A Biologist by Chance and Necessity

Patrizia Lavia

Abstract Jacques Monod's *Chance and necessity* was my life-changing book. It turned me from being a prospective student in humanities, as I had always thought I would be, into a student in biology and, later, a Life Sciences researcher. In my research journey, I have been fortunate to live through an extraordinary time, in which thrilling discoveries have been accomplished. In the twentieth century biology has been revolutionised by our understanding of the genome. Jacob and Monod exemplify the strength of idea-driven, intuitive, almost handicraft activity yielding conceptual breakthrough. They announced an era, later called the molecular revolution era, that symbolizes to me the human quest towards progress. The curiosity, strive, efforts, and persistence that lead to discovery found a fertile humus in the molecular revolution: novel ideas were seeded, blossomed and generated new hypotheses, new efforts, and yet new discoveries in a collective effort to understand as complex a problem as the organization of our genome and molecular evolution. It has been an extraordinary privilege to see that progress develop. We have acquired the ability to work with DNA: the discoveries that followed confronted us with unprecedented questions and possibilities. Modern biology is now changing with the development of powerful technologies. It is progressing through high-resolution, automated techniques, generating "big data" requiring artificial intelligence for interpretation, and drawing global profiles of cells and organisms. We must regard these "big" approaches as knowledge-generating tools that can open up now venues we could never have explored otherwise, yet must remain aware that data generation must not overshadow human curiosity and intuition. We are still only beginning to understand fascinating processes in the life sciences. There is still much to be expected for those who have the passion, drive and patience to live through the lights and shadows of research.

P. Lavia (✉)
Institute of Molecular Biology and Pathology, CNR National Research Council of Italy, 00185 Rome, Italy
e-mail: patrizia.lavia@cnr.it

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1 Motivations: How I Developed an Interest in Science

My motivation to study biology was a revelation to myself, which I had not suspected until the age of 18, when a book marked a turning point: "*Le hasard et la nécessité"* (*Chance and necessity*), by Jacques Monod. That happened by chance—and the book's name contained what was going to have a fatal impact on me.

I had always enjoyed learning at school. In the early '70s, my last three years in High School were amazing: the world was changing around us. People all over the world demanded freedom, civil rights and peace; we would sing to "*Give peace a chance*" and John Lennon's *Imagine.* The future seemed to hold a promise of change. We were exposed to a tourbillion of novelty in music, movies, literature, and philosophy. In high school we were fortunate to have excellent teachers who helped us reasoning through these ideas. I was looking forward to taking humanities at University. Everybody in my family had taken studies in humanities or law, which also seemed a natural culmination of my education at that point.

Then came the Monod book, in my last year in High School. Like many of my generation in the '70s, I was fervently committed to the ideal of equality and justice. I haven't changed my mind as to the ethical value of justice and equality, but I realize that my views then had the inflexibility, strength, and naiveté of a teen-ager with a dogmatic approach to reality. I am sure my assays in philosophy conveyed a complete lack of nuanced, critical reasoning, and yet, at the same time, a genuine desire to gain knowledge. Our Philosophy teacher tried to stimulate our critical thinking. In addition to ordinary lectures, he used to assign books for us to study and report on to the class. My assignment was "*Chance and Necessity"*, by Jacques Monod, Subtitle: "*an Essay on the natural Philosophy of modern Biology*" (Monod 1970). I think my Professor intended to stimulate me to think about how knowledge of reality can be gained and how it feeds back on our thoughts, beyond preconceived ideas. That was a revelation. I read about the "mystery" of the genetic code and the "mystery" of the functioning of the brain, as Monod described them. I came in contact with topics I had only marginally encountered up to that point. I was struck by the concepts flowing from the book, which shattered my programme to take humanities at University. Now I thought nothing could possibly be more interesting and worth dedicating one's efforts than biology.

Years later, I met Agnes Ullmann, who had been a close collaborator of Jacques Monod in Paris and the author of "*The origins of Molecular biology—A tribute to Jacques Monod"* (Ullmann 2014). Mme Ullmann was asking everybody at that party what had moved them towards biology. When I told her my story, she encouraged me: that's a wonderful story, you have to let your Professor know!

