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I have been asked to introduce the round table on the dynamics of molecular biology and to take the opportunity to express my personal view on that question. "Molecular biology" is a widely accepted term. Numerous excellent studies on the multiple aspects of its history and epistemology, as well as the history of institutions where it took form, have been published, and some have been discussed in the present workshop. Everything has already been discussed and published. I thus stand here more as a witness of the changes in the ways of using the words "molecular biology" which I noticed as a scientist working in fields related to, or part of, molecular biology, at the Institut Pasteur[1].

To the best of my memory, I cannot remember having heard of the expression "molecular biology" during the biology courses delivered at the University of Paris (1961 to 1962), which I listened to in the context of the *licence de sciences naturelles*[2]. I also had no lectures dealing specifically with "molecular biology" at the *Ecole normale supérieure*, although it was considered to be among the best French teaching structures in biology. Nor did I have lessons on the topics in the certificate of biochemistry. Only André Lwoff (then Professor at the University of Paris and Department head at the Institut Pasteur) did give in 1962 a series of lessons on bacterial genetics, on the lactose operon and on DNA and phage replication, in the frame of the *certificat de biochimie, microbiologie et physiologie végétale*

at the university. I did not attend Monod's university lectures on metabolism. From what I learned later by discussing with other fellow scientists, with the exception of the University of Strasbourg (Prof. B. Hirth) and possibly few others, the classics of molecular biology (from

[1] I do not intend to discuss the manner research in biology was carried out. A number of interesting testimonies on the topics can be found in A. Lwoff and A. Ullmann, *Hommage à Jacques Monod. Les origines de la biologie moléculaire*. Etudes vivantes: Paris et Montreal, 1980. Molecular biology is not an expression much used by the contributors, despite the title of the book, but the meaning they gave to it, its content within the envelope of the word for the period 1945-1965 at the Institut Pasteur, clearly emerges from the reading.

[2] The obtention of a *licence* allowed teaching in secondary schools. A *licence* in natural sciences was constituted by the following certificates: zoology, botany, physiology, geology and general biology to which was added a certificate either covering biochemistry-microbiology-plant physiology or advanced geology. Specialized certificates were awarded for advanced study in other fields, such as genetics, biochemistry etc.

DNA structure to bacterial genetics) appeared not to have been taught in French universities in the early 1960s, but has sometimes surreptitiously been added to official teaching programs. I can thus presume that before the Nobel Prize was awarded in 1965 to Lwoff, Monod and Jacob, the content of the expression "molecular biology", not to say the words themselves, were largely ignored in France by all but a handful of lucky students, those who had teachers working in the domain, and presumably by future researchers attending advanced genetics courses[3].

However, the flavour of modernity associated to molecular biology was certainly perceived in other laboratories as the emergence of a kind of new scientific content, rich in future developments and anyway going far beyond classical biochemistry. Following the advice of P. Buser, a neurophysiologist, I myself moved in 1964 from his laboratory of neural sciences to Monod's laboratory, because studies on the nervous system had to become molecular in some way and because the Institut Pasteur was the best place in Paris to learn the proper techniques. I remember Buser argumenting about the choice, imperative to his opinion for young scientists, of moving from "telephone" studies between cortical structures which most neurophysiologists did, either to simpler oligo-synaptic model systems like *Aplysia*, or to molecules. However, I still wonder if in the early 1960s, outside of the small tribe of self-named "molecular biologists", molecular biology was perceived by other scientists as a discipline, as we often tend to superficially describe it. I do not think so.

