



Geometries of the Living

Alain Prochiantz

Collège de France
Inaugural Lectures



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Geometries of the Living

Inaugural Lecture delivered on Thursday 4 October 2007

Alain Prochiantz

Translator: Liz Libbrecht

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My idea of a theory in biology is quite different from the theoretical biology that is expressed as equations of observed or photographed phenomena. I have a simpler, more concrete conception. Not a mathematical description of what is seen, but an evolving model, a tool developed through *bricolage*, with mathematics perhaps, but also natural language: one that serves above all to understand the unseen; to guess, beneath the visible, the invisible dimensions of life forms, the underlying “logic”.

ALAIN PROCHIANTZ

Alain Prochiantz, born in 1948, is a neurobiologist. He is the Director of the Center for Interdisciplinary Research in Biology at the Collège de France, and author of *Stratégies de l'embryon* (1987), *Claude Bernard: la révolution physiologique* (1990), *La Biologie dans le boudoir* (1995), *Les Anatomies de la pensée* (1997), *Machine-esprit* (2001), *Qu'est-ce que le vivant?* (2012) and, with Jean-François Peyret, of *La Génisse et le pythagoricien* (2002) and *Les Variations Darwin* (2005). He has held the Chair of Morphogenetic Processes at the Collège de France since 2007, and is the Collège de France Administrator since 2015.

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Alain Prochiantz

Introduction

Pierre Corvol

Translation : Liz Libbrecht

- 1 Dear Alain Prochiantz,
- 2 For many years you have been studying the creation and evolution of forms, a central theme in biology. Your curiosity in this field was stimulated by a completely unexpected observation that you made when, as a young student of the École normale supérieure, you were working in Jacques Glowinski's laboratory at the Collège de France. You noticed that an exchange of information took place between two cell types concerning their position and that it determined the form of one of these categories of cells, in the case in point, the neurons. A seminal observation can feed an entire research field but it requires intelligence, courage and persistence, none of which you have lacked to support assumptions which initially went against established theories. Your results were disturbing in more ways than one: proteins supposed to reside in the nucleus, capable of being exported and of crossing through cell membranes and inducing a new type of signalling. In just under twenty years, you have gradually solved many of the questions raised by that early research: proteins and peptides are indeed capable of crossing through cell membranes. And this system of signalling serves in the navigation and positioning of neurons during the development of the nervous system. Your research at the École normale supérieure – and tomorrow at the Collège de France – is now internationally recognized and opens up new perspectives. Protein and peptide vectors are used to introduce various components into cells. You show how this information system is involved in nerve cells' navigation and in the preservation of memory during evolution, and finally its possible involvement in adult morphogenesis, and thus in physiology.
- 3 There is another Alain Prochiantz known for his books and theatrical projects. Actually, it is the same Alain Prochiantz, as this literary activity that you call “nocturnal science” is something that you see as consubstantial to your work as a researcher. You believe that making science part of culture is essential to the democratization of scientific knowledge. We are very pleased to welcome the original researcher that you are, with your concern to communicate with the general public. You are putting morphogenetic processes – which is the title of your Chair – back into an evolutionary perspective right at a time

when the issue of evolution is philosophically – and even, might I say, politically – sensitive, in fact highly sensitive in certain countries.

AUTHORS

PIERRE CORVOL

Administrator of the Collège de France

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Alain Prochiantz

Translation : Liz Libbrecht

EDITOR'S NOTE

This text has been translated by Liz Libbrecht in collaboration with Céline Surprenant (Collège de France).