My former Philosophy Professor had moved to France and I had lost contact with him. Years later the occasion arose. With my schoolmates we organised a reunion to celebrate the 40th anniversary of our Baccalauréat and did a systematic search to invite our former teachers. After a bit of web searching, I found his e-mail and invited him to join our reunion, then added a few personal lines, telling him I was sure he couldn't possibly remember having assigned to me "*Chance and necessity*"

forty years earlier, but that book had changed my life, after which I had taken biology and spent the rest of my life in research. My Professor's reply was moving: "I know few who can gratify a teacher so much. It has made me happy in more than one way: for the somewhat narcissistic feeling of learning that I played a role, albeit a very modest one, in determining your professional orientation. Above all, I am delighted to hear that you now carry out as noble and essential an activity as the one you have chosen, so please accept my whole-hearted congratulations".

Thanks to my Philosophy teacher, *Le hasard et la nécéssité* has been my life-changing book.

2 Work Done: My Personal Scientific Approach

I can't trace my personal path without sketching the context. My first acquaintance with research in biology took place at an extraordinarily stimulating time—possibly, one of the most exciting times in biology.

I enrolled in Biology at Sapienza University in Rome in 1973. In that same year, Herbert Boyer and Stanley Cohen accomplished the very first genetic engineering experiment: they were the first to transfer a plasmid from one bacterial type into a different one, proving for the first time that genetic information could be transferred across genomes. Only a few months earlier, Paul Berg had created the first recombinant DNA molecule, demonstrating that a gene could be isolated, manipulated, cloned and amplified in the manipulated version, thus propagating novel genetic information. It is fascinating to listen to the account of those discoveries by Berg himself (https://www.youtube.com/watch?v=ZVK5MHieDAM) and read the account of how he got to make these discoveries in his Nobel lecture (Berg 1980), a prize shared with Walter Gilbert and Frederick Sanger, the pioneers who devised the method for DNA sequencing, starting the journey to deciphering the genome.

Listening to my University professors debating the implications of those molecular discoveries was a blessing for a first-year student. These groundbreaking discoveries raised hopes for those who saw science as progress, but triggered fears in those who saw scientists as Frankenstein creators. The implications of these discoveries stimulated thoughts I may define "à la Monod", reaching beyond the boundaries of Universities and research centers. At that time it was impossible to anticipate the long-term consequences of transferring DNA from an organism to another one. In 1975, Berg and other world-leading molecular biologists who had developed the recombinant DNA technology held the historical conference of Asilomar, California, where they established self-imposed regulations for manipulating genes and genomes (Berg et al. 1975). The Asilomar conference marks a milestone in self-reflection on science by scientists, where they established a model for self-regulation. The Asilomar manifesto read: *"Although there has as yet been no practical application of the new techniques, there is every reason to believe that they will have significant practical utility in the future"*. As knowledge advanced in the following years, the regulations evolved, but the insight of the Asilomar scientists in foreseeing the impact that

genetic engineering techniques were going to have remains unsurpassed. Looking back, I realise how privileged I have been to start my studies at the time of a scientific and cultural revolution. Biology was revealing the unexpected, seeding novel ideas, evolving fast, and promising life-changing progress. The feeling of embarking in a wonderful adventure was there. With progress advancing, I was confident that some answers to the fundamental questions asked by Monod could now be expected.

Besides the understanding of how to manipulate genes, a growing understanding of how genomes are organised was beginning to accumulate. It was becoming clear that, in higher eukaryotes, genomes are composed of diversified regions, some containing the genes that determine our characters, while others contained repetitive DNA that did not encode protein products. It also became clear that the genomic DNA was not "naked", but was associated with proteins that gave it a higher-order organization. That triggered an era of fundamental experiments to understand whether that organization had a functional significance, possibly related to the capacity of expression of different genome regions. Many laboratories began to study the genome organization during development and across species. It emerged that genome regions containing protein-coding genes, defined "euchromatin", shared "organisational" features that rendered them preferentially accessible to the machineries for replicating the DNA, transcribing the information in messenger RNA, and repairing any occurring damage, compared to the "heterochromatin", mostly made up of non-coding repetitive DNA. Scientists were puzzled about all that genomic material apparently devoid of coding functions: was it residual "junk" from evolutionary remnants, or did it have some purpose? We now know that this part of the genome has important regulatory roles in genome function and in evolution. That was the context I had the privilege to live through as a student: an era of groundbreaking discoveries fuelling continuous curiosity and enthusiasm.

