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Jacques Monod – A theorist in the era of molecular biology / Un théoricien à l'ère de la biologie moléculaire

Science and the applications of science from Louis Pasteur to Jacques Monod



La science et les applications de la science de Louis Pasteur à Jacques Monod

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ABSTRACT

Jacques Monod's ideas on the applications of science came within the scope of a long tradition at the Institut Pasteur. Louis Pasteur, whose scientific career was characterized by a permanent come and go between science and its applications, long opposed the idea of getting any income from his research, until the financial needs of the Institut Pasteur made him change his mind. As for Jacques Monod, he remained a fervent supporter of basic science during his whole scientific career. However, once he became director of the Institut Pasteur, he realized that the applications of research had to be developed to support the institute from a financial point of view. Thus, he reorganized the valorization of research in the institute, through an incitation of scientists to develop projects with possible applications, and by creating a company, Institut Pasteur Production, for which he had a factory built, and which was in charge of producing and commercializing the vaccines and reagents stemming from the research at the Institut Pasteur.

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R É S U M É

Les idées de Jacques Monod sur les applications de la recherche se sont inscrites dans la tradition pasteurienne. Louis Pasteur, dont la carrière a été marquée par un va-et-vient continu entre la recherche et ses applications, a longtemps été opposé à l'idée selon laquelle les applications pourraient apporter des revenus, jusqu'à ce que la nécessité de financer l'Institut Pasteur le fasse changer d'avis. Jacques Monod fut, quant à lui, durant sa carrière scientifique, un fervent défenseur de la recherche dite fondamentale. Devenu directeur de l'Institut Pasteur, il prit conscience de la nécessité de développer la valorisation de la recherche afin d'en tirer des revenus. Cela l'a conduit à réorganiser ce secteur en incitant les chercheurs à rechercher et développer des applications de leurs travaux et en créant une société, Institut Pasteur Production, qu'il a dotée d'une usine et a chargée de produire et commercialiser les vaccins et réactifs issus de la recherche pasteurienne.

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1. Introduction

When Giuseppe Baldacci asked me to give a talk during the commemoration of the 100th birthday of Jacques Monod from which this text is issued, I could not refuse. Indeed, Jacques Monod was my mentor. He welcomed me in his laboratory at the beginning of my career, thus proceeding to turn a student coming from the École polytechnique into a molecular biologist, something which had never been done before. Then, the confidence he never ceased to grant me was of immense importance to me. Finally, at an early stage, and without letting me know, he decided that I should later become a director of the Institut Pasteur, and he must have been able to convince his entourage, since this is exactly what happened 12 years after his demise. Therefore, how could I have refused to pay homage to his memory?

I was asked by Giuseppe Baldacci to recall in what Jacques Monod's ideas were concerning the relations between biological research and their socio-economic applications. Since the ideas of Jacques Monod on this matter emerged from a long tradition at Institut Pasteur, I will start by recalling Louis Pasteur's view on the subject before analyzing Monod's. I will end by a few words on the "after Monod", to show the influence he had on what is now called "la valorisation de la recherche", i.e. the development of the applications of research.

2. Louis Pasteur

2.1. The patron saint of biotechnologists

For many, Pasteur is the precursor and model, the patron saint, of biotechnologists. Indeed, was it not upon a request from a Lille manufacturer that he started his much celebrated work on fermentation? Did he not follow up this work to improve the manufacture of vinegar, wine and beer? And, if he started working on infectious diseases, was it not to help first French sericulture confronted with a mysterious disease of silkworms, and then cattle breeders, who saw their cows and sheep decimated by anthrax? And if he became interested in vaccines, it was obviously to protect humanity against plague, cholera, and several other scourges.

2.2. The basic scientist

But then, if Pasteur was only interested in finding solutions to practical problems, why did he make the following declaration to the students while inaugurating, in 1854, the faculty of Sciences at the University of Lille?

"It will be up to us, especially, not to share the opinion of these narrow minds that disdain all that in the sciences has no immediate application. You know the charming word of Franklin. He attends the first demonstration of a purely scientific discovery, and is being asked: 'What will be its use?' Franklin answers: 'Of what use is the child just born?'" [1]

Is this the language of a hard line biotechnologist?

All the same, when he writes several years later, in 1865:

"It is unique to scientific discoveries to surpass one another. The field of science is inexhaustible. The more it is ploughed, the greatest are the treasures it reveals" [2].

