

## The mobility principle: How I became a molecular biologist

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### 1. Introduction

It took me quite some time in my scientific career to become what people call a “molecular biologist”: that is to say, someone interested in the relationship of structure to function in macromolecules and in the mechanisms of information transfer. My professional life has been far from following a linear path. I have frequently changed scientific environments, research themes, experimental models as well sources of inspiration originating from very diverse – and, fortunately, prestigious – mentors. In a sense, I have applied, whether purposely or not, the so called “mobility principle” which is so frequently preached by our institutions to the ears of young scientists.

### 2. First encounter with biochemistry

My early research activity as a biologist was contemporaneous with the state of knowledge that prevailed in Europe at the immediate post-war period. I was 21 years old when, in 1946, I first joined a research laboratory. It was in the biochemistry department of the Pasteur Institute, headed by Michel Macheboeuf, a well known lipid specialist, who died in 1951. Progress in European Science had been frozen because of the war or largely disconnected from whatever scientific advances had been made in the USA. During this period federal organizations such as EMBO or EMBL did not yet exist. The dominating discipline was analytical biochemistry, often inspired by medical considerations. At an academic level, biochemistry was regarded as a branch of organic chemistry. One was at that period in the history of the life sciences whose aim was chiefly the characterization and measurement of the main chemical components of the cell: proteins, lipids, hydrocarbons, but also vitamins and hormones. Instrumentation was still in the infancy. Enzymology presented itself as the “voie royale”, at least as the only one that could be regarded as offering some kind of a precise formalism to the biology of that time. This

was something that biologists were very proud of, for it afforded to their discipline a clear demarcation from organic chemistry. Accordingly, great emphasis was placed on the enzymes’s specificity, on the kinetics of its action. From a more holistic standpoint the cell was regarded as an energy-consuming or producing machine operated by a plurality of enzymes. Great focus was placed on the Krebs cycle, glycolysis and the central role of ATP. In continuity with Louis Pasteur’s work and of the studies made by a generation of German biochemists who had provided a clear picture of the chemical intermediates in the pathway of fermentation in yeast or during muscle contraction, bioenergetics was at the focal point of life sciences.

In sustaining the life of the cell, such a preeminent role was ascribed to proteins that they were implicitly regarded as being responsible for the biochemistry of heredity. By contrast, nucleic acids still remained “in the dark”. Before the early 1950’s, Avery’s (Avery *et al* 1944) studies carried out at the Rockefeller Institute, pointing to the role of DNA as a carrier of genetic information, had but a faint echo in Europe. DNA and RNA were regarded as mere curiosities! This, in spite of the work of cytologists who had shown that DNA resided in the nucleus of the cell (the existence of cytoplasmic DNA was not yet clearly established) and RNA in the cytoplasm. Very few biochemists were conscious of, or even concerned about, their role in the cell economy and fate. For instance a few even believed that RNA was some kind of a ‘reservoir’ of phosphorus.

A strange period, indeed, when I began studying biochemistry. Not only, as I have said, was the biochemistry of heredity almost nonexistent, but, more generally speaking, scientists remain ignorant about the ways in which metabolites and the cell’s principal biopolymers, such as proteins, were formed. For example, regarding the mechanisms of protein synthesis, some biochemists were of the belief that peptide bond synthesis could result from a shift in equilibrium during the catalytic action of proteolytic enzymes. More generally speaking, rare were the cases in which biochemistry and genetics were seen to be joined

together. Genes were of course known from the beginning of the 20th century, but their role still remained mysterious. The “one gene, one enzyme hypothesis” of Beadle and Tatum (1941) was known to very few specialists in Europe. Once again, in the immediate surroundings of my laboratory, but also most probably outside, the key to explain the life of the cell was ATP. Biochemists were particularly proud of the Krebs cycle, the elucidation of the glycolytic pathways, and the Menten-Michaelis concepts about enzymatic reactions.

This being said, while the functioning of the cell factory remained ill-defined, or totally mis-interpreted, other fields of life sciences had already been explored with success for many decades. Such was the case, for example, for taxonomy (and in particular for bacterial systematics) but also for the general physiology of higher organisms. The main stages of embryological development following fertilization had been extensively analysed, especially in amphibians. Theories of evolution were indeed well known, including neo-Darwinism, although most University Professors in France were reluctant about the role of natural selection and preferred neo-Lamarckism. The general features of humoral immunity had been described. Moreover, much had already been achieved by neuroanatomists and neurophysiologists, while knowledge of neurotransmitters was at its early beginning. In brief, while the general features of the physiology of cells, organs, and whole organisms was already quite advanced and the biochemistry of proteins, enzymes and the metabolic pathways reasonably well understood, one was still far from being in the position to describe cell function, and even less cell reproduction, in molecular terms.