In 1976 I started my thesis in Drosophila genetics and, a few years later, my first post-doc in human cytogenetics. The "fil rouge" in my early research experience was the effort to understand the functional organization of the genome. In the Drosophila project, I characterized differential features in the non-coding fraction (heterochromatin) of the genomes of closely related species, but could not formally underpin their evolutionary function. I felt a mixture of enthusiasm and frustration, as I felt the field had exceeded my capacity: I had remained on the surface of observational correlations, but had not identified a mechanism for how things worked. Nevertheless, my internship marked an extremely important time that was going to leave a mark on me: my mentors had shown me how to ask an interesting question and how to build up a scientific reasoning.

By the time I finished University, it was clear that we have a lot more genomic DNA than is actually expressed at any given time in any given cell. A concept was beginning to take shape: different genomic regions must be endowed with some reversible capacity to enable or disable their expression. Many laboratories had come to realize that the DNA in mammalian genomes could be reversibly modified at one of the four DNA bases, cytosine, via the addition of a methyl group. Intuitively, that modification could have provided the sought after, reversible switch regulating the genome expression. Early discoveries held promises in terms of understanding

genome functions, and also hinted at possible therapeutic opportunities for certain genetic diseases: indeed, turning a specific gene on or off by acting on its epigenetic control might now be envisaged as a tool to correct a pathological phenotype. The following decades have uncovered a broader array of finely tuned mechanisms to achieve that regulation, in addition to DNA methylation, shaping the field of epigenetics.

After graduation I joined the Human Cytogenetics laboratory, still at Sapienza University, whose research focus was on ribosomal genes. These genes exist in multiple copies, some of which are active, while others are silent, providing an informative system in which alternative functional states can be studied for genes with identical DNA sequence. We could demonstrate that ribosomal genes transmit their methylation status through cell division and that the newly generated cells inherited therefore the "blueprints" for expression of specific genes via their DNA methylation marks. With those results, we had entered the arena of epigenetic control. When, on a heavily rainy day, we were walking to the main post office in Rome to mail our manuscript to a US-based journal, my supervisor Marina Ferraro slipped on the wet pavement, fell over, and the manuscript single sheets fluctuated all over the street. Computers were still to come and we had nothing like a "virtual memory" of our work. Without the faintest sign of giving up, Marina just got up at once, walked to the middle of the street and—as if that was the most natural thing on earth—arrested the chaotic traffic in Rome waving at the cars, with the risk of getting continuously ran over, until she picked up every single sheet! Eventually we managed to submit the paper, which had a good recognition, compensating all the efforts and risks!

My research training in Drosophila heterochromatin and in methylation-directed gene regulation represented key experiences in what was going to be my future research. Albeit intertwined with errors and frustration, they were never disjoined from enthusiasm and a desire to learn more. In 1984, I was awarded a position at the Italian National Research Council (CNR) and, at almost the same time, an EMBO fellowship I had previously applied for. The CNR—the largest public research organization in Italy—allowed me to accept the EMBO fellowship while postponing my research start-up. I will always be grateful to the CNR for that. As an EMBO fellow, I joined the MRC Mammalian Genome Unit in Edinburgh, one of the top laboratories in the DNA methylation field, then directed by Ed Southern. He and Adrian Bird had devised methods to recognize methylated and unmethylated regions in the genome, rendering epigenetics studies amenable to unprecedented molecular detail. That led to the discovery that the human genome, albeit being largely methylated overall, contained discrete regions, or "islands", free of methylation, associated with expressed genes. At that time, the idea of achieving the human genome sequence was still far away: thus, the identification of unmethylated DNA islands as gene landmarks provided a molecular tool to identify new genes, including disease-causing genes, from the then undeciphered genome. In addition to that important outcome, which we would now define "translational", enormous progress was being made in understanding epigenetic control.