- 1 Mr Administrator,
Professors,
My dear colleagues,
My Friends,
- 2 In 1984, in Jacques Glowinski's laboratory, we witnessed the fact that the form and polarity of cerebral neurons cultivated in contact with non-neuronal cells – astrocytes – vary according to the topological origin of these two cell populations. We could have chosen to study astrocyte heterogeneity, which was a novel idea, but I was mainly struck by the link between form and position that this observation suggested. Having attended François Jacob's lectures, as many of us had, I knew of the existence of mutations associating a genetic algorithm to a position, and a position to a form, that of an organ. In such mutants, embryonic cells wrongly interpret their position and trigger inappropriate morphogenetic programmes. In flies, for example, antennae can be replaced by legs, or wings by eyes.
- 3 Three years and a trip to New York later, I decided to study the role of homeogenes in the coding of neuron shape. These genes encode transcription factors, homeoproteins, which all bind DNA through a conserved polypeptide structure: the homeodomain. In order to test the role of homeoproteins in neuronal morphogenesis, we decided to inject a homeodomain into neurons and thus to drive the endogenous homeoproteins away from their DNA-binding sites. The assumption that this would provoke a change of form proved to hold true. Yet in a control experiment, we noticed that adding the

homeodomain outside of the neurons induced the same changes. Instead of immediately concluding to an artefact, we marked the homeodomain with a fluorescent probe and were surprised to see it cross through the membranes and invade the cytoplasm and the nucleus of live cells. Soon we generalized this observation to full-length homeoproteins. Thank you Antoine Triller for having let us use your Pasteurian confocal microscope, late in the evening with Henri Korn's vague complicity, thus allowing us to observe zebrafishes swimming in the fluorescent homeodomain internalized by their nerve cells. Science is also an affair of friendship.

- 4 The key concept that arose from these first experiments, and that we have been studying since 1988, is simple. Two cells exchanging transcription factors of this family thereby exchange information on their respective positions, and respond to that information through a change in the expression of various morphogenesis effectors. Thus, while homeoproteins are indeed transcription factors acting in the nucleus, they are also real morphogens: messenger proteins capable of gaining access to the extra-cellular milieu to penetrate neighbouring cells and modify many of their characteristics, including their form. At the time, this idea challenged a number of dogmas.
- 5 A first dogma was that transcription factors work within the nucleus, do not leave cells, and do not enter them either: they are not equipped for that. A second one was that membranes are barriers impermeable to hydrophilic agents. Hence, the idea that physiological mechanisms can destabilize membranes to the extent of making them permeable to heavy molecular-weight proteins was inconceivable. Finally, homeogenes were believed to regulate the form of organs, not of that of cells. Yet, what we observed implied that the same genes, and therefore probably similar mechanisms, act at both the cellular and pluricellular levels of morphogenesis.
- 6 These objections persisted for a long time. Alain Joliot's research team and my own demonstrated the secretion and internalization of these factors, identified the sequences responsible for these properties, and furthered our understanding of the mechanisms involved. As a result, the field of peptide vectors able to travel across membranes – opened in close collaboration with the team of Gérard Chassaing, a chemist colleague and a friend – is now flourishing. In parallel, the myth of impervious membranes has lost its credential, and the idea that they are unstable structures no longer surprises anyone. Finally, who remembers that the idea of homeogenes as regulators of cell shape ever was an issue?
- 7 Yet, the idea that a transcription factor can be a morphogen or, more broadly, a factor of intercellular communication, is still questioned here and there. Let us be clear: even if the work is far from complete, that this mode of signalling participates in crucial stages of development is a sound assumption, based on experimentally-proven facts. These stages, all of which have been studied in the visual system, include the formation of territories within the neuroepithelium, the guidance of axons during the establishment of neuronal networks, and the regulation of the critical period for binocular vision. I will add that, in many of these phenomena, homeoproteins are regulators not only of gene transcription to generate messenger RNAs, but also of the translation of these messengers into proteins, a property that plays an important role in homeoprotein signal transduction activity.
- 8 Briefly getting back to the way in which our hypothesis was received, I would like to point out that, from the outset, several colleagues deemed it to be interesting enough to give it a chance. I would therefore like to thank Spyros Artavanis, Denis Duboule, Antony

Durston, Walter Gehring, Christopher Henderson, Eric Kandel, Daniel Louvard and Pasko Rakic, among others. Each in his own way has enabled us to carry on, not so much out of friendship (although that sometimes came later), or loyalty, but rather in the name of a certain conception of science.

