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What Happened to Molecular Biology?

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Abstract
'Molecular biology' emerged in the first half of the twentieth century as a fundamentally novel type of biology. Its coming into being was by no means simply a linear continuation of classical genetics, the biological Leitwissenschaft *of the time, and it took much more than new methods and technologies for the new discipline to arise. In this article I outline the development of molecular biology—from its beginnings to its zenith and dissolution as a discipline in its own right—in its historical context and from an epistemological perspective.*

Keywords Assemblage, History, Molecular Biology

> Treating the science of former times in its own context is very different from treating contemporary science in its current context, because, as inhabitants of the present, historians must make concerted efforts to enter the mental world of scientists of the past. When dealing with contemporary science, on the other hand, we must make a concerted effort to escape from a mental world we may share with our subjects, if we are to view them with appropriate detachment. (Holmes, 1997: 166)

So remarked the historian of science Larry Holmes, who devoted his last big case studies to a couple of classic experiments in molecular biology: the demonstration of the semiconservative replication of DNA by Matthew Meselson and Frank Stahl (Holmes, 2002) and the genetic fine-structure mapping of the rII region of bacteriophage by Seymour Benzer (Holmes, 2006).

In other words, to understand the science of the past, one must try to assimilate oneself as far as possible with the context of that past; to understand recent science, one must try to detach oneself from the present as far as possible. Such is the paradox of retrospection. The point of inversion between past science and present science, however, cannot be defined in terms of a certain number of years or generations; it is bound to the changing pace of science itself. It may, in times of retardation, be further extended; in times of acceleration, it may be reached more quickly. Where do we stand with respect to the history of molecular biology? A few historical reflections may help to clarify the matter.

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Michel Morange, a French molecular biologist and historian of science, once described molecular biology briefly, almost to the point of a tautology, as 'all those techniques and discoveries that make it possible to carry out molecular analyses of the most fundamental biological processes—those involved in the stability, survival, and reproduction of organisms' (1998: 1). Of course, he quickly added that it is not at all easy to decide what exactly falls under this definition and what does not. In his opinion, however, relatively clear chronological boundaries can be defined for what he and others call the 'molecular revolution'. To quote him again: 'The new conceptual tools for analyzing biological phenomena were forged between 1940 and 1965' and 'The consequent operational control was acquired between 1972 and 1980' (Morange, 1998: 2).

Despite this relatively precise timing, the coming into being of molecular biology was certainly not a *project* in the sense of, for instance, the human genome initiative in the late 1980s. Historians of molecular biology rightly emphasize that Warren Weaver, and with him, the American Rockefeller Foundation, played a crucial role in the very early years of this new type of biology, that is, in the late 1930s and throughout the 1940s (Abir-Am, 1982, 2002; Kohler, 1991; Olby, 1974). Weaver is also credited with having coined the term 'molecular biology' (Abir-Am, 1982: 344–345; Rockefeller Foundation, 1938: 34–39, 203–251). I do not intend to question such a role, but want to single out one phenomenon that could be called the 'politics of sources'. It points to the extent to which the histories that both scientists and historians can write are artifacts of the available sources. The Rockefeller Foundation not only opened its archives very early on for historical work,[1] but also invested a lot in making the archives readily available for historical exploration. During the 1980s, many young historians took advantage of this opportunity. Thus, in a relatively early phase of the professional historiography of molecular biology, one could have gained the impression that the development of the new biology as a whole was a bio-politically directed enterprise of the Rockefeller Foundation sustained by the vision that social processes could ultimately be controlled by biological processes.

However, according to our present knowledge, molecular biology is rather an 'assemblage' as described by Paul Rabinow. According to Rabinow, an assemblage 'emerges out of a lot of small decisions; decisions that, for sure, are all conditioned, but not completely predetermined' (2004: 63). 'From time to time,' he continues in another essay, 'new forms emerge that have something significant about them, something that catalyzes previously present actors, things, institutions into a new mode of existence, a new assemblage, an assemblage that ma[k]e[s] things work in a different manner' (2000: 44).

The molecular biological shift

The history of molecular biology appears to be punctuated by two such decisive shifts of assemblage—and both shifts were essentially unprecedented in the form they took. And it could well be that we are currently on the verge of a third shift.

