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The Birth of the Operon

WHAT IS THE OPERON, WHOSE 50TH ANNIVERSARY IS BEING CELEBRATED THIS WEEK? THE WORD heralded the discovery of how genes are turned on and off, and it launched the now-immense field of gene regulation. The idea was born in André Lwoff's laboratory at the Institut Pasteur. At one end of a long corridor in the loft of a building devoted to research on bacteria were Lwoff, Elie Wollman, and myself. At the other end were Jacques Monod and his group. Lwoff studied lysogenic *Eschericia coli* bacteria capable of producing bacteriophage without infection. Monod was analyzing the properties of the β -galactosidase enzyme in the same bacterium: an enzyme required for the metabolism of lactose that was produced only when the culture medium contained galactosides. To all and sundry the two systems appeared mechanistically miles apart. But their juxtaposition would produce a critical breakthrough for our understanding of life, demonstrating that we cannot presume to know how new ideas will arise and where scientific research will lead.

Toward the end of the 1940s, after 2 years of hospital care for my wounds from the war and a rather slapdash end to my medical studies, I wandered aimlessly in Paris. Unable to realize my dream of becoming a surgeon, I was persuaded by a cousin to launch out into the newly hatching science of biology, and I decided to join a laboratory. After several unsuccessful attempts, no doubt due to my notorious incompetence, I was kindly received by Professor Tréfouel, the director of the Institut Pasteur. He quizzed me on my wartime escapades; explained the importance of sulphamides, of which he was one of the fathers; described the wartime horrors at the Institut; and finally offered me a research bursary.

I spent the first year taking the "Grand Cours," learning bacteriology, immunology, and virology, and then sought a lab in which to use my newfound talents. There were two exceptional labs in Paris: that of Boris Ephrussi and that of André Lwoff. After several fruitless visits, I returned to see Lwoff again. His eyes seemed bluer, the turn of his head more dignified, and his manner warmer. Without giving me time to either display ignorance or express my wishes, he said "We've just discovered how to induce the prophage." I didn't know what a prophage was, let alone what it meant to induce it. Nevertheless, I retorted immediately "That's exactly what I'd like to work on." And Lwoff agreed.

Much later came a day in 1958 when, my mind wandering on a lazy July evening, I sensed in a flash that there were important analogies between the systems studied at the two ends of our corridor: In both cases, the expression of a cluster of structural genes directed the synthesis of several proteins, and this expression was modulated by a "repressor" encoded by an adjacent regulatory gene. Monod and I baptized this structural gene-regulatory gene ensemble an "operon" (from "to operate"), and we quickly recognized that the operon-repressor system could be combined ad infinitum to produce circuits of increasing complexity, adapting to the demands of the cell. Thus did we discover a "mechanism fundamental to all living beings from their very beginnings, and that would persist as long as they exist . . . More than ever, research seemed to be identified with human nature . . . It was by far the best means found by man to face the chaos of the universe."*

Our breakthrough was the result of "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."** In today's vastly expanded scientific enterprise, obsessed with impact factors and competition, we will need much more night science to unveil the many mysteries that remain about the workings of organisms.

— François Jacob

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*F. Jacob, J. Monod, *J. Mol. Biol.* **3**, 318 (1961). **F. Jacob, *The Statue Within: An Autobiography* (Unwin Hyman, London, 1988).