My experience at the MRC in Edinburgh also showed me a very different lab model from those I had known. Those were the years of Mrs Thatcher and public

expense was being cut down in the UK, including in public research. Nevertheless, despite of financial cuts, the resources were intelligently utilised to sustain a rational organization, with excellent technical services, a collaborative attitude of the leading scientists and a constant effort to foster independence in the post-docs and facilitate their independent growth.

Such a system would have been unthinkable of in Italy. The inadequacy of funding remains a major issue for Italian research, with obnoxious consequences at least at three levels. First, it directly damages research in that it prevents many research groups from accessing experimental and infrastructural conditions of excellent quality. Second, it limits intellectual diversification, pushing practically all biologists to develop "fundable" projects with some applicable outcome (e.g., cancer, infections, genetic diseases, etc.), with severe limitations to fundamental research, when every discovery that has proved useful to human health comes from fundamental research. Third, it pushes scientists to oscillate between an individualistic strive to prevail over others, and an opposite effort to access the limited financial resources via "alliances" that are often more political than genuine scientific collaborations. That limits the cross-fertilization that comes from true scientific exchange and represents a self-defeating limitation of the Italian system—which includes otherwise many excellent, courageous scientists. Science is a collective effort and needs humus to grow: it needs confrontation, frank discussions, and collaboration. All major scientific discoveries have become ripe in a community. The Asilomar conference is the paradigm of self-critical science: no single scientist could have reached the intellectual, scientific and ethic insight that they reached as members of that community.

When I returned to the CNR in Rome funding was not as limited as it presently is. I have had the opportunity to establish my group. In Edinburgh I had cloned some new genes for being unmethylated, but their function was unknown. On characterising them, one turned out to encode a regulator of the GTPase RAN, which regulates macromolecular transport in and out of the nucleus. A series of unexpected findings led me to find a link between the mammalian RAN GTPase, the cell cycle and mitosis, which I have continued to pursue, with various ramifications, in my career. It has been difficult at times. Sometimes we have underplayed our results or have not pushed at the right gear. But, overall, I have enjoyed it a lot. I have had the pleasure and the honour to witness the field take shape and to play a small part in studying RAN and nuclear transport receptors in cell division, which has been both exciting and rewarding.

3 Science Today and Tomorrow

From reductionism to systems

Biology is literally "the discourse about life". What we have learnt in the last three centuries has been wonderfully gratifying in elucidating the mechanisms of life. In the

last decades, we have come to appreciate that the molecular complexity of systems—an organism, a cell, or an organelle—relies on multiple circuits, networks and interactions, each made up of many molecules that operate simultaneously, dynamically, and influencing one another in complex programs. The reductionist approach consisted in altering one single gene or protein at a time to isolate the specific function of that gene or protein. That has yielded the founding stones, which we can now combine and build upon to understand the big picture. In the last few years, tools have been developed to study living systems at a global level, generating"big data" in high-throughput (globally profiling many genes, many transcripts, many proteins, many modifications) and high-content (to what extent, in which spatial localisation, in relation to which temporal events, associated with which other variations) modes. Artificial intelligence (AI) is growingly called upon to process and rationalise these data.