1 The Rockefeller Archive Center, a division of the Rockefeller University, was established in 1974 to assemble, process and make available for scholarly research the papers of the Rockefeller family and the records of various philanthropic and educational institutions founded by the family, including the Rockefeller University, the Rockefeller Foundation and the Rockefeller Brothers Fund.

The first shift happened between the 1940s and the 1960s. Its point of crystallization was at the beginning of the 1950s, with the characterization of the structure of the DNA double helix. It reached its zenith between 1960 and 1965, with the deciphering of the genetic code. What were the ingredients of this shift? In general terms, the 'path to the double helix' was characterized by three significant changes in the material and social structure of scientific practice in the life sciences. The first—and probably most important change—was the introduction of a series of new analytical techniques: ultracentrifugation, electron microscopy, X-ray structure analysis, radioactive tracing, chromatography and electrophoresis, to name only the most prominent ones. To use the term coined by the sociologist of science Terry Shinn, these were mostly 'research technologies' (Shinn and Joerges, 2002), that is, technologies mainly developed for research purposes. These techniques had their origins in widely different research contexts that initially were often rather far removed from biology.

The second change was characterized by the transition from the classical biological model organisms, such as *Drosophila*, corn or snapdragon (*Antirrhinum*), to new models such as lower fungi (*Neurospora*, yeast), bacteria (*Escherichia coli*) and viruses, such as tobacco mosaic virus and T-phages.

The third change involved vital cooperations that extended over several disciplines, in particular biophysics, biochemistry and genetics. It was the combination of these three changes that prepared the ground for molecular biology.

According to the assemblage hypothesis, molecular biology was therefore by no means simply the next step in a linear continuation of classical genetics, which had advanced to *the* biological *Leitwissenschaft* over the first three decades of the twentieth century after the rediscovery of Mendel's laws. On the contrary, molecular biology came to form an active assemblage in its own right. On the level of methodology, this can be seen in the deliberate and massive import of analytical procedures from biophysics and biochemistry into biology. On the conceptual level, between 1945 and 1955, the 'protein paradigm of life' became replaced by the 'nucleic acid paradigm of life'. What stood in the centre of the conceptual shift of the 1950s was a new notion of biological specificity that found its expression in the idea of 'genetic information' and 'genetic programme' as the new key words, notions that had been completely absent from biology before.

The gene technological shift

The second shift of assemblage occurred during the 1970s. It marked the beginning of 'gene technology' or 'genetic engineering'. Again, this shift brought completely new kinds of technology into play, essentially the introduction of *molecular* technologies in the proper sense of the word—technologies in which the functions of biological macromolecules themselves, in particular enzymes and nucleic acids, play a central role. Restriction and ligation enzymes, plasmids and other vectors and polymerases are examples of such molecular biological tools. In an earlier article, I described the decisive step in this phase as the transition from the 'extracellular' test tube representation of intracellular structures and processes to the 'intracellular' realization of an extracellular project (Rheinberger, 2000). One could say that *classical* molecular biology was governed by the methods of biophysics and biochemistry, heavy analytical apparatuses, large machines. *Gene technological* molecular

biology, however, is governed by methods rooted in the molecular tools that operate in the living cell itself. It is thoroughly constructive and synthetic. As Waclaw Szybalski, an oncologist, stated in 1978, on the occasion of the Nobel Prize award to Werner Arber, Hamilton Smith and Daniel Nathans:

> The work on restriction nucleases not only permits us easily to construct recombinant DNA molecules and to analyze individual genes but also has led us into the new era of 'synthetic biology' where not only existing genes are described and analyzed but also new gene arrangements can be constructed and evaluated. (Szybalski and Skalka, 1978)

As of the later 1970s, the *in-vitro* culture of classical molecular biology was paralleled by a new *in-vivo* culture—the manipulations were shifted back from the test tube into the cell. Earlier technologies were not replaced, but rather supplemented by a new mode of doing biology by making use of the organism's own macromolecules.