- 9 With hindsight, I must however admit that, lacking the necessary background in developmental biology, we were naively enthusiastic and partially blind to the provocative nature of our propositions. Our innocence was fortunate, even if we sowed some confusion in the minds of those wary of the assumption's novelty. Their attitude was shared by most publishers of the leading scientific journals which forge, or rather follow, opinion. I would like to thank them too: by forcing us to multiply our proofs, they too helped us to develop this project. They also opened our eyes to the social structure of the scientific community.
- 10 So why did we stick to it, and how did we do so? The latter point is important, as research is carried out in the real world; it requires institutional and financial support. We therefore jealously guarded our administrative and financial independence. To keep going, I preferred not to have to put myself under the protection of princes who might have dropped us along the way, no doubt for our own good. And so we set out in search of funding. But the crucial issue was how to finance, from 1990, a project that was not formally acknowledged until 2002.
- 11 From 1990 to 2001 we developed programmes on penetrating peptides, Alzheimer's disease, Parkinson's disease, vesicular release, neuronal polarity, and the extracellular matrix. These were all fascinating subjects that took up ninety percent of our energy and secured the careers of almost all the students, post-docs and researchers who came to work with me. Diverting a small portion of our funding from its stated aim, with a few colleagues, primarily Alain Joliot, Brigitte Lesaffre, Alain Trembleau and Michel Volovitch – all established and out of danger –, we continued to work on our hypothesis. Until 2002, the other members of the team participated in this project only indirectly, never upfront. The entire laboratory has joined in since, with the help of our colleagues abroad: William Harris, Takao Hensch, Christine Holt, Andrea Wiezenmann, Wolfgang Wurst, and their colleagues. I wish to extend my gratitude to all of them, without forgetting Isabelle Brunet, a brave student who performed a series of decisive experiments, often in difficult circumstances.
- 12 The question of why naturally arises. Why did we persist, beyond what was reasonable? Why did we pursue an idea that many saw as fanciful? Even though we were not sure of being right, some degree of certainty, a minimum of conviction, was needed. Where did that conviction come from? Actually, I have no idea. It was probably partially based on a rational analysis, but only partially. I therefore have to offer the word *intuition* here, and accept its irrational component. Even if this undermines a belief that is widely held among biologists, I would say that gaining knowledge often occurs in a grey area where intuition conflicts with pure logic, or rather paves the way for it; for logic must always prevail, at least in science.
- 13 As regards rational analysis, I tried to put the parts together. First, facts are facts, and we have no right to ignore them once they have been established. Following Walter Gehring's advice, we multiplied controls by producing mutated homeodomains. It appeared that certain mutations blocked the internalization of the homeodomain, others not; and then that, among the internalized variants, only those that bind DNA had a morphogenetic activity. It was therefore not a common artefact. In these conditions, and despite the

risks, not carrying on would have run counter to the idea of science that I shared – and this was decisive – with Michel Volovitch and Alain Joliot, stemming from the former’s ideological commitment, and the latter’s family tradition. For all three of us, it would have been immoral to stop there.

