventor of teratocarcinoma.

In the 1970s, fewer than ten laboratories (Chris Graham, Mc Burney, Davor Solter, Brinster, Edidin, Mike Sherman, Gail Martin, Martin Evans, Béatrice Mintz, and Barry Pierce), all indebted to Roy Stevens (who invented the teratocarcinoma [11] and demonstrated the equivalence between

² The Logic of Life, François Jacob, Princeton University Press 1993 ; originally published as La logique du vivant: une histoire de l'hérédité, Editions Gallimard, Paris, 1970.

³ Le Jeu des possibles : Essai sur la diversité du vivant, François Jacob, Fayard, Paris, 1981.

⁴ Of Flies, Mice, and Men, François Jacob, Harvard University Press, 1998 ; originally published as La souris, la mouche et l'homme, Editions Odile Jacob, Paris, 1997

⁵ Travaux scientifiques de François Jacob, Morange, M. Peyrieras, N., Editions Odile Jacob, Paris, 2002.

teratocarcinoma stem cells and those of the embryo [10]), and Boris Ephrussi (who isolated the first teratocarcinoma cell line [2]), - exchanged tools, researchers, and concepts more or less freely around this theme, with François Jacob as the leader.

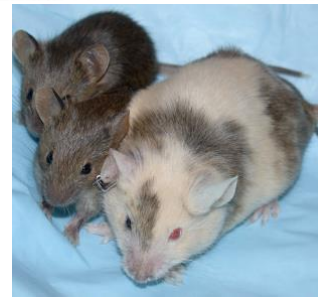


Boris Ephrussi : the first teratocarcinoma cell line.

These laboratories were all more or less doing the same thing. In Paris, Hedwig Jakob isolated new teratocarcinoma cell lines [5], just like Gail Martin, Martin Evans, or Mike Sherman, and Charles Babinet, Hubert Condamine, with the help of Marie-Thérèse Schnebelen, injected PCC3 cells, a lineage with astonishing properties, into blastocysts. Brinster and Béatrice Mintz did the same with cells from the same tumors obtained from Roy Stevens, and I couldn't say which of them had this crazy idea (Béatrice Mintz had already aggregated mouse embryos and had drawn major developmental insights from them).

After many failures in Paris and elsewhere and as a result of remarkable persistence fueled by fierce competition between these laboratories, Brinster and Mintz independently obtained somatic

contributions first, then Béatrice Mintz and Karl Illmensee a contribution to the germline [6]. Later, combined with genetic engineering techniques, a new way of doing genetics was invented.



Béatrice Mintz : mice derived from teratocarcinoma cells

Today, it may be difficult to imagine how the idea of correcting tumor cells, and even transforming them into normal embryonic cells, simply by putting them in contact with normal cells could seem both simplistic and unrealistic, even ludicrous. Would this system exist today if François Jacob had chosen another model system for development? Would as many laboratories have participated in the teratocarcinoma adventure? The number of scientists who visited Paris, if only to see what teratocarcinoma stem cells looked like, attests to the role played by François Jacob's team during this period. Would the laboratories that contributed to this story have participated? And if so, would they have put in all the persistence it took to obtain germline contributions?

The mouse was about to prevail; it remains the major model in genetic analysis of development and far beyond. But for this to happen, among the other model systems of the 1970s, there had to be one that could overcome the final obstacle. Was this breakthrough the result of considerable intellectual effort (as was, I believe, the teratocarcinoma T/t complex model)? Of a new intuition or concept? Well, no. The model that enabled the characterization of the first key developmental genes (excluding homeotic mutants) and then, to general astonishment, allowed these same genes to be found in all animals examined, is one that, had the question been posed thus, nobody would have bet on. It was the study of development, entirely atypical, occurring in a syncytial structure, meaning without cells, of the fruit fly, using a perfectly classical genetic screen aimed at blindly identifying (not yet embryonic lethals, remember the embryonic lethals) genes involved in the early stages of development [9] that led to this breakthrough. An approach without hypothesis or bias, which could very well have been implemented at least ten years earlier!⁶

It is the very atypical nature of this development that, by bypassing cell-cell dialogue via signaling pathways, made this pure sequence of direct interactions between transcription factors and their DNA targets accessible to analysis. But also, another circumstance overlooked at the time, the absence of genetic redundancy in invertebrates, contrasting with the situation in vertebrates where for every invertebrate ortholog, there are no fewer than four homologous genes, reflecting the two successive genome duplications that accompanied evolution in this phylum. The same genetic screen, carried out in a model

vertebrate, would have failed. And the extraordinary pattern of genetic interactions that was developed with the fruit fly—a foundational pattern, so close to the 1961 patterns of Jacob and Monod—would hardly have come to light. Once again, the role of chance and randomness, contingency in this extraordinary story, is evident.

It is in this sense that François Jacob's phrases must be interpreted: "Science is unpredictable... It is futile to hope to predict the direction that a science may take... Research is an endless process whose evolution can never be foretold." Phrases so profoundly true and relevant, with such significant implications for the way real science is conducted, both collectively and personally. Phrases also imbued with humility: in the battles that scientists wage, the victors are never quite as great as they would have us believe, and defeats are not always as useless as one might imagine.

Allow me to conclude on this slide:

"In art as in science, the essential thing is to try" (François Jacob).

K. Artzt, P. Avner, C. Babinet, O. Bensauade, T. Boon, P. Brulet, M.H. Buc-Caron, H. Condamine, M. Darmon, F. De Vitry, B. Dove, P. Dubois, P. Duprey, H. Eisen, R.M. Fauve, M. Fellous, G. Gachelin, J. Gaillard, J.-L. Guènet, M. Hofnung, F. Hyafil, H. Jakob, F. Kelly, O. Kellerman, R. Kemler, J.A. Levy, G. Lindahl, D. Louvard, M. Morange, D. Morello, T. Muramatsu, J.-F. Nicolas, A. Novick, D. Paulin, N. Peyrieras, S.E. Pfeiffer, Y.Reisner, J.L. Rubenstein, M.T. Schnebelen, M. Vasseur.

These are some of those who had the privilege to "try" with François Jacob in his laboratory, in the 1970s-80s, here at the Pasteur Institute. May they all be associated with this tribute.

Thank you for your attention.

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⁶ See also : Embryology, from vertigo to vertigo. A narrative of the impact of genetics and molecular genetics on embryology in the last century and the early 21st century Jean François Nicolas, 2022 : <https://hal.science/hal-04494411> and La Fabrique des Organismes : Le Développement embryonnaire vu par la Génétique moléculaire et l'Évolution, Jean François Nicolas, 2020 <https://hal.science/hal-02890738>

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