When he says so, he knows what he is speaking about. He describes the deep pleasure, almost sensual, that a scientist feels when he succeeds in increasing human knowledge, similar to that felt by a painter achieving a work of art.

His work on tartaric acid and his amazing intuitions on molecular dissymmetry, his refutation of spontaneous generation, his reflections on virulence factors and mechanisms of immunity were, more than anything, motivated by his desire to understand, common to all true scientists.

2.3. Science and the applications of science

Therefore, and this is why he constitutes a model, Pasteur was at the same time, using expressions that he refuted, an "applied scientist" and a "basic scientist". In his mind, the will to control Nature for practical uses and the desire to increase knowledge always co-existed. If one looks carefully, his scientific career was characterized by a permanent come and go between the search for solutions to practical problems and reflections on theoretical questions.

If he answered the request of the manufacturer in Lille, it was because his theoretical work on tartaric acid had aroused his interest in fermentations, tartaric acid being a side product of such a process. Conversely, his applied work on fermentations led him to wonder about the origin of the microorganisms responsible for these phenomena and thus to tackle the very theoretical question of spontaneous generation, and of the origin of life.

This is really the lesson taught by Pasteur, summarized in this famous sentence:

"There is no kind of science that could be given the name of applied science. There is science and the applications of science, bound to each other as the fruit to the tree that bore it" [3].

Science and its applications fertilize each other. The tree gives the fruit and the fruit gives the tree. Applications result from the advancement of science and the search for applications brings to light new theoretical questions that science must solve.

A corollary is that fruitful applications can only derive from good science.

This message is simple, and the debate should have been closed. However, this is not the case. The pressure is high from industrialists, from many politicians and a great part of the general public, that science be conducted only because of its applications. This is why, as we shall see, Jacques Monod, in his turn, will have to drive this point home.

2.4. The selfless scholar

But the time when things started to get complicated, as always when money is at stake, was when the question came of the financial returns from the applications of research.

For many, Pasteur was the very example of the selfless scholar, only interested in the well-being of humanity. He obtained patents on fermentations, on the making and conservation of vinegar, wine and beer, and was even the first to obtain a patent specifically protecting the use of a microorganism. However, he put these patents in the public domain. He did not even apply for patents for veterinary vaccines, such as the one against anthrax, which was to be used by cattle breeders worldwide. Furthermore, to a financier who offered him a considerable amount of money in exchange for a right to exploit the procedure for anthrax vaccination, Pasteur answered that he could not accept because, having been honored by a government subsidy, the product of his discoveries belonged to the nation. As for the vaccine against rabies, which promoted Pasteur to the title of “Benefactor of Humanity”, it was never patented either.

Thus, the selflessness of Pasteur seems to be in accordance with the legend.

2.5. The limits of selflessness

However, during the last period of his life, Pasteur's state of mind was to change slightly. The reason was the creation of the Institut Pasteur, in 1887–1888.

The acquisition of the grounds, the building of the institute, its initial equipment, were covered as a result of an international fund-raising campaign, but the amounts of money collected could not allow the institute to operate for a long period of time. In the new institute, on the walls of the waiting rooms for patients, one could read the following inscription: “All services are free—We accept offerings, even the most modest.”

Selflessness is here—vaccination is free—but its limits too—money is needed to prepare the vaccine. Unfortunately, the “offerings” timidly solicited did not suffice. Pasteur had to resolve getting a financial benefit from his inventions. “The benefits of the delivery in France of the vaccines discovered in the laboratory of ‘Monsieur Pasteur’... before the opening of the institute” were to appear as part of the annual income of the Institut Pasteur in its first statutes.

Therefore, as we can see, even for Pasteur, selflessness had its limits. In the liberal economy that is going on in our countries, those who contribute to offer products or procedures useful for health or, more generally, for the well-being of humanity, must be able to cover their expenses and invest in research so as to be able to offer new products, new procedures.

3. Jacques Monod

The ideas of Jacques Monod on the applications of science followed an evolution very similar to those of Louis Pasteur.

3.1. The basic scientist

However, contrary to Pasteur, Monod remained almost exclusively a basic scientist. His work on bacterial growth, on the regulation of protein synthesis and on allostery belongs to what is now called “cognitive research”. One day, while he walked out of his office after having elaborated the concept of allostery, he told his secretary, very modestly, that he had discovered the second secret of life (the first having been the elucidation of DNA structure)!

