© 1987 Elsevier Science Publishers B.V. (Biomedical Division)
From Enzyme Adaptation to Natural Philosophy:
Heritage from Jacques Monod
E. Quagliariello, G. Bernardi and A. Ullmann, editors

ORDER AND NECESSITY

A. DANCHIN
Unité de Régulation de l'Expression Génétique, Institute Pasteur,
28 Rue du Dr Roux, 75724 Paris Cedex, France.

Jacques Monod has been celebrated not only for his scientific contribution, well known and still up to date, but also for his thought on the status of life. In a world dominated by the growing power of radical empiricism and operational controls, his contribution is both original and of prime importance. This makes his premature disappearance even more unfortunate. Not only is there much to say about Science as we practice it, but also it seems necessary to bring our interrogations into the limelight. The industrial revolution has separated Science from Philosophy, so as to avoid questions that might be raised against production and profit. It was thus important that a scientist from an emerging discipline (and a major one!) would ask questions on the nature of the processes underlying creation of the corresponding knowledge. In what follows I shall try to place Jacques Monod's thinking into the highly evolving context of concept production in Biology. And what will help me is the fact that Jacques Monod's thinking was precisely undergoing a steady evolution by itself. For those who knew him well, what I shall say will probably appear either as a truism or a misunderstanding (according to their sympathy for Monod's personnality). For me he was a young mind, almost adolescent, am I tempted to say, with the corresponding qualities and failings. This means enthousiasm, ingenuousness, deep intuition, dogmatism and changeability. This also means that his thought is a milestone, not a final thought: every step is carefully built on bases temporarily accepted as final, but meant to be challenged. Thus, the questions I shall develop below should be understood as a tribute, not a criticism. Indeed what can be more desirable for a scientist than an evergoing questioning of the very bases of his knowledge?

I. A philosophy of adaptation: teleonomy

Biology, because it puts Man into question, from its origins to the rules that have allowed emergence of consciousness, is the privileged target of a finalistic approach, that permits, using implicit postulates, to avoid a large number of ethical problem as well as eschatological prospects without gods. Jacques Monod's position in this debate is, in a sense, "premolecular": he remains highly sensitive to the meaning of things; and this is the reason for a concept he presents as essential to his thinking, the concept of teleonomy. For the theme that is at the heart of his quest is adaptation, and its origin, a theme that was central to his finest scientific discoveries. But adaptation implies a goal, and indeed, the most aggressive among the adversaries of molecular biology in general, and of Monod in particular, would recurrently give examples of adaptation as impossible to explain without asking for an explicit finality. One finds in the word "teleonomy" two superimposed concepts, that of a law, a reason (a nomos) and, precisely, that of a finality, an intention, a goal. We have here a remarkable revival of Aristotle's entelechy, understood as a necessity, by a scientist well known for his "reductionism"! Now, it seems to me, and this was the occasion for a very stormy (but fascinating) discussion with Jacques Monod, that this residuum of finalism is not only useless but noxious, and due to an erroneous interpretation of the concept of chance. Thus, for me, this concept is but a step in the progression of Monod's thought towards a vision of Life as a pure and bare consequence of the complete absence of will or desire in the birth of living organisms. This would have certainly led to the deep feeling of complete solitude that Jacques Monod appeared to both loathe and like, and for which he created, quite unnecessarily, his own vision of chance.