The process of understanding in past and future science

A recent webinar has elaborated on the concept that "*the lab of the future will not be bounded by walls*." The bottom line is that the scale of the experimental work has moved to a level that incorporates automated pipelines, robotics, connectedness, digital results, AI-driven analyses, transforming not only experimental practices but even the laboratory setting: fewer benches, more integrated platforms, larger space for computer hubs and workstations, virtual space to manage and store large datasets. For scientists of my generation, who identified "their" bench with their second home, it is a big transformation. Our experiments were mostly handcrafted; no robotics for sample handling, no automated pipelines, no artificial understanding of the data. Experiments took energy, patience, perseverance, restarting over and over again, adjusting conditions, even gestures. These crafting efforts generated a mastering of the experimental process, yet entailed a slow progress and a small scale of information that are no longer adequate. We have probably been the first generation of scientists to train in the recombinant DNA era, and the last to take notes by hand in a notebook. For us, writing down lab notes and drawing schemes by hand was an integral part of the process of understanding. Do technical innovations trigger the same learning processes in the researcher's brain? Every time I think about this, for example getting numerical measures from multiple series of stacks of a digital picture, I think back of Walther Flemming (1843–1905), considered the founder of cytogenetics (Paweletz 2001) and a striking example of understanding by drawing. Flemming understood chromosome segregation while drawing the process, 65 years before the DNA was known, and before its structure motivated the famous anticipation of the mechanism of replication: "*It has not escaped our notice that the specific pairing we have postulated immediately suggests a possible copying mechanism for the genetic material*" (Watson and Crick 1953), which entailed segregation of the replicated molecules at some point. When Flemming illustrated mitosis (Fig. 1), he was not even aware of Mendel's laws for the segregation of characters.

Using large Salamander cells, and aniline-derived dyes, Flemming was capable to accurately describe the sequence of events leading to chromosome partitioning during cell division in a manner that has remained unsurpassed in intuition: he realised