The Pasteur Institute, whose doors had just opened for the young student I was, was regarded as being at the forefront of microbiology and, in particular of the study of bacterial or viral associated pathology. Antibiotics had just been discovered, opening a new era in the fight against pathogens. In this context, no wonder that the first research project I was given for my Ph.D. thesis was to analyse the effects of the recently discovered antibiotics (chiefly penicillin) on certain classes of pathogenic bacteria. This early study, carried out during 4–5 years, and essentially directed towards the antibiotics’ effects on the energy metabolism of sensitive bacterial strains, hardly reflected a “molecular inspiration”. Yet, some of my observations dealing with the penicillin effect on the bacterial growth were at the origin of my first connection with Jacques Monod. At that time Monod was particularly interested in analysing some special features of bacterial growth in the presence of various hydrocarbon sources. Although I did not yet belong to Monod’s lab, I became rapidly acquainted with his personality and his ongoing concepts regarding the phenomenon of enzymatic adaptation. Monod advised me to make my post-doctoral training in the USA and supported my applications, for we

had both agreed that at my return to France I would join his group. I left France in 1953. From this very day my scientific life would enter a new phase.

### 3. Life as a post-doc in America – Urbana and New York – Spiegelman, Hotchkiss and Leo Szilard

My serious introduction to genetics occurred at the University of Illinois in Urbana while working with S Spiegelman and taking Luria’s courses on the bacteriophage. As pointed out already, at that time very few biologists showed any interest in the role of RNA in the cell. This was in spite of the famous pioneering work of Jean Brachet from Belgium (Brachet 1952) and Torbjörn Caspersson from Sweden (Casperson 1941), who had already observed a relationship between the cellular RNA content and the intensity of protein synthesis. Spiegelman, a biologist with a great intuitive mind, was analysing the effects of purine and pyrimidine analogues on the induced synthesis of maltase in yeast. He invited me to collaborate on this theme. Although the results were promising, they were not fully conclusive. At any rate this work constituted my first experimental acquaintance with RNA metabolism, for it involved the utilization of radioactive analogues and special techniques for RNA extraction and analysis.

A year later, in 1954, at the end of my stay, I moved to New York to work with Rollin D Hotchkiss at the Rockefeller Institute. There, I became rapidly familiar with DNA, since Rollin, as a former colleague of Avery and McCarty, was working on the transforming principle, attempting to put the phenomenon on a more quantitative basis (Hotchkiss 1960). In Rollin’s laboratory we had fascinating discussions with a certain Leo Szilard, a great physicist and Rollin’s close friend. These discussions bore on some of the most recent discoveries in biology. Szilard’s mind was that of a true universalist. He was equally at ease in sustaining a discussion with Albert Einstein on the theory of Relativity or debating about genetics with the great biologists of that time. Like many renowned physicists of the early fifties, such as Erwin Schrödinger, Max Delbrück, Gunther Stent and Linus Pauling, he was convinced that the life sciences were at the verge of a conceptual revolution. We had, indeed, many matters to discuss. For example, there was the discovery of the polynucleotide phosphorylase by Grunberg-Manago and Ochoa (1955), the first enzyme capable of synthesizing *in vitro* an RNA-like polymer. Other key achievements were also at focus. Such were the experiments by Lederberg’s group (Cavalli *et al* 1953) and by E Wollman and F Jacob (Jacob and Wollman 1961) on bacterial sexuality, by S Luria and M Delbrück in favour of the Darwinian theory in bacterial genetics, or by André Lwoff and Niels Kjelgaard (Lwoff 1954; Lwoff *et al* 1950) concerning the induction of lysogenic bacteria. Indeed, Szilard was well aware of

Monod and Cohn's (1952) work on enzyme induction. He was a supporter of negative controlling mechanisms, although at the time the repressor had not yet come of age. With Szilard, we often embarked on passionate discussions on the latest results from Rollin's lab concerning DNA-induced transformation in *Pneumococci*. But what sounded like the most provocative and hence revolutionary finding was certainly the Watson-Crick-Wilkins (Watson and Crick 1953) model for DNA that had just been published in the 1953 issue of *Nature*.