Indeed Monod has certainly evolved in his own vision of life, starting, as almost everyone does, from a purely "instructive" attitude (meant to answer to the implicit question: why?) to a very "selective" view (meant to answer, in most cases, to the mechanistic question: how?). Whereas he wrote in 1949: "L'hypothèse essentielle, pour expliquer l'accroissement "autocatalytique" de l'activité enzymatique, c'est de supposer que les rencontres "efficaces" entre amorces spécifiques et "matériaux de construction" non spécifiques, seraient favorisées par la présence de molécules du même type déjà formées. En d'autres termes, la probabilité de formation d'une structure active donnée serait d'autant plus élevée que cette structure serait déjà représentée à un plus grand nombre d'exemplaires. L'effet du substrat serait de stabiliser les structures déjà formées, et de favoriser ainsi la naissance de nouvelles structures semblables. On voit facilement comment, même si l'effet primaire était assez petit, il pourrait se traduire (par suite de la compétition entre les différents types de molécules pour les matériaux non spécifiques) par un accroissement relatif considérable."[1], which is a remarkable foreshadowing of the "selective stabilisation" hypothesis underlying his theory of allostery, one finds, in the text written in 1961 together with F. Jacob, where the term "allosteric inhibition" was first proposed, clear traces of a purely "instructive" approach ("Studies of the structure of the two (allosteric and catalytic) sites and of their interaction, using analogues of the substrate and inhibitor, might conceivably lead to interpretations in terms of the "induced-fit" theory of Koshland (1959)"), in a very "selective" background ("This brings up another issue which must be mentioned at this point, although it was not discussed during the conference, evidently because it is implicitly considered as settled. A few years ago, the question was often debated whether any further (non-genetic) structural information needed to be furnished, or might conceivably be used in some cases, at the stage of tertiary folding in protein synthesis. Such a "finishing touch" has been considered as one of the possible mechanisms which might account for the effect of antigen in antibody synthesis (Pauling, 1940) and of inducer in enzymatic adaptation (Monod and Cohn, 1952). In the latter case, no evidence against this possibility has accumulated (cf. Monod, 1956, Jacob and Monod, 1961) and proof has been obtained that inducer action is completely unrelated to the structure of the binding site of the induced enzyme (Perrin et al., 1960). In the meantime, speculations on the origin of antibodies reverted from "instructive" to purely "selective" theories (Burnet, 1959 ; Lederberg, 1959))[2]. The "induced-fit" process was rejected by him a few years later, on the ground that it was clearly "instructive"[3].

Perhaps should I make clearer these concepts. "Instructive" theories postulate the existence of a causal agent, exterior to the system, that directs its evolution. A deeper analysis permits us to distinguish two levels of instructive theory[4]: the approach that I shall term "animist" (which is typically represented by the evolutionist theory of JB de Lamarck) supposes the existence of a motor that can be interiorised and can drive the system's evolution; the model that I shall term "attractive", more recent in biology (but quite similar to Pythagorean or Platonic models) supposes that there exists, in essence, forms that are able to act as "attractors" and thus shape material systems. "Selective" theories, on the opposite, leave to contingent interactions the only driving force that makes living systems evolve[5]. Here, once again, it seems possible to separate between two types of models. The "preformist" model assumes (as does the attractive model, but inside the system) the existence of preexisting stable forms, that are not visible at the start, then progressively actualized through selective interactions with the environment. Finally, the "generative" model refuses - in spite of the hypothesis of a local determinism -to predict specific structures, but postulates that the very existence of living systems (contingent a priori but necessary a posteriori) implied, as soon as the first organized systems existed (due to contingent interactions), a further evolution generated by the interactions (necessary, because everything is in movement) of the system with its environment. During this evolution only stable structures can persist long enough to constitute a living system: this is the work of selection, purely passive, and the result is constant production of emergent structures.

In the instructive model one postulates the existence of both preexisting external forms and a mover that is able to have them imprinted on the system under study: the attitude that follows tends to abandon such vitalistic constraints. A simple way out is to postulate that innate structures preexist: they are present inside rather than outside the system. This is what Jacques Monod does, as one can see for instance in his insistence on the role of symmetry in the theory of allosteric inhibition. The preformist selective theory is still slightly impregnated with some instructivism: a living system will be perceived as having a goal, as reflected in the word "teleonomy". The problem is then to find what are the innate structures, as well as to describe a process permitting to actualize them. One remarks here that such a solution of the problem posed by the existence of living systems leads to a major question: if form is inside the system, can it have the global properties of the whole? The answer must be negative, and this leads Monod, in order to keep to the founding postulates, to reject the "holistic" explanation as non pertinent. This is why his writings look so "reductionist", as emphasized by his adversaries. But one has to replace the holistic interpretation by a new one: in the most modern approaches, that would certainly have been chosen by Jacques Monod, had he lived longer, there is no goal, there exists only the consequence of contingent interference of independent causal series, due to necessity of laws that must be identified. A living system is the result of a structure and a process: the structure possesses features of a memory, and the process uses the structure as a pattern to build the organism. One will separate, according to the generally accepted terms, between a genetic program, and an actualization of the program. The result is, in evolution, of a progressive alteration of the program, after modification of the hereditary memory, and during ontogeny, of every living system's identity, as a function of the environment in which it develops. Thus, perturbations in the environment will be, after a kind of "sifting", integrated to the individual, which, accordingly, will behave as an image of the world. One should no longer speak of adaptation but of adequation instead.