If molecular biology once existed as a regular discipline in the traditional sense of a scientific discipline, then it was sometime between 1960 and 1980, that is, the time between the two shifts of assemblage described above. This was a time in which university chairs, journals—for example the *Journal of Molecular Biology*—and organizations—such as the European Molecular Biology Organization (EMBO)—were named after it. Since then, and more or less simultaneously with the biggest single project ever carried out in the history of the life sciences—the complete sequencing of the human genome—molecular biology can no longer be considered as a discipline of its own. Today, it appears rather that molecular biology has wound its way, in the form of a wide variety of molecular biological procedures, into all of the life sciences, in particular cell biology, developmental biology, evolutionary biology and, most significantly, the molecular study of disease. As a result, the history of classical molecular biology as a discipline has itself been relegated to the realms of history, that is, to the past as characterized at the beginning of this article.

The advent of molecular biotechnology in a changing societal climate

The change from *classical* to *gene technological* molecular biology was not simply a technical one. In a recent book, the American historian Eric Vettel traced the origins of molecular biotechnology in California's Bay Area, in particular at Stanford University and the Universities of California at Berkeley and San Francisco. He did this with the eye of a general historian interested in the changing cultural and economic atmosphere of science after the Second World War (Vettel, 2006).

Using the example of biochemist Wendell Stanley's Virus Laboratory established in Berkeley in 1948, Vettel highlights two aspects of American bioscience policy that he considers characteristic of the first two decades after the Second World War: first, the transition from selective philanthropic funding, such as practiced by the Rockefeller Foundation, to massive federal funding in the immediate post-war period that was unprecedented in its dimensions; and, second, an equally unprecedented emphasis on basic research, together with a concomitant explicit effort to sever traditional links of biological research to medical

and agricultural departments and practices. Stanley's laboratory, with its emphasis on the physics and chemistry of life, was 'freestanding' and not—as many biological departments and biologists used to be—an integral part of a medical school or an agricultural station. The laboratory's success served as an incentive for Stanford University and the University of California at San Francisco to reshape their life science research programmes accordingly.

According to Vettel, this change in research structure, in particular around Berkeley, went hand in hand with profound societal changes: the rise of an academic as well as popular counterculture that emphasized environment and health—issues that the basic life sciences of the time did not appear to address enough. In addition, the protagonists of this counterculture had detached themselves from their parents' generation that was perceived to have lost sight of the values of *real life* and that had led America into the war in Vietnam.

At the federal level, this societal movement coincided with a policy shift initiated under Lyndon Johnson and continued under Richard Nixon. On the one hand, the new policies emphasized the need for practical returns from the basic biosciences. On the other hand, in response to the economic depression during the late 1960s, they brought an end to the miraculous increase in federal research money that had characterized the decade immediately after the Second World War and the decade following the Sputnik shock. This is the climate in which Vettel places the origins of *molecular biotechnology*, a development that resulted in a complete realignment of the relation between basic and applied research and with it, a drastic shift in the academic self-perception of a new generation of bioscientists. Besides continuing to serve academic functions, many of them became entrepreneurs. This was paralleled by a realignment between academia and industry exemplified by Cetus, history's first biotechnology company, founded in Berkeley in 1972.

A third shift?

The 1980s brought a second wave of molecular technologies that included artificial chromosomes, automatized procedures of sequencing and synthesizing nucleic acids, the polymerase chain reaction, new ways of physically mapping chromosomes and new forms of electrophoresis. With this bundle of biotechnological developments, the first projects of sequencing whole genomes, in particular the human genome, were soon to become reality. For quite some time, the 'noise' around the human genome project and its worldwide organization appeared to dissolve all of molecular biology into one big technical feat. The voices that placed genome sequencing on a par with a march to the holy grail of life became loud and dominant. Had it not been for molecular developmental biology that, in parallel, expanded its reach to the genetic determinants of embryogenesis, one could have spoken of an age in which conceptual pretensions faded out, an age in which the 'makers' took over. In this respect, a sentence from François Jacob's *Logic of life*, published in 1970, could be read as a sober anticipation of a trend that has been increasing ever since. The biology of our days, it reads, 'no longer seeks the truth. It constructs its truth' (1970: 24). We should not forget, however, that Jacob meant this eminently in an epistemological sense. For it means that scientists need to remain aware of the deep historicity of the concepts, the technological and theoretical nets with which they catch the objects of the world. And so, Jacob's quote continues: 'Reality then appears as an ever labile equilibrium' (1970: 24).

