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EDITORIAL

Day Science, Night Science

Science is often described as basic or applied, good or bad, useful or useless (esoteric, may be less dismissive). I was puzzled by the terms 'night science' and 'day science' which appeared in a recent essay (Jacob, F., *Science*, 2011, **332**, 767). The author, Francois Jacob, a recipient of the 1965 Nobel Prize in Physiology or Medicine, was reflecting on the 50th anniversary of the birth of the 'operon' in molecular biology. By the late 1950s, the gene as a DNA molecule was an established fact and the chemistry of heredity seemed to emerge seamlessly from the complementarity of the double helix. The genetic code was just over the horizon. Genes led to proteins, which in turn controlled the myriad pathways of biochemistry. Control in turning genes on and off seemed necessary to explain the amazing coherence of life's chemistry. The seminal paper that launched the 'operon' and opened the field of gene regulation was written almost exactly half a century ago, by Francois Jacob and Jacques Monod. Entitled, 'Genetic regulatory mechanisms in the synthesis of proteins' (*J. Mol. Biol*., 1961, **3**, 318), the article introduced the idea of a switch, controlling the 'expression of a cluster of structural genes' that directed the synthesis of several proteins, responsible for connected biochemical tasks. Switches could be turned on and off by specific interactions between molecules, DNA and proteins amongst them. The ideas of operators, repressors and inducers emerged from this study; terms commonplace in molecular biology today. The 1961 paper was pathbreaking, laying bare in Jacob's words: '… 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.' Jacob adds, undoubtedly aided by the wisdom of hindsight: '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".' Puzzled, as I was, by an unfamiliar description of different styles of science, there seemed no alternative but to turn to the reference provided by the author: *The Statue Within: An Autobiography* (Jacob, F., Unwin Hyman, London, 1988).

Jacob's book is unusual for an account of a life in science. A very large part of the narrative describes his early years; a youth rudely interrupted by the war years. Curiously, the book begins by considering suicide and death; Cleopatra 'holding out an arm to the asp rising, hissing from the figs' and 'Socrates in prison, meditating and holding in his hand the goblet of hemlock' are the images he evokes. Jacob writes, at times hauntingly, about aging and death: '… a life that shrivels up, slowly rots, goes soft as a pulp. This worry about decline grabs me by the throat as I awake.' He justifies writing about his life: 'I am neither to wallow in the mire of self satisfaction nor to settle old scores, but rather to set myself a new purpose, and thus a new existence. It is to take my past and produce the future.' Jacob's urge 'to do' has its corollaries: 'This endless race with time, this preference for desire over enjoyment is not without its drawbacks. Too often, it prevents us from understanding, and nurtures the illusion of life rather than life itself.' Jacob is reflective and must strike a chord in readers who think about science: 'It took me a long time to realize that this drive towards tomorrow has an advantage in at least one domain – in research. Late, very late, I discovered the true nature of science, of how it proceeds, of the men who do it. I came to understand that contrary to what I had believed, the march of science does not consist in a series of inevitable conquests, or advance along the royal road of human reason, or result necessarily and inevitably from conclusive observations dictated by experiment and argumentation.… To my surprise, those who achieved the unexpected and invented the possible were not simply men of learning and method. More than anything else, they possessed extraordinary minds, enjoyed the difficult and often were creatures of amazing vision. Those in the front ranks displayed exotic blends of passion and indifference, of rigor and whimsy, of naivete and the will to power, in a triumph of individuality.' Jacob worked at the Pasteur Institute in Paris, a centre with a rich tradition of the finest research in biology. Jacob describes the Institute as 'a curious mixture of excellent science and *laissez-faire*, of boldness and routine, of paternalism and incompetence…'.

Pasteur is venerated in France. Jacob describes an annual event at the end of September where the institution commemorates 'the death of its founder', and a solemn procession enters a 'mausoleum out of Byzantium'. Jacob recalls a childhood devotion to Napoleon and a