Perturbations are necessary simply because the underlying physico-chemical processes must have some variability. What the program prescribes are rules for the average unfolding of an average organization in an average environment. This has a specific consequence: the actual number of molecules specified by a given gene is often small (this is true in particular of molecules involved in regulation, and also, because of amplification at the level of translation, of the number of mRNA molecules); therefore, the corresponding behaviour of individual cells is submitted to Poissonian statistics; thus, even if one assumes that the program is reproduced with rigorous accuracy, in a constant environment, the progeny of a starting cell must vary, quite significantly. This means that there always exists some cellular individuality. As a consequence a given program can

have various actualizations, even in a given environment, and it is not possible to predict whether it will be adapted. What the external medium does is simply to stabilize selectively all that is not completely incompatible. Because of the variations in expression of a given program -actualized in individuals - it becomes difficult to tell whether a given variation (a mutation in a broad sense) is positive, neutral or deleterious, for this would be meaningful only in a specific environment, depending on the number of individuals considered... Thus, processes controlled by selective stabilization, without breaking the constraints imposed by the laws of physics and chemistry, explain some of the rules which produce living systems, without asking for an unnecessary finalism. It should be emphasized here that whereas these processes are deterministic, this by no means implies that their consequences are foreseable!

With respect to this scheme, which I think self consistent, Jacques Monod's thought represents a crucial step, the passage from a macroscopic level to the microscopic. But this passage could not be operated without difficulties, and it is quite understandable that his thought was still penetrated, in spite of his denial, with a finalistic flavour. He certainly had well known precedents: Darwin himself did not escape, and when Spencer formulates his theory as "selection of the fittest" one is compelled to discover the existence of an internal finalism (who is able to tell what is the fittest?) inside a selective approach. This is also the reason for the concept of teleonomy that postulates a kind of prescience of adaptation. Also, in a more subtle way, Jacques Monod intoduces another "motor", "attractive" this time (as did Pythagore or Thom), when he calls for a general constraint of symmetry.

I now come to a crucial point in my argument. Trying to substantiate his thought with the authority of two millenaries, Jacques Monod, being confident in his memory, wrote as an epigraph for his famous book, a sentence attributed to Democritus. What remains from the presocratic philosophers is not much, so that it is rather easy to find out all what remains from Democritus: when looking into the few hundred thoughts left by this author I failed to find the corresponding sentence. Where does this memory come from? Looking into the collection of pre-Socratic philosophical remains I found a sentence, from a man who might have been a master of Democritus, Leucippus, in which an epigraph, very similar yet absolutely contradictory to that of Monod features:

οὐδὲν χρῆμα μάτην γίνεται· ἀλλὰ πάντα ἐκ λόγου τε καὶ ὑπ' ἀνάγκης [6]

"Nothing comes to be at random, but all things for a reason and of necessity" (translation WCK Guthrie[7])

Certainly, Logos cannot be interpreted as chance! But this reflects a typically Greek thought, typically *scientific*. Thus, one should get rid of chance, or, at least discuss its form, which I shall do in what follows. Curiously, I think this will stay in the line that Monod initiated, in spite of the disputable use of the word he made.

II. *The secrets of Life*

In an unpublished theatre play, *Le puits de Syène*, Monod stages the fight between Science and all obscurantisms (including quest for power or glory), in hellenistic Egypt. And the hero to which he identifies, Epistemos, says for instance: "Asservir la nature?... Etrange expression. Pour y parvenir, Philokratos, il faut d'abord la respecter, l'écouter, lui obéir. C'est ce que j'essaie de faire, maladroitement. Vois cette toupie. Je puis la lancer, non l'asservir; ce n'est pas à moi qu'elle obéit, mais à une loi (...), une loi que j'ignore encore" (Jacques Monod, *Le Puits de Syène*, unpublished). This is a view of science that owes nothing to chance!, and I shall try to show below how much looking for Laws can bring to Biology.

Greek thinkers did not use the concept of chance as we do today (following a most popular interpretation of quantum mechanics), as meaning "indeterminism". They had for this concept two words τύχη (which one is still in use) and αὐτόματον, which express that things are contingent, that the movement of atoms is eternal and without necessary external first cause. Greek chance is contingency, precisely what Jacques Monod describes in his book when Dr Dupont is hit by the hammer falling from the hand of M. Dubois; this is also the case when Monod, using a word borrowed from André Gide, speaks of a "gratuitous" inducer. This kind of chance is not indeterministic, but corresponds to unpredictable interference of causal series. Contingency gives varied environments as space for the evolution of living systems: this is the basis for a (passive!) sieving that leads to phylogenesis. This is where appears a fundamental facet of Jacques Monod's thought, his extension of the role of selection at the molecular level. The theory of allosteric inhibition, still often misunderstood, is a paragon of the role of selection in a mechanical process that operates not during a million years of evolution, but immediately, in present day living organisms.