On my side, I believe that I first encountered the expression "molecular biology" at the very beginning of my thesis work, in October 1964, when seeing an issue of the *Journal of Molecular Biology,* a journal then considered in the laboratory the smartest of the best journals in modern biology. However, even in Monod's and Jacob's laboratories, the words "molecular biology" were not in routine use among us, whereas bacterial genetics, gene expression, negative and positive regulation, models, biophysics, operon, replication and replicon, etc were much more frequently used to speak of what was going on. I am not

[3] J. Monod had been professor of *Biochimie du métabolisme* at the university of Paris from 1959 to 1966. The name of his chair was changed into *Biologie moléculaire* in April 1966.

speaking of the discussions among the heads of the laboratories[4]. The biological phenomena we were studying were part of microbiology, however modern or unusual the approaches we used might have been compared to classical microbiology. A highly convenient model, *Escherichia coli,* was used to answer questions relevant to basic life processes in microorganisms, a bit too fast assumed to be of general significance[5]. A rapid survey of the history of the laboratories of the Institut Pasteur (first Lwoff's, later Monod's, Jacob's, Wollman's, Aubert's etc.) out of which pasteurian molecular biology emerged, is informative concerning the constancy of the interest for a particular topics, I mean the questions they wanted to answer. The main research theme, which we would now name control of gene expression, was rooted in studies on *biological adaptation*, a concept locally developed by protozoologists and entomologists of the Institut before WWII[6]. Indeed, the first major contribution of pasteurian molecular biologists concerns differential gene expression (diauxy) and prophage expression (lysogeny) as the consequence of adaptive processes. Research exclusively used simple and clever microbial genetics techniques. The resolution algorithms were taken from logics and physics[7]. The second major contribution, largely due to Monod's laboratory, concerned concerted structural changes, better known as allosteric transitions. The way it has been built has been discussed by Henri Buc in the present meeting. Most of the experiments on allostery relied on re-examination of enzymatic kinetics, and the results got later inserted into theoretical developments on structure-function relationships, themselves embedded in the general frame of the response to changes. Allosteric transitions were considered by Monod, (see his Nobel lecture) as the second (the operon being first) fundamental law governing adaptation of organisms to their environment. The equipment of the laboratory for structural studies of macromolecules was more impressive (analytical centrifuges, light scattering apparatus for example) than frequently used, as compared to what happened in equivalent laboratories in Great Britain or the USA. The few laboratories

[4] Although in his book "*Le hasard et la nécessité*" Editions du Seuil Paris 1970, J. Monod did not speak of molecular biology, but rather of "molecular theory of the genetic code, "microcybernetics" and "modern biology". Molecular biology is mentioned in his Nobel lecture (1965) assigning a date of birth:1954 with the structure of DNA.

[5] R. M Burian "How the coice of experimental organisms matters : epistemological reflections on an aspect of biological practice. *J. History of Biology*, 1993 *26*, 351

[6] In this respect, it is worth noting that Lwoff, though a physician, had worked on marine invertebrates and stayed in Mesnil's laboratory (laboratory of parasitology, close to that of Roubaud, entomologist) at the Institut Pasteur working on protists and bacteria dependency upon certain nutrients (growth factors). J. Monod himself worked for several years on protests in Chatton's laboratory in Strasbourg.

[7] Note the marked influence of Leo Szilard and Aaron Novick, both nuclear physicists, on the setting up of the logics of the operon model, through the conception of the notions of repressor and anti-repressor.

involved, probably never exceeding a total of 50 persons, were located close to each other in the same building, that of "Chimie biologique", nearly all of them in the so-called Bertrand wing. Research carried out elsewhere in the Institut Pasteur did not deal with that kind of approach to microbiological or virological problems. It can also be said that the relations between "molecular biologists" and the others on the campus, were not excellent. The work which led to the 1965 Nobel Prize was largely considered by the institution at large, as a somehow marginal production by a small team of researchers all interested in giving genetic and molecular clues to adaptation and phages features, both highly theoretical problems, far removed from the practical questions studied by classical microbiology and virology[8]. We also should note that the biochemical mechanisms *per se* underlying gene control did not receive much interest, in terms of research investment, among local molecular biologists. They were in close contact with people working on mechanisms, but they did not really work on the latter. As an example, the fundamental work of François Gros on mRNAs as the intermediary support of genetic information, was carried out in 1961 abroad, in Watson's laboratory in Harvard Biology Department. Similarly, few studies were carried out at the Institut Pasteur on the mechanisms of protein synthesis, the nature of the genetic code, X-ray determination of 3-D structures etc. The department of biophysics was working on the interaction between water molecules and biological macromolecules. Only rare researchers (as in the small groups headed by H. Buc, J.P. Changeux and M. Goldberg) got involved in structural studies of proteins, at first concerning allosteric transitions. Despite a later evolution towards the increased use of physical methods, it can be concluded that elegantly designed and rapid genetic analysis was largely preferred by most Pasteur molecular biologists.