At no point was his research dictated by the wish to solve a practical problem, even though he sometimes mentioned possible applications of his work. The only patent he obtained, in 1951, was on the “bactogen”, a process for obtaining a permanent growth of bacterial cultures.

As a consequence, he was a devoted defender of basic research, even though he was convinced, just like Pasteur, that useful applications can only result from excellent basic research. The first “colloque de Caen”, in 1956, provided him with an opportunity to express this opinion clearly.

3.2. The “colloques de Caen”

The idea to hold the first of these conferences had emerged in 1955, in great part under the impulsion of Pierre Mendès France, then Prime Minister. It is him, even though his government had been brought down meanwhile, who delivered the opening speech, on November 1st, 1956. One of his first sentences summarized the purpose of the meeting:

“Ladies and Gentlemen, at the Parliament as well as in universities, in public laboratories as well as in industry, and even in the countryside, numerous are the French citizens who feel today a deep concern in face of the disarray and weakness of scientific research in this country, many are those who understand that, in this century, power and prosperity can only result from science and technique, many are those who understand the necessity to achieve in this domain a considerable effort on which our future depends” [4].

The meeting was to offer solutions to get over this catastrophic situation.

Scientists and university personnel, who constituted the hard core of this conference, were young for the most part and enjoyed an excellent reputation. Among them, Jacques Monod played an important role. With his colleagues, he developed a central idea: basic research must become a priority in universities; it must be its spearhead. “Without a basic research both full of life and expanding, applied research, which must permanently alter its aims according to the evolution of needs, soon becomes dependent on foreign countries.” [5]

The second “colloque de Caen”, held in 1966, was to analyze more deeply the question of the relations between science and its applications. The speech of Alain Peyrefitte, Minister of Research and Universities, gave this as an objective to the participants. However, rather than

focusing on this question, the second meeting centered mainly on universities and on their relation with research.

3.3. DGRST

In 1959, shortly after the return to power of General de Gaulle, the DGRST (General Delegation for Scientific and Technical Research) is created. This new structure, directly attached to the Prime Minister, was to support the sectors where France was behind other developed countries: among those, molecular biology, a discipline just emerging. Behind this choice, one can easily recognize the influence of Jacques Monod, who was one of the inspirers of the creation of DGRST, with the unexpected support of General de Gaulle, who declared:

“One could think that a general would be particularly responsive to spectacular projects that he understands, which he agrees with, and the development and consequences of which he appreciates fully, such as, among those that I just heard about, energy conversion, the conquest of space, the exploitation of oceans. However, deeply inside, I wonder whether this mysterious molecular biology, of which I do not understand anything and shall never understand anything, is not more promising of medium-term unpredictable, rich developments, which may advance our understanding of basic phenomena of life and its disorders, and which, perhaps, will form the basis of a new medicine that we cannot foresee but that could be the medicine of the 21st century.” [6]

Jacques Monod was immediately charged with a preliminary report on the orientations of the “Concerted action in molecular biology”.

He followed up the idea that no good applied research can exist in the absence of strong basic research in biology. This idea remained in the final report, delivered in 1960, where one could read: “The clinical and therapeutic applications will only follow the progress in basic knowledge of which we only catch glimpses at this time” [7].

Therefore, for Jacques Monod, the most important was to perform good basic science, without being too preoccupied by its applications. However, this attitude was to undergo a slight shift after 1971, when he became director of the Institut Pasteur. His ideas then followed the same evolution as Pasteur’s, about a century before, when confronted to the same problem: how to finance the Institut Pasteur’s activities?

3.4. The director of the Institut Pasteur

3.4.1. Restructuring the valorization sector

When Monod took over the direction of the Institut Pasteur, the institute was in a very worrying state, for several reasons. The scientific activity, excepts in some rare sectors such as molecular biology, tended to rest on its laurels and lacked dynamism. The buildings and equipment were timeworn. The financial situation was dramatic since the institute was to be declared insolvent by 1976. Quite simply, the cost of research was increasing

while resources decreased. Among the latter, the revenues from the commercialization of vaccines and diagnostic tests ought to have helped equilibrate the budget. Unfortunately, this commercial activity, a continuation of the commercialization of the anthrax vaccine by Pasteur, suffered from a lack of organization and from the competition with French and foreign pharmaceutical companies.

Monod then realized that, if he was to rescue the institute, the basic scientist that he was had to start taking an active interest in the spin-off of research and in the income that may result from it. He must modernize the manufacturing and marketing of the products and mobilize the Pasteur scientists in such a way that they contribute to research projects likely to result in applications.