grandfather's admonition: 'Admīre, yes. Idolīze, no. Neither gods nor men. Not gods, for they do not exist. Not men, for they are not gods.' The scene at the tomb evokes wonder: 'On the walls to either side of the tomb were marble panels on which were carved like Napoleon's victories in the Invalides, Pasteur's victories. Instead of the battles of Austerlitz, Jena and Friedland, one read of molecular dissymmetry, fermentation; so-called spontaneous generation; studies on wine; silkworm diseases; studies on beer; virulent diseases; vaccines; prophylaxis against rabies. … how could one not marvel at this unbroken series of triumphs, at this sure ability to deduce, from a theory, its applications or, on the contrary, to extract from the most theoretical problem, the most concrete aspects? How could one not admire this scientific odyssey, this vaulting from one domain to another, of going from chemistry and crystallography to the study of living things, from the diseases of beer to those of man?… Like Napoleon, Pasteur had fought many battles.… Like Napoleon's, Pasteur's art consisted in always joining the battle at the moment of his own choosing, at the place of his own choosing, on his own ground. And his ground was the laboratory; his weapons were experiments, protocols, the culture flasks. Whatever new domain he entered … Pasteur sought each time to transform the problem, to translate it into other terms, to open it to experiment.… It is Pasteur and this strategy that began modern medicine and what is now called "public health". Without a doubt, Pasteur's saga was as stirring as Napoleon's!' The Pasteur Institute provided Jacob a unique ambience, working between two men who would years later share a Nobel prize with him, Andre Lwoff and Jacques Monod. In linking the apparently distinct lines of research in the laboratories of his collaborators, Jacob chanced upon his breakthrough, a consequence of what he calls 'night science'.

Jacob argues that 'once admitted, once taught, science is cold. As cold as the techniques that derive from it. As cold as the texts explaining its content or the books reporting its history. Science in the works has two aspects: what could be called day science and night science. Day science employs reasoning that meshes like gears and achieves results with the force of certainty. One admires its majestic arrangement as that of a da Vinci painting or a Bach fugue.… Conscious of its progress, proud of its past, sure of its future, day science advances in light and glory. Night science, on the other hand, wanders blindly. It hesitates, stumbles, falls back, sweats, wakes with a start. Doubting everything, it feels its way, questions itself, constantly pulls itself together. It is a sort of workshop of the possible, where are elaborated what will become the building materials of science. Where hypotheses take the form of vague presentiments, of hazy sensations.… It is impossible to predict whether night science will ever pass to the day condition…. When that happens, it happens fortuitously, like a freak…. What guides the mind then, is not logic. It is instinct, intuition.' These reflections precede Jacob's account of his famous work with Monod, who from all accounts could be described as a practitioner of 'day science'.

Reading about Monod and his style, I turned, inevitably, to a compelling account of biology, written by him forty years ago. *Chance and Necessity* (Monod, J., William Collins Sons, Glasgow, 1972) begins with a quote from Democritus: 'Everything existing in the Universe is the fruit of chance and of necessity.' Monod argues with the sureness of a 'day scientist' that biology and life as we know it must be a one off occurrence and that life has originated by chance, unlikely and improbable in the Universe. Biology, in his assessment, 'occupies a position among the sciences both marginal and central. Marginal because, the living world constituting only a tiny and very "special" part of the universe, it does not seem likely that the study of living beings will ever uncover general laws applicable outside the biosphere. But if the ultimate aim of the whole of science is indeed … to clarify man's relationship to the universe, then biology must be accorded a central position, since of all the disciplines it is the one that endeavours to go most directly to the heart of the problems that must be resolved.' Monod's book provides a deeply insightful analysis of many problems that continue to attract attention today. In an essay entitled 'Maxwell's demons' he provides a view of enzymes and catalysis, linking to modern views of 'the equivalence between information and negative entropy'. In a chapter titled 'Microscopic cybernetics' he outlines the logic of regulation, that underlies the growing discipline of systems biology. Monod introduced the idea of 'allostery' in 1965 to explain how isolated oxygen binding sites on hemoglobin could 'sense' one another; another example of 'on–off' regulation. This was an example of a conjecture developing into a theory. Max Perutz independently established allostery experimentally, by X-ray diffraction. Years later he wrote: 'There are two ways out of an impasse in science: to experiment or to think. By temperament, perhaps, I experimented, whereas Jacques Monod thought. In the end our paths converged' (*I Wish I'd Made You Angry Earlier: Essays on Science and Scientists*, Perutz, M., Oxford University Press, 1998).

In thinking about experiment and theory, night science and day science I must return to Jacob's recent editorial essay: '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.' There is something appealing about Jacob's 'night science', stumbling along in the dark, hoping that chance will illuminate the transformation into 'day science'.

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