There was an example of a biological law, of a "secret of life", as Jacques Monod once said[8]. This is for me a hint that he was on the way of Leucippus sentence: what counts for the origin of the living is the existence of laws, specific to life, superimposed on the ordinary physicochemical world. Such laws, conceptually extremely deep and abstract, are not initially *geometrical* (as is symmetry, for instance) as are the laws of physics or chemistry. What are they?

It is possible, bearing in mind that these are not the *only* laws of life, to enumerate a few. The one which seems to me the most important, by far, and which would ask for a description much longer than this text, is the law of *coding*[9]. This law tells how it is possible for a material system to act both as a *template*, allowing construction of objects chemically and structurally different from itself, and a *substrate* for the action of the latter objects. This law has been operating at least twice: by founding the genetic code, and being at the root of language. Other examples are being discovered: one can think that forms of *hierarchy* play a major role in living organisms autonomy (it may have a geometrical dimension, permitting the separation of inside and outside); also, and to the contrary, it seems to me that *acentered* systems, endowed of global properties may have a major role in the differentiation of organisms (they may be operating in the formation of the immune network). To these laws are associated geometrical structures: the tree to the former, the helix (or the circle when the geometrical constraint is two-dimensional), to the latter. Finally there is a law, relected in the process of "genetic takeover" as described by Cairns-Smith that may be central to metabolic processes, and which is associated to the geometrical structure of the rope, made of hundreds of small fibers, building a macroscopic structure[10].

III. *Ethics and materialism: the postulate of objectivity*

Jacques Monod's main purpose when he wrote his book was both epistemological and ethical, as he answered during an interview a few years later: "J'ai tout de même abordé le plus redoutable de tous les problèmes: les rapports entre l'éthique et la connaissance. Cette question m'a toujours profondément tourmenté (...) et (...) je ne vous cache pas qu'il n'y a pas à sortir du dilemme que j'ai posé, on y est complètement enfermé. Ce dilemme est le suivant si je reviens au postulat d'objectivité. Si l'on accepte cet axiome, qui se révèle très efficace, comme la science moderne le prouve, pour construire la connaissance, on admet aussi que l'univers est sans objet et objectif. (...) . Tout le problème est de savoir s'il est possible de construire un système, et là je me place uniquement du point de vue de la logique, où il n'y aurait plus cette imperméabilité totale entre l'éthique et la connaissance objective, celle reconnue comme telle, celle qui ne viole pas le postulat d'objectivité. (...) Ce que j'ai voulu proposer est ceci: dans un monde où les systèmes d'éthique traditionnelle sont ruinés, dans la mesure où personne n'y croit, pas même ceux qui y adhèrent encore, le seul système éthique acceptable et qui pourrait ne pas être en contradiction avec la construction d'une connaissance et d'une technologie scientifiques, est un système de valeurs franchement et ouvertement existentiel, se fondant sur le postulat initial que l'on sait être un postulat mais que l'on a choisi pour tel. C'est la définition de ce que j'ai appelé "l'éthique de la connaissance""[11].

Thus, at the heart of his thought one finds the postulate of objectivity. Postulate, therefore metaphysical, from which every scientist places his own quest in the sociocultural context of his time, and which allows him to approach the subject by objectiving reality. Curiously, this function led Monod to perceive the position of Man in the Universe as unique, and subject to an irremediable solitude, interpreted as the sign of an utter originality, prooving that life is the result of pure chance, without any determinism. This is why he marvelled at the strange features of living organisms, features that he reduced to esthetical "universals": what is true for E.coli must be true for the elephant[2]. In turn these universals must impose their rule, and genetical constraints are absolute: the pathway for innovation is restricted, and one may fear that Man could evolve towards decline, because of the progresses of medicine[12]... One is therefore far from the revolutionary biology of recent years, during which genomes appeared as "fluid", while many universals have been questioned!