When Monod was elected, the decision has already been taken to individualize the production sector, previously intertwined with the research sector. To host the production activity, Monod initiated the construction of a factory in Louviers (Normandy), which was to start its operations in 1973. Simultaneously, and in accordance with a wish of the government, which made it a condition for an increase of the financial support to the institute, the production sector was individualized in 1972, with the statute of a public company, Institut Pasteur Production (IPP), distinct from the Institut Pasteur, a private Foundation, but of which, at the beginning, the Institut Pasteur was the sole shareholder. Jacques Monod was designated president of the board of directors of this company, for which he rapidly found a director.

In 1975, 1 year before his demise, in order to mobilize the Pasteur scientists, he created a Direction for Development and External Relations within the Foundation and asked Joël de Rosnay to be its director as well as to assume the scientific direction of IPP. He also created a department in charge of the patents that the scientists were encouraged to apply for. At that time, this was a novel kind of endeavor, and not everybody agreed with it.

Even before the creation of a direction for development, Monod showed the way to the institute’s scientists. Not all of his initiatives were successful, and some of them look somewhat amusing today, but I will mention a few to show that he took an immediate interest in this spin-off of research that he previously considered as secondary.

3.4.2. Cholera, lactoserum and β -glucuronidase

One day, Jacques Monod came to see me in my office and explained that I ought to develop the genetics of the cholera vibrio. Indeed, cholera was periodically posing major problems in third-world countries and the existing vaccine, manufactured by the Institut Pasteur, was not very efficient. Since I was a bacterial geneticist, having worked for several years on *Escherichia coli*, I ought to be able to transpose the techniques I used for *E. coli* to *Vibrio cholerae*. The purpose was to obtain attenuated mutants that could be used as a vaccine. I did not accept this challenge, which, before the emergence of genetic engineering, would have implied the construction of a genetic map for this bacterium, and this would have taken several years of hard work. However, this request brought

to light Monod's wish to introduce the concepts and techniques of molecular biology in the study of pathogenic microorganisms. Although not fulfilled during his lifetime, this wish was to become a reality 10 years later, when I became a scientific director, and then the director of the institute.

Another episode, in which Agnès Ullmann and I were involved, was of a very different nature. It dealt with the treatment of lactoserum, the component of milk that remains after the precipitation of casein in the making of cheese. A manufacturer in the food-processing industry had contacted Monod, known as a specialist of β -galactosidase, in order to find a procedure to get rid of the lactose from lactoserum, which was a 10^{-1} molar solution of this sugar. Initially, the manufacturer wished to decrease the degree of pollution resulting from the discharge of lactoserum in rivers. He had tried to get the lactoserum go through a column with β -galactosidase, with little success. Monod then asked Agnès Ullmann and I to try and find a bacterium that would do the job. Thus, I started to prepare cottage cheese in my laboratory, and to use lactoserum as a culture medium, first for *E. coli*, then for other enterobacteria, and finally seed it with some earth or other material that could contain an adequate bacterium. The problem turned out to be that most bacteria tested failed to eat up more than 60% of the lactose. Eventually, the miracle bacterium appeared—a case of spontaneous generation in the institute of Monsieur Pasteur!—in a flask of lactoserum that had been left for the weekend in the refrigerator. This bacterium, a strain of *Serratia liquefaciens*, eliminated close to 100% of the lactose in the lactoserum. In theory, we had solved the problem. But, meanwhile, the manufacturer expressed the wish that the bacteria that had eaten up the lactose could serve as cattle feed. He prepared tons of our bacterium, and fed it to calves. . . , which did not like it. He then mixed the bacteria with yeast, but the calves that had been given our bacterium grew more slowly than the controls. And this was the end of our project. . . , which, however, had an unexpected consequence. Indeed, we found that the Lac+ character of our *Serratia* resulted from the fact that it harbored two plasmids. At the time, the existence of Lac+ plasmids in nature had just been recognized and our finding was sufficiently original that it deserved a publication [8]: a new example of a “basic” discovery resulting from the search of a solution for a practical problem!