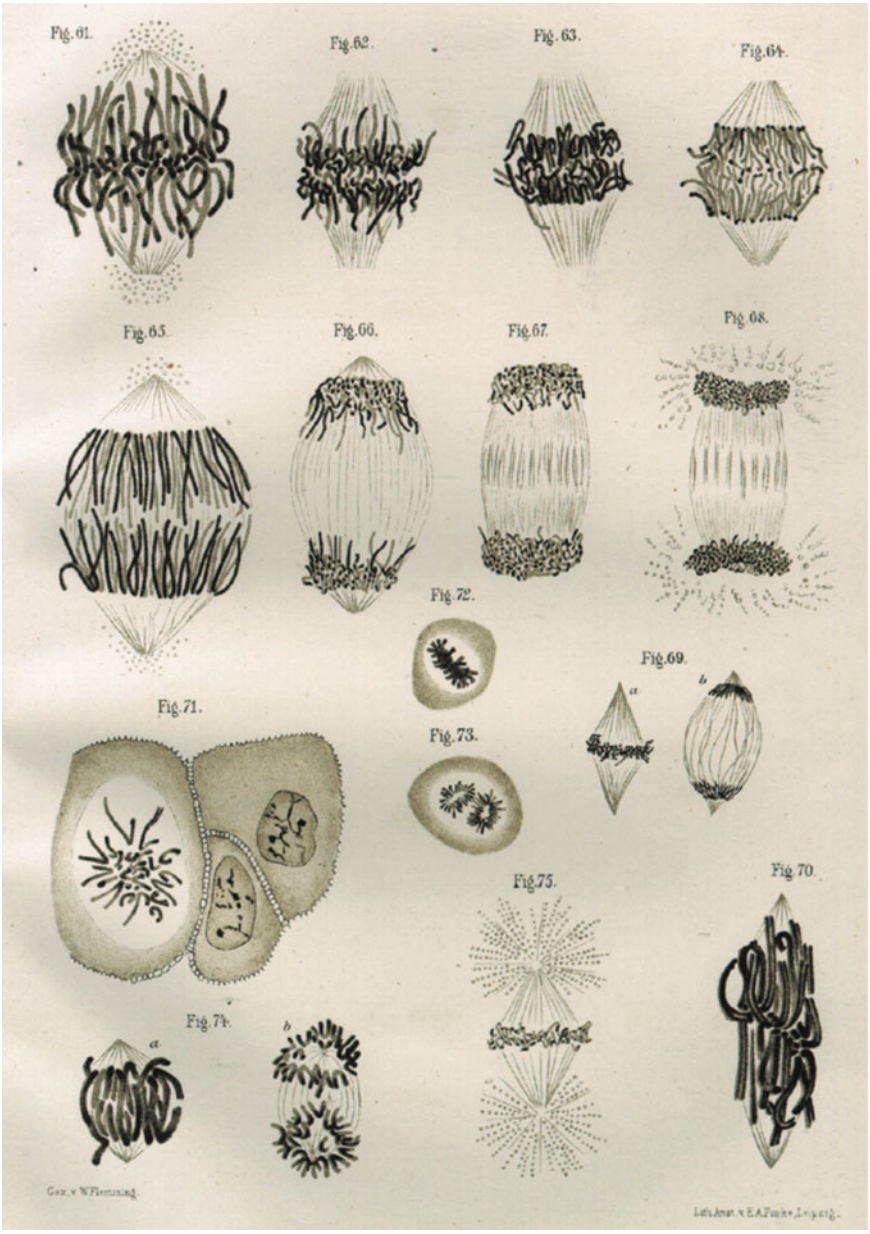

Fig. 1 Flemming's original drawings of cell division, representing progressive stages of the process of chromosome partitioning in two daughter cells, before being aware of Mendel's laws of heredity

that the nucleus contained stainable material (the chromatin) that could organize in threads (the chromosomes), that split longitudinally at some point; each half then moved to opposite sides of the cell. He first understood that all cell nuclei came from a predecessor nucleus (he coined the phrase *omnis nucleus e nucleo*, after Virchow's *omnis cellula e cellula*)(Flemming 1882).

The implications of Flemming's work for heredity were only fully understood after the recognition of Mendel's principles of heredity. Flemming was gifted with extraordinary intuition and drawing has likely nurtured his intuition. An interesting article in the E-life series on "Philosophy of Biology" speculates, "*drawing may be a way to better understand a biological process and to explore and develop scientific ideas"* (Anderson et al. 2019). The passage from handicraft to automation marks revolutionary change in experimentation and might change not only the object of our knowledge, but also the very structure of our learning processes.

3.1 What's Ahead in Science and Technology in the Life Sciences?

With the increase in the informational power in the life sciences, it is important to remain alerted on possible issues. The automation of experimental processes, the global profiling of cells, tissues, and organisms, are generating more data than the human mind can control, requiring artificial intelligence-driven analyses to be made sense of. This level of study clearly increases enormously the information capacity of biology. Might there be a risk that the interpretation of the data is eventually entirely transferred to an AI?

A related question comes from the notion that making advance on the large scale represented by complex phenomena in which multiple components interact dynamically requires large groups, but just putting together people with different expertise will not suffice: we need a common intellectual language and mindset capable of mutual understanding across as different frame of minds as those of "wet" and "dry" laboratories. With some foresight, the EU has made efforts to support multidisciplinary training projects for "new generation scientists", which have now been running for almost 20 years. After this long, we may ask: have these programmes been effective? Can the "new scientists" move easily from biological reasoning and experimental design of biological goals, to mastering in silico experiments and AI-driven data analyses?

The development of technology has become central to research, and may even grow to overshadow the purpose of a scientific question rather than providing a set of tools to develop it. Original ideas with true science-advancing power, disruptive rather than descriptive, have historically formed from the combination of two sources: the "humus" offered by the collective knowledge reached by the scientific community, and the focussed development in small groups, offering a compact, agile environment in which the fertilization, discussion and testing of ideas can be achieved

promptly. Let's take, for example, the "RNA interference" defence system of plants and its adaptation to silence unwanted genes, or the CRISPR-Cas9 system to edit gene sequences: both of these discoveries come from innovative ideas conceived in small teams, with tremendous applications for human health and biotechnology recognized with Nobel awards. At the scale of "systems" understanding needed to dissect complex processes, the unexpected, odd intuition that might generate a good idea may no longer find opportunities to arise.

As we become more aware of the biological complexity compared to the era of reductionistic approaches, but also of disruptive science by small groups, new funding issues arise. Large groups working on a large scale need correspondingly large grants. The issue is not just the need to find big investors, but also quality investors. Are funders going to be willing to invest large financial efforts on an expensive project, if it entails a fraction of a risky idea? Can public institutions afford them? What is the chance for an emerging scientist to access an opportunity to develop a good idea? These are some of the challenges that I think modern biology is going to face, that my generation has not been confronted with.