In Jacques Monod's words living organisms are defined by the fact that they go after a goal, and a major part of his argument is to define the conditions required for building materially such goals. This is the reason for proposing the interaction of chance, perceived as essential, and necessity. Chance is the motor that permits constitution of a goal, and this is related to the familiar, but to my mind erroneous, interpretation of the second law of thermodynamics, suggesting that every material system would spontaneously evolve towards disorder. Is it really necessary? And can't one go without both chance and goals?

It seems to me that a reappraisal of the second law of thermodynamics, looking for an interpretation more consistent with the physical laws underlying material living systems, can solve the problem. Entropy and disorder: if one needs two words for a single concept, this suggests that ideology is present at least in one among the two. Thermodynamics was created at the start of the industrial era, it was meant to be the science of work. Work represents the usable form of energy, which implies that there exists a corrupt form, and a process a completely unprobable creation: the necessity for evolving leads to a statistical mechanics standpoint, the philosophy of work was shifted towards a philosophy of order. A social analogy was immediately apparent (and still is nowadays where one can find (sic) thermodynamical models of economy or all kinds of social phenomena!) and it was parallel to a reflection on mankind's degeneration, starting during the XIXth century (see Gobineau for instance) and pursued in well known circumstances during the XXth. The analogy between entropy and disorder is therefore far from being harmless, because of the cultural connotations it conveys. Thus, Life would be a permanent strive against corruption (genetical in particular) and the "struggle for life" would correspond to a struggle against an increase of entropy... In fact, entropy is but one of the measures of the tendency, for a material system, to evolve (towards equilibrium); it reflects the aptitude for exploration of all accessible energy states (including space) for all components of the system. Such exploration can lead to orderly or disorderly structures (but always more stable than the original state, i.e. more probable). In the case of living systems evolution, which depends on entropy increase, leads to exploration of a large number of potentialities, including those that are, as stated above, structured according to the abstract laws which are specific of life (coding for instance). Some among such systems (i.e. material sets constituted of a structure and a dynamic organization) are locally (in time and space) stable; they derive from selective constraints (selective stabilization) and make living systems as observed. Finally, the inescapable increase of entropy forces evolution as soon as environmental conditions are changed (which is inevitable because living systems are growing systems). This is reflected both in the structure of phylogeny: it is a tree structure, and in the very small number of material objects that are at the basis of life. We are, as a matter of fact, very far from chance.

Contrary to what is usually thought, indeed, the actual number of molecular species derived from living organisms is very limited, as compared to what would be produced by chance combination: there are certainly less than 10^{15} different protein types; this looks large but is nothing when compared to the random possibilities for a protein of 100 amino acids (20^{100}). Phylogenic linkage still reduces the choice inside related families, which implies that the proteins present in a species have specific features (not yet unraveled!). In particular one can think that there exists a system for scavenging erroneously translated proteins (this will also scavenge foreign proteins): the "self" proteins would be protected simply because they have coevolved with the scavenging system. This would imply that each species possesses a "protein landscape" specific to it, thus adding to the constraints.

Rather than universals (apart from the abstract biological laws), as Jacques Monod expected, we shall be confronted to entire families of related objects and discover constraints at the level of RNA, proteins and DNA. We are still very near to the origin of life. It becomes therefore vain to see life as a completely unprobable creation: the necessity for evolving leads to a systematic exploration of reality, everywhere in the Universe. Only the specific way is unique, as well as individual systems: it becomes even more fascinating to try understand the underlying laws.

REFERENCES

1. Monod J (1949) In: Unités biologique douées de continuité génétique. CNRS, Paris pp 181-199
2. Monod J & Jacob F (1961) Cold Spring Harb Symp Quant Biol 26:389-399
3. Monod J, Wyman J & Changeux JP (1965) J Mol Biol 12:88-118
4. Danchin A (1979) Rev Ques Sci 150:151-164
5. Danchin A (1979) Rev Ques Sci 150:323-337
6. Diels H (1901) Die Fragmente der Vorsokratiker. Weidmannsche Buchhandlung
7. Guthrie WKC (1962 rep 1978) A history of Greek philosophy. Cambridge University Press Cambridge
8. Ullmann A (1979) In: Lwoff A & Ullmann A (eds) Origins of molecular biology. Academic Press, New York pp 165-170
9. Danchin A (1983) L'oeuf et la poule. Fayard, Paris
10. Cairns-Smith (1983) Genetic takeover. Cambridge University Press, Cambridge
11. Monod J (1977) Prospective et Santé 1:11-22
12. Monod (1970) Le hasard et la nécessité. Le Seuil, Paris