A much more fructuous episode was that of the β -glucuronidase. One evening during the spring of 1971, just after he had taken over the direction of the institute, Monod asked Agnès Ullmann: “How could we make money?” “With diagnostic tests, perhaps”, answered Agnès. After having visited a dozen of clinical laboratories, she found that, in order to assay hormones in urine, it is necessary to hydrolyze glycoconjugates, and that the laboratories used β -glucuronidase preparations from *Helix pomatia* (snail) to perform this hydrolysis. Not only were these preparations very expensive, but they were also quite inefficient, the hydrolysis taking 24 hours. Agnès was aware that Monod's strain collection included a strain of *E. coli* constitutive for β -glucuronidase production. She then tested this enzyme and found it considerably more

active than that from snail. Therefore, she sent samples to several laboratories, and they found the results miraculous. With a thousand fold dilution of the bacterial extract the hydrolysis was complete in 1 hour. From 1973 until 1983, Agnès provided IPP with 2600 liters of extract that she had prepared herself. Later on, the production was performed by the company. Between 1983 and 1990, IPP made a gross sale of 14 million francs on this product, the Institut Pasteur getting a 6% royalty on this amount.

3.4.3. Growth hormone and genetic engineering

Finally, here are two last examples of Monod's determination to develop the applications of science. One had dramatic consequences; the other, in contrast, turned out to be very fruitful.

The first was his decision, in 1973, to ask Fernand Dray, an endocrinologist that he had recruited at the Institut Pasteur, to undertake the purification of growth hormone from human pituitaries for the treatment of children with pituitary dwarfism. He was thus answering a wish of Pierre Royer, a famous pediatrician who was then chairman of the board of directors at the institute, and he was only asking Fernand Dray to reproduce what was already being done in other countries. During about 20 years, this was a very successful operation. Unfortunately, during the 1990s, the first cases of Creutzfeldt–Jakob disease appeared in children or young adults who had been treated with growth hormone during the period 1983–1985. What happened next is well known.

The second was the decision of Jacques Monod, only a few months before his demise, to create a Unit for genetic engineering. Genetic engineering was then an emerging technology and Monod understood immediately all the benefits that could result from it, both in basic research and in its applications. This very atypical unit, constituted of groups coming from other units, and headed by well-established scientists, such as Maurice Hofnung, Philippe Kourilsky, David Perrin, Alain Rambach, François Rougeon, and Pierre Tiollais, was to play a major role in the establishment of the techniques of genetic engineering both at the Institut Pasteur and in several other laboratories in France. Furthermore, as Jacques Monod had foreseen, important applications were to result from the work of members of this unit: for instance a vaccine against hepatitis B, which was to bring important royalties to the institute, non-radioactive probes for DNA sequences, and the production of growth hormone, which was to replace that obtained from human pituitaries.

4. After Monod

Jacques Monod left us 39 years ago. Six Institut Pasteur directors came after him: François Gros, Raymond Dedonder, I, Philippe Kourilsky, Alice Dautry, and now Christian Bréchet. In many sectors, they only followed the directions that he had given. This was the case, particularly, in research valorization.

IPP does not exist as such anymore. It was first split into two companies, one specialized in vaccines, and the other in diagnostic, these two companies being in turn taken over by larger ones. However, the relations with the latter,

today Sanofi and Biorad, still obey the same principles as those that governed the relations with IPP: a priority in the access to the research performed by the Institut Pasteur and the payment to the institute of royalties for this privileged access and on the income from patents belonging to the institute.

Within the institute, the structures created by Jacques Monod to make easier the valorization of the work of Pasteur scientists were highly developed. This is what allowed the institute, among other things, to collect important royalties from AIDS diagnostic tests and vaccines against hepatitis B.

A new endeavor has been the creation of “start-up companies” by the institute, the first ones having been created when I was the director. But, was it really a new thing? Were not IPP, and even the Institut Pasteur itself, some kind of start-up companies, long before the word was coined?

As a result of this policy, during these past few years, 40% of the Institut Pasteur budget came from its relations with industry. This in no way altered the freedom of the scientists to choose their research projects, even if they have now more systematically taken into account possible applications of their work.

The change in the relations between scientists and industry at the institute foreshadowed what was to happen, more generally, in French biological research. It seems clear that scientists at CNRS, INSERM and universities are paying attention, much more than before, to the possible applications of their work. However, most of them remain strongly attached to their liberty of research, not wanting to see their projects dictated by industry. In so doing, they follow the example of Louis Pasteur as well as that of Jacques Monod.

Finally, I would like to recall a famous saying by Jacques Monod that Louis Pasteur would not have disavowed,

because it summarizes their philosophy about the financial returns of the applications of science: “While private industry does research to make money, we want to make money to do research.” [9]

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