As far as I remember, it took some time before the model was fully accepted by the scientific community. Some scientists were of the opinion that it was too simple to account for such a complex mechanism as the maintenance of hereditary properties among species. Others were puzzled about the mechanism involved in the separation of the two sister strands during replication. Some physico-chemists (from the Sloan-Kettering Institute, geographically close to the Rockefeller Institute) were preaching in favour of the existence of a four-strand structure. In short, everyone had his own view and his own model. Definitive acceptance of the DNA double helix had to await for the famous Meselson and Stahl (1958) experiment which evacuated all the doubts. DNA heat denaturation and re-annealing studies by

Marmur and Doty (1959) provided also a good support. As far as Arthur Kornberg's first characterization of a DNA-dependent DNA polymerase (Kornberg 1978), it appeared to offer a solution to the problem of the biochemical basis of DNA replication (even if it has since been established that DNA polymerase I is more involved in DNA repair mechanisms than in its replication).

#### 4. Return to the Pasteur; I become an "RNA man"

After two years in the United States, I finally returned to the Pasteur Institute in 1955 to join what had become, in the meantime, Jacques Monod's "Service de Biochimie" (Department of Biochemistry). I was well informed about what Monod and his colleagues had achieved during the time I had been away from Paris. Monod and I had regular exchanges of letters and, when I returned, I already knew a lot about what had become the "lactose model". I had already learned about the so called 'gratuitous' induction of  $\beta$ -galactosidase (with Melvin Cohn), the "glucose effect" etc. It would nevertheless take more time before the emergence of the complete story concerning the operon model (Jacob *et al* 1960) and the repressor hypothesis (Müller-Hill *et al* 1968), imposed itself on people's minds.



**Figure 1.** Jacob, Monod and Lwoff discussing the role of symmetry in protein regulation.

When Monod asked me what I would like to work on, now that I was in his lab, he was quite surprised to hear me speak about nucleic acids and, more precisely, about RNA. From an historical standpoint, it is interesting to point out the fact that, in 1955, the future father of the messenger hypothesis was giving very little attention to nucleic acids in general, presumably because he regarded them as being devoid of the molecular flexibility and adaptability that proteins were known to display. Although he had heard about the work of Brachet (1952) and Caspersson (1941), he was waiting for more solid evidence. Yet, generous and open-minded as he was, he left me totally free to continue what I had begun at Urbana, namely to test the effects of nucleic acid base analogs on enzyme synthesis, provided that *Escherichia coli*, rather than yeast, would be the target system (Bussard *et al* 1960; Naono and Gros 1960). Some results were encouraging but we were not yet in the position to draw a clear-cut interpretation. At any rate, my decision was taken. I would, from then on become an RNA biochemist, an RNA man!

Nothing concerning RNA and its role in protein synthesis should be foreign to me. This explains why, in the time gap between 1955 and 1960, before the messenger story, my work became fully oriented towards understanding the role played by the different classes of RNA in the cell. Examples can be found in the first *in vivo* study I made with S Lacks (Lacks and Gros 1959) on the amino-acyl-tRNA pool in growing cultures of *E. coli*. t-RNA and activating enzymes had just been characterized by Hoagland *et al* (1957) but many people were questioning their role in protein synthesis within the cell. With an American post-doc, Fred Neidhardt (Neidhardt and Gros 1957), I observed that the RNA moiety present in the “chloramphenicol particles” (a kind of ribonucleoprotein that accumulates when protein synthesis is inhibited by chloramphenicol) was metabolically unstable. Incidentally this was the first demonstration that in growing *E. coli*, a macromolecule such as RNA could display metabolic instability. With Françoise Gros (Gros and Gros 1958), and later with J Gallant, simultaneously with A Pardee and E Borek, I co-discovered what turned-out to be the “stringent control” of RNA synthesis: a complete inhibition of RNA synthesis which is exerted after amino-acid starvation in amino-acid dependent strains of *E. coli*. I was also fascinated by the nature and function of ribosomes, which had been shown by the group of the Carnegie Institute to carry the nascent polypeptide chains, and the RNA of which had been shown to be metabolically stable (Davern and Meselson 1960).