It is difficult to delineate plausible scenarios as the effort to grasp complexity (the "systems" level) builds up, and yet we need to keep track of our "human" intelligence. A beautiful, condensed article by Paul Nurse offers inspiring, stimulating thoughts, suggesting that paradigm shifts should be consciously considered to make sure that research is led by theory and knowledge (Nurse 2021): an article that all students and scientists should read and meditate about when thinking where research in the life sciences is heading to.

4 Advice to the Next Generation of Scientists

Biology is expanding in novel directions, gaining a reach it has never had before in health, reproduction, evolution, the environment, food, and in the use of biotechnologies for the benefit of society. Biology is one of the sciences called to address central aspects of our life on this planet (and maybe on others, as NASA and ESA programmes suggest). That sets the grounds for a wonderful, exciting time for new starters. The more we understand the better we can apply that understanding to challenge inequalities, both among individuals, among species and among areas of the globe. That can make a strong drive in wanting to do research in the field. Young scientists may be confronted with a broad range of new professions and will have chances to think about which path best fits their nature.

While preparing this chapter, I have travelled back through my own journey through research, recalling the knowledge I have been exposed to, re-weighting turning points, still resenting the inevitable mistakes, but reviving the feelings of expectation and excitement. The stories I have recalled (Drosophila heterochromatin, the inheritance of methylation of ribosomal genes, the fortuitous cloning of a RAN regulator by proximity with an unmethylated DNA island), have paved my research path and have given me the opportunity to project towards important biological

processes, with a long-standing focus on the RAN GTPase network in the cell cycle and mitosis. But that sort of approach would not be at the adequate scale today, as we become aware of biological complexity, as I have described in paragraph 3. A corollary is that researchers in biology will need to approach complexity with multifaceted skills, including collaborative and communication skills, superseding the romantic idea of the inspired scientist pursuing their little piece of knowledge. Because the practice of research in the life sciences is undergoing such transformation, it is difficult to give any advice to young scientists. But a couple of things remain true. First, I am convinced that the moments of joy and reward haven't changed in nature. Researchers still feel good when their experiment looks good, no matter how tiny a tile of a big piece it may be. If the feelings of stress and struggle prevail, then it may be worth reconsidering if you truly want to be in research. Research can be tough, full of repetitions, subjected to go astray any minute, stressful, so if you don't feel the reward of the beauty of the experiment, then there is little compensation, and in the long run it may become difficult to sustain it. Second, intuition has still a big part to play. My advice could sum up to that: cherish intuition. A good idea often grows from a well-formalised intuition. An intuition might come from anywhere, while listening to a seminar distant from your subject, or in a conversation apparently unrelated to your actual project. It may come from something you read, or come across unexpectedly, then sticks in your brain and eventually triggers connections you would not have rationally envisaged. To make a good connection that will generate a worthy idea, we need to find moments where we keep to ourselves—we need that moment of silent synthesis.

Both of these points may sound trivial, but if I distil my own experience, then I see that those two moments—conceiving an idea from intuition, and getting good-looking results—make the drive that renders all efforts worth doing.

I haven't touched yet on personal ambition, yet it has a role in research. It is very personal for each one of us. Ambition, like competition, has a dual value: it can either push us to try and do as best we can to gain more knowledge and understanding; or, it can push us to do best in order to prove ourselves and be recognized. These are two distinct scenarios. The best reflection I have found about this was offered by Robert Pirsig in his *Zen and the Art of Motorcycle Maintenance (Pirsig,* 1974*)*, a rather popular book in the 1970–80s. Without any idea of giving it any moral nuance—which would be out of place here—one type of ambition is ego-less, it is the ambition driven towards understanding something outside of me; the other type is ego-centered, it is the ambition to prove myself. There a mixture of both in every researcher, and each type of ambition may prevail under different circumstances for every one of us. I will quote Pirsig: to illustrate how the ego affects the quality of research, he uses a metaphor, describing the motivation for a pilgrimage to a holy mountain in the Himalayas.