Later on, at the end of the 1960s, the research carried out by most of these members of the above-mentioned laboratories who had remained at the Institut Pasteur, questioned the biology of eukaryotes. These researchers used experimental approaches far from being all molecular or genetic. This move is by no means characteristic of the Institut Pasteur and is a well-known world trend of the end of the 1960s. Did the intellectual strategies used in earlier studies on bacterial genetics contribute to the success of research on eukaryotes? This appears obvious considering, as an example, the work locally carried out on *Dictyostelium discoideum,* and abroad in S. Brenner's laboratory on the biology of nematodes: the continuity was determined by the nature of the model organism considered. The question remains

[8] An interview of R. Dedonder, Director of the Institut Pasteur between 1982 and 1987 illustrates well the nature of the relations between the molecular biologists and the campus;
http://picardp1.ivry.cnrs.fr/Dedonder.html

difficult to answer concerning research fields dealing with vertebrates, at the Institut Pasteur. The trajectory of F. Jacob, the only Nobel Prize winner to have kept to experimental work, and some of his former students such as C. Babinet and H. Condamine who continued working with him, is informative in that respect. Jacob's early work on the teratocarcinoma system (1970-1978), an original approach to mouse embryonic development, combined immunological and cell culture techniques. The control of embryonic development was then supposed to be determined by serial cell-to-cell contacts through cell surface molecules as postulated by E. Boyse and L. Old in 1969. The algorithm which drove Jacob's research on development program during mouse embryogeneisis, was based on topology, on patterns of molecules, and thus was markedly differed from those used in bacterial genetics. Moreover, the use of the latter in the approach to certain mouse mutants, such as functioning of master genes, roughly speaking considered as operators, and T-locus, taken as a kind of operon controlling developmental steps, largely proved misleading. The search for mutant teratocarcinoma cell lines (I do not refer to modified ES cells but to chemical mutagenesis of teratocarcinoma stem cells), a strategy mimicking bacterial genetics, did not prove efficient. The conception and time scale of experiments also was radically different, as were the material and the ways of looking at the results. The mouse was simply not amenable to the practices of molecular genetics: the transposition of concepts and methods from bacterial genetics to eukaryotic cell biology proved difficult, at least in the context considered. Recombinant DNA techniques were not introduced in Jacob's laboratory before 1979 and they were "imported" by a young few post-doctoral scientists. It is thus far from evident that even a great expertise in bacterial genetics and concepts had been of significant help in studies on eukaryotes, at least as performed in that precise laboratory. This may be due as well to the intellectual tradition of a particular laboratory or the choice of a model organism[9]. Concerning mouse development, the continuation of the use of the most modern biochemical techniques including early usage of recombinant DNA technology, (i.e. molecular biology in its general meaning) in F. Gros' laboratory founded a differently productive approach to mouse development.