A Japanese post-doc working in Jim Watson’s lab, M Nomura, had similar interests to mine. He too was studying the dynamics of ribosome formation in *E. coli*, and was analysing the metabolic fate of the “chloramphenicol particles”, thinking that they could represent some sort

of intermediates during the maturation of fully stable ribosomes. This is why, when I met Watson in the late 60’s, I accepted his invitation to come to Harvard University to work for a few months on the chloramphenicol particles.

## 5. Second move to the USA and the discovery of messenger RNA

While leaving Paris, on my way to Harvard, I was fully aware of the hypotheses, based upon a series of experiments [such as the famous PaJaMo experiments from Pardee, Jacob and Monod (Pardee *et al* 1959), on the kinetics of induced synthesis of  $\beta$ -galactosidase] that had led to the postulate of the existence of a new RNA entity, called messenger RNA, whose role would be to serve as an unstable template for the synthesis of proteins. But, apart from an old publication by Volkin and Astrachan (1957), describing a new form of RNA in T2-infected *E. coli* cells, whose base composition was quite similar to that of the phage DNA – a pioneering observation, but one which was regarded as illustrating a situation appropriate to infected cells – the experimental proof for the *general* existence of a messenger RNA involved in the transfer of genetic information was still lacking.

As is known from the literature, the discovery of the messenger came about as the result of two sets of independent, albeit simultaneous, experiments. One was realized at Caltech, by S Brenner, F Jacob, and M Meselson (Brenner *et al* 1961), using phage-infected cells, and the other by the Harvard team during my visit in Watson’s laboratory, on normal populations of *E. coli* (Gros *et al* 1961). The results from both groups were published in 1961 in the same issue of *Nature*. Does this publication mark the time I really became a “molecular biologist”? I could not say. Whatever it is, my status of post-doc changed rapidly into that of ‘patron’ and laboratory head. Between 1961 and 1996, I have had many students and coworkers, some of whom occupy today prominent positions in various institutions and are responsible for big departments. I too moved to take important responsibilities in different institutions, but finally returned to the Pasteur to run the new Department of Biochemistry and then to become the Pasteur Institute’s Director General, while being at the same time elected at the chair of cell biochemistry at the College de France, which is a kind of Institute for Advanced Studies founded in the 16th century by François the first.

During the long period of activity that followed the messenger story, my scientific interest logically concerned the mechanisms involved in messenger RNA synthesis from the DNA template (the step known as ‘transcription’) and in its translation into proteins. Regarding ‘translation’, Michel Revel and I (Revel and Gros 1966) first reported about the existence of “translation initiation factors” in

*E. coli* (simultaneously with S Ochoa and A Wabba); with Moshe Yaniv (Yaniv and Gros 1969), we isolated the first temperature-sensitive mutant of amino-acyl tRNA synthetases. Then I switched for quite some time to the study of transcriptional control and signalling following the induction of the bacteriophage lambda (with P Kourilsky, and S Naono (Kourilsky *et al* 1970), or of the galactose operon in *E. coli* (Attardi *et al* 1963).

## 6. Developmental biology and after

Finally, under the (friendly) pressure exerted by F Jacob, like many others I realized that the time had come to make a conversion into developmental biology. This was in 1968 and coincided with the student reformation movement in France. As a result of this change, during a little more than two decades, my colleagues and I have paid a great tribute to the field of somatic cell differentiation by analysing gene regulatory mechanisms, either during myogenesis (chiefly with Margaret Buckingham who has succeeded me in the early 80's as head of the Pasteur' Biochemistry Unit) (Buckingham 1985) or during the terminal maturation of neuroblastic cells (at the College de France; Denoulet *et al* 1982).

Today, the old man I am is mostly engaged in a new fight. This fight is to help in strengthening sciences in the developing world, for I think that after all, this constitutes one of the most important challenges for a scientist who has benefited, like I did, from all the training and research facilities that were available to me, and who could move freely from one institution to another.

In my 60 years' long career, I have been a sort of witness, contemplating the astonishingly rapid evolution of molecular biology, at times participating actively in it. While observing the contemporary breakthroughs in genomics, proteomics, transcriptomics and so on, not to mention "systems biology", I cannot but dream, a little anxious but passionate as I am, about the fate of the life sciences, and of their future in the very complex world we are living in presently.

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