For the last decade or so, the coordinate system of the molecular life sciences again seems to have been changing. In the late 1990s, scientists, among them Ludwig Winnacker, who was president of the German Research Foundation (DFG) at the time, talked of the beginning of a new age, the age of *postgenomics*. Statements began to be heard such as 'It is time to transcend old reductionisms,' and 'What must come into view again is the whole of the organism in the full broadness of its functions on the level of cells, tissues, and organs and in the depth of its development.' However, my opinion is that no really convincing conceptual effort for accomplishing this has so far been witnessed. Nevertheless, such an effort will be necessary to forge a really new holistic perspective to meet the great challenge of bringing together not only genomic, but also proteomic and maybe even 'organomic' knowledge. At the end of his book, Jacob vaguely alluded to such a new Russian puppet that he was unable to name. How will this puppet be dressed in the future?

Time perspectives

At the end of his book on the history of molecular biology—in a section most interestingly missing from the American translation—Michel Morange reminds us of Fernand Braudel's (1975 [1949]) reflections on the differentiation of historical times and rhythms (Morange, 1994). He suggests the use of Braudel's differentiations for the history of science, and more specifically for the history of molecular biology. Braudel distinguishes three currents or layers, three different time regimes, each of a different duration, and each of them generating different questions.

There is, first, the 'layer of reduction' which has characterized Western science for about four centuries. It embeds the history of molecular biology in the secular process of reducing the phenomena of the world, including the living world, to their physico-chemical basis. In the framework of such a long-term history, we must surely ask whether our understanding of the living (and the life sciences) as a whole has changed due to the molecular approach to life that evolved around the middle of the twentieth century. As Michel Foucault (1973), François Jacob (1993) and others have argued, biology came into existence as a science of its own around 1800 by assembling, in a thoroughly materialistic perspective, around the question of the specific difference between living beings and non-living systems. The question continued to haunt the life sciences throughout the nineteenth century, the tendency at that time being to equate living and non-living systems. For example, are today's molecular definitions of biological specificity, in particular, the concept of genetic information (for the phenomena of reproduction) and genetic programme (for the phenomena of development), the final answer? And if not, what are the alternatives?

Following Morange and Braudel, another layer is superimposed on the first one and can be equated with a history of disciplines. What influence did the molecularization of life have on the history of the biological disciplines? Above I briefly outlined the institutionalization of molecular biology and its subsequent transformation. However, these descriptions need to be seen in context, that is, viewed in the light of the dynamics that came into the discipline of biology as a whole during the twentieth century. One must also consider whether these dynamics extended beyond biology, for example whether they also profoundly redefined

the boundaries between biology and medicine. The coining of the term 'biomedicine' is itself an indicator of such a reconfiguration.

Moreover, a further—admittedly strong—hypothesis would have to be considered: have the classical disciplines, as shaped during the nineteenth century, begun to dissolve altogether? And is the molecularization of biology only a particularly prominent example of this process? This will not then be without repercussions for the possibility—or the growing impossibility—of conceiving and understanding the dynamics of the contemporary sciences in the framework of histories of the disciplines. Historian of science Paul Forman has remarked that the 'devaluation of disciplines' is mainly based on two features: 'This reorientation toward the market,' Forman postulates, 'together with the increasing orientation toward the particular problem, works powerfully to dissolve the scientist's attachment to his discipline, indeed to dissolve the disciplines themselves and their disciplinary authority' (1997: 185, 189). The question then is: what kind of institutional structures are actually taking the place of the disciplines?

Finally, then, for Morange, there is the third layer, the short-range history, that is, the history of experimental systems. This layer comprises the twists involving theorems, model organisms, instruments and the whole plethora of cultural, institutional, social and political factors that govern the actual, concrete course of the development of the sciences. To date, most of the case studies on the history of molecular biology are at this level. My own forays into the history of experimental systems operate in the same realm—but they also try to show an alternative to the history of disciplines. Here Rabinow's apt concept of 'assemblage'—the roughly equivalent term I have been using is 'conjuncture' (Rheinberger, 1997)—appears to be very appropriate for describing the specific configurations in which and by which conditions are set for the generation of new and unprecedented knowledge.

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