The diversity of the research carried out in the building of Molecular Biology of the Institut Pasteur between 1971 and 1980 reflects well the meaning given to the expression: it has become merely equivalent to "modern biology". The most significant change in the sense

[9] However, the technique of in vivo follow up of the fate of individual cellular clones during mouse development, as designed around 2000 by J.-F. Nicolas, a former student of F. Jacob, can be viewed as a kind of successful introduction of the way of thinking of bacterial genetics into mouse development. See, as an example, Mathis L, Nicolas JF. "Cellular patterning of the vertebrate embryo" *Trends Genet*. 2002 *18* 627-35.

of the expression "molecular biology" occurred at the end of the 1970s, when it became widely used as the equivalent of genetic engineering and molecular genetics. Molecular biology took over the fuzzy meaning it presently has. The spreading of the thus defined molecular biology as the paradigm of research about all biological phenomena also occurred in two main steps, clearly identified at the Institut Pasteur through the survey of laboratory life. Those scientists who had kept to the developments of bacterial genetics regained the dominant place they had lost after 1965: the fundamental techniques of the emerging new molecular biology were anchored in the mastering of *E. coli* and lambda phage genetics. In general however, it can be said once more that only a small number of scientists from within the Institut Pasteur have been genuine leaders in development of recombinant DNA technologies. These techniques were rather gradually brought in after 1974, by outsiders (A. Rambach, P. Kourilsky, F. Rougeon and a handful of others) not initially members of the staff of the institute, trained abroad and specifically recruited for introducing these novel techniques for studies on eukaryotes and for the expected development of biotechnologies. They could be seen as the genuine continuors of the original group of molecular biologists of the Institut Pasteur. Some analogies between the two stories are worth being stressed. Their laboratories were clustered in the so-called Fourneau wing of the *Chimie biologique* building, surprisingly far away from the newly erected (1971) building of Molecular Biology in which most of Monod and Jacob's former companions had moved. Physical clustering and collective use of concepts and techniques that were new and even not understandable by most others (in addition techniques and reagents all had to be empirically set up) could be taken as indicative of the emergence of a new kind of power in biological research, as bacterial genetics had been in the 1950s. The development and use of these techniques certainly did not fit the scientific traditions of an institute still more oriented towards classical microbiology and virology and the diseases they cause. To a certain extent, the newcomers and their local companions were considered as those who mastered techniques that the others could not even envisage. As for the early bacterial geneticists, they were faced with definite hostility/admiration from the majority of the campus, an attitude strengthened by heated debates on genetic engineering.

In that context, the diffusion of molecular biology procedures into the different fields of research carried out at the Institut Pasteur, actually the distributed use of a set of techniques focussed on recombinant DNA technology (whatever epistemological presuppositions the latter is based on), did not occur before mid-1980s. Most laboratories on the campus started using recombinant DNA technology when vectors, restriction enzymes, polymerases, ligases and a variety of reagents and mini-equipment had became commercially available, had

become easily usable and could be applied to any research topic, from virology to mouse development. This means that diffusion of the concepts and methods of molecular biology occurred when the techniques could be used by nearly anyone even one possessing only a rudimentary knowledge of what underlies recombinant DNA technology. Spreading did not benefit much from the presence on the campus of well-known groups working in that field. The study on the development of the use of molecular techniques would probably be conveniently approached through the study of reagents, services, equipment and animal catalogues over the period 1975-1990. We anyway still live on this recently acquired meaning of molecular biology, simultaneously restricted and diffuse.