> "He never reached the mountain.
>
> After the third day he gave up exhausted, and the pilgrimage went on without him. He said he had the physical strength but that physical strength wasn't enough.

> He had the intellectual motivation but that wasn't enough either.
>
> He didn't think he had been arrogant but thought that he was undertaking the pilgrimage to broaden his experience, to gain understanding of himself.
>
> He was trying to use the mountain for his own purposes and the pilgrimage too.
>
> He regarded himself as the fixed entity, not the pilgrimage or the mountain, and thus wasn't ready for it.
>
> He speculated that the other pilgrims, the ones who reached the mountain, probably sensed the holiness of the mountain so intensely that each footstep was an act of devotion, an act of submission to this holiness. The holiness of the mountain infused into their own spirits enabled them to endure far more than anything he, with his greater physical strength, could take [….]".

Now, Pirsig's view may appear naïve and clashes with the dominant demand that achievements be made, and within a defined time schedule. That description must not be taken literally, but it is worth accepting the suggestion to check, time and again, whether we are regarding ourselves as the fixed entity. We should avoid being blinded by worries about our next achievement, our performance, and our success. Those who think research is a quest to assess one's own value will be bitterly disappointed, because there will be many more hardships than success. As Pirsig put it, you have to climb the mountain selflessly, not to assert yourself.

Concluding with Jacques Monod

I have opened this chapter with Jacques Monod and, in conclusion, here he comes again, with one of the most profound remarks a scientist may formulate, accompanying the Obituary published in the *Nouvel Observateur* magazine (Serres, 1976) (Fig. 2): *"In science, self-satisfaction is death. Personal self-satisfaction is the death of a scientist. Collective self-satisfaction is the death of research. It is restlessness, anxiety, dissatisfaction, agony of mind that nourish science"*.

I couldn't close with a more intense remark, which I would like to dedicate to all those that are starting in research in the life sciences. Any additional word would spoil it.


Monod

SES REPONSES AU
- NOUVEL OBSERVATEUR -

• J'ai écrit, dans ma leçon inaugurale au Collège de France, au grand scandale des marxistes, que le langage a fait l'homme au moins autant que l'homme a fait le langage. Cela signifie que le langage a contribué à l'évolution physique de l'homme et pas seulement à son évolution culturelle. • [...]

• En science, l'autosatisfaction, c'est la mort. L'autosatisfaction personnelle, c'est la mort du savant. L'autosatisfaction collective, c'est la mort de la recherche. C'est l'inquiétude, l'anxiété, l'insatisfaction, le tourment qui nourrissent la science. •

• J'ai toujours pensé que le Nobel était plus malfaisant qu'utile dans la communauté scientifique elle-même mais il reste extrêmement important dans la communauté en général. •

• "Tout ce qui existe dans l'univers est le fruit du hasard et de la nécessité." Quand j'ai découvert cette citation de Démocrite, j'en avais presque les larmes aux yeux : penser que cela avait été écrit il y a 2 500 ans ! •

Jacques Monod au quartier Latin en mai 1968

Fig. 2 *Le Nouvel Observateur* issue of 07/06/1976, reporting one of the best Monod's quotes in a dedicated homage soon after he had passed away

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Patrizia Lavia graduated in Biology in 1978 at Sapienza University, Rome (Italy). After training in Genetics and Human Cytogenetics at Sapienza University, she joined the MRC Mammalian Genome Unit in Edinburgh (UK). In 1991 she established her research group at the CNR Center of Evolutionary Genetics, hosted at Sapienza University and later incorporated in the Institute of Molecular Biology and Pathology, which she has directed (2016–20). Since establishing the laboratory, she led research in control of cell cycle genes, with a special interest on how their deregulation might be linked to cancer onset. Gradually, the research has focused on mitotic control and how nuclear transport factors regulate mitosis. She has held teaching positions and has served in committees and working groups (e.g. EU Life Science Panel of Experts).