Is the existence of several sequential steps in the definition and use of the expression "molecular biology" a distinctive feature of the Institut Pasteur, or do these steps reflect the sociological singularities of that institution? Continuity has certainly existed elsewhere. In order to get some insight into that question, I tested the appropriation by the community of biologists, of the word "molecular" or of the expression "molecular biology" through a rapid survey of the evolution in titles of scientific journals. Out of all journals available at the Institut Pasteur library (a total of about 1250 titles), 171 in the period 1945-2005 used the word *biology* in their title, 140 *molecular*, and only 24 out of the above-mentioned journals used *molecular biology* at some location in their title. The earliest to use *molecular biology* was the *Journal of Molecular Biology,* created in 1959. The *EMBO Journal* was launched in 1982. The launching of the *Journal of Molecular Biology* (Editor in Chief J. Kendrew, a crystallographer) resounds as the hallmark of a novel discipline, since it then possessed its flag, its own journal. On its side, the *EMBO Journal* reflects the success of one of the biggest achievements of European research in biology, the creation of the European Molecular Biology Organization (EMBO) in 1964, around R. Apleyard, J. Tooze and F. Gannon and later on of the European molecular biology laboratory in Heidelberg in 1975[10]. With the exception of the *Journal of Molecular Evolution* in 1971 and *Molecular and Cellular Biology* in 1981, all of the other journals with "molecular and biology" in their title appeared later, most of them after 1985, either as changes in the title of an already existing journal or as the titles of newly created, more specialized journals. Rapid change in titles thus correlates well with the spreading of molecular approaches to all kinds of problems in biology and medicine,

[10] Discussion concerning the creation of EMBL were initiated in 1962 by L. Szilard, J. Watson and J. Kendrew

largely facilitated by molecular technology offered in a kit form. What I described is certainly not specific of attitudes in the Institut Pasteur.

In my opinion, the stepwise generalization of the use of "molecular" and "molecular biology" reflects distinct periods of doing science through molecular approaches, but does not attribute a unified meaning to the expression "molecular biology". Early work in molecular biology (say, before 1960) was mostly published in the usual journals of biology and medicine. The first titles enunciating molecular biology as a discipline, are correlate with the final success of bacterial genetics[11] and appear to have been used to promote the emergence of a new scientific attitude aimed at describing biological phenomena, particularly genetics, at the tiniest molecular possible level. It was not the attitude of the majority of the biologists of the time but rather that of small and active groups. It may also be considered the success of a model organism, *Escherichia coli* and its bacteriophages in answering the long-studied question of control of gene expression. Use of the expression "molecular biology" in journals and proposals in the late 1950s was then a kind of manifesto for modern biology largely written by molecular geneticists. If one excepts the latter, approaches to biological phenomena, particularly biochemical and structural, including studies on DNA and metabolism, were in the continuation of a general trend rooted in the mid-war period and claiming for a move of biology towards molecular studies. the joining of the two occured later. Indeed, the period after 1980, corresponds to the appropriation of the techniques of recombinant DNA by all fields of research in biology, now including those that had been left aside by molecular genetics and molecular studies. Then, physiology, plant biology, taxonomy, development, medicine, criminal investigation etc, could become molecular, merely because of the use of common techniques, and with no deep thinking the meaning an expression like "molecular biology of the gene"[12] could have. All that obviously have introduced changes in the manner problems of biology are now envisaged and have become acceptable by scientists and by the public: consider for example the heated debate between paleontologists, morphologists and DNA-prone researchers about computation of phylogenetic trees and the definition of characters and gaps. A general conclusion is that molecular biology is no longer defined as a set of rules governing organisms or, more generally, as Monod said with, "the ambition to interpret the essential properties of organisms

[11] Note Stent's book for example (G. S. Stent, *Molecular biology of bacterial viruses,* W. H. Freeman: New York 1963)

[12] *Molecular Biology of the gene* is the name of a famous book, several times published, written by J.Watson (first edition, A. J. Benjamin, New York, 1970. It also was the name taken in 1978 by the laboratory I worked in. The title and the name can be considered as a metaphor rather than the description of a research scheme or synthesis.

in terms of molecular structures" [13], but rather as a set of techniques ranging from DNA analysis to models of 3-D structures or algorithmic analysis of DNA sequences, which finally inscribe genetics and ultimately the sequence of nucleic acids, in the very centre of biology and medicine: after all, is not the DNA double helix emblematic of modern biology[14]?

[13] Jacques Monod, Nobel lecture 1965.
[14] Considering the celebration of the 50th anniversary of the discovery of the double helix.