- 14 The second incentive to carry on was theoretical. It seemed to me that this mechanism of direct exchange of information on position corresponded logically to the convergence between genetics, developmental biology, and evolutionism that we saw unfold with the discovery of developmental genes. For this to make sense, we must remember the context of the eighties.
- 15 First, cellular biology: in embryology, at the time, cell biologists still invoked the cellular cybernetics paradigm, which saw the cell as a closed space, or almost. Cell theory was essentially a theory of information, derived from the notion of entropy and thus from the second principle of thermodynamics. Genetic activity – judging from the work of Léon Brillouin, Jacques Monod and François Jacob – was one of Maxwell’s demons which maintained order in a cell that did not communicate with the outside – or to an extent that was irrelevant. That is why development was essentially thought of from the angle of cellular differentiation: how do cells differentiate themselves into neurons, fibroblasts, or any other cell type, by playing on the wide range of expressed genes? The question of how these cells actually assembled, whether into a hand or a foot, an antenna or a leg, following a real code of cellular interactions, was almost never studied by cell specialists of the time.
- 16 This question of the form of organs was however raised at three levels. The genetic level, first, was based on formerly observed homeotic mutations such as the transformation in the fly of antennae into legs, or of eyes into wings. These mutations led Edward Lewis to propose a model of positional coding of appendices in arthropods, and resulted in the discovery of homeotic genes that mark the position of a cell and play a crucial role in the coding of cellular interactions, differentiation, and morphogenesis in all animals. With the first genetic manipulations it was possible to identify the main features of the role of these genes, first in invertebrates and soon afterwards in vertebrates.
- 17 The mechanisms at play remained nevertheless unknown and secondary compared to the observation of anatomic modifications triggered by directed mutations. With few exceptions, exploring the cellular and molecular details was not part of geneticists’ agendas. What was however immediately sensed was that knowledge of the genes that established the plan of the organism and transmitted it across generations was leading to new speculation on evolution, and that modifications of the structure of these genes and variations in the duration or sites of their expression could spawn new animal and plant forms. The link between development and evolution – foreseen by many naturalists and embryologists, especially Ernst Haeckel – found a material grounding here, and thus a field of experimentation.
- 18 Experimental embryology was the second approach to the question of the form of organs. Born before genetics in the nineteenth century, and pursued in its almost perfect ignorance, it afforded an understanding of the role of tissue and molecular environment in cell differentiation and morphogenesis. It also established several seminal concepts, including those of induction systems and of morphogenetic fields and gradients. Great names such as Hans Spemann, Viktor Hamburger and Rita Lévi-Montalcini, of course, mark the history of this discipline. Its late merging with developmental genetics soon

proved decisive, to both partners' benefit. In France the work of Nicole Le Douarin's team illustrates this approach at the highest level.

- 19 Finally, the third approach was mathematical. After a long period of purgatory, it is once again arousing developmental biologists' interest. Its contribution to informing several generations of embryologists' reflection, through the theorization of the concepts of morphogenetic field and gradient, is often overlooked. I will pause mainly on Alan Turing and Lewis Wolpert, provisionally leaving aside many significant theoreticians, especially Conrad Hal Waddington whose ideas of channels, evolvability and robustness are currently making a powerful comeback.
- 20 Alan Turing, the mathematician and philosopher also famous for his tragic biography, endowed the collective imaginary with the principle of the "computer brain". Although it played an important and positive role, the notion became problematic when this model was transformed into a dogmatic representation of the brain as a "logical machine". We know how long it took for the ideas of cell renewal and morphological plasticity in the nervous system to be accepted. The conception of the brain as a computer was obviously appealing from the perspective of control over what happens "up there". But it was not convincing enough. Cells had already ceased to be thermodynamic fortresses; this thing at the forefront of our body was clearly alive, it moved and breathed. Worse still, this dangerous organ could have a mind of its own that partly defied our consciousness; it could know before us, and better than us, what we thought or desired. Anxiety under a skull! It is not because you wish to be a machine that you are one.
- 21 Yet it was his epigones who were responsible for this creationist conception, rather than Turing himself. In an article published in 1950, he put forward the idea of a developing brain, that of a child, as the model of future machines.¹ The ensuing interest in biological morphogenesis, two years before his suicide, materialized in Turing's still famous article "The Chemical Basis of Morphogenesis"², in which he defined morphogens as "evocators of form" a somewhat vague term borrowed from Waddington. Turing's problem was with creating patterns, such as that of the leopard's spots, or boundaries, with two morphogens A and B expressed at the same stochastic levels in a morphogenetic field.
- 22 To that end, he laid down the following conditions: A and B induce their own synthesis, reciprocally inhibit each other, and diffuse in a field whose cells have no membranes. He deduced that beyond a concentration differential between A and B, born from a diffusion differential, the properties of mutual self-activation and inhibition lead to the formation of borders between purely A and purely B territories. Turing made two observations: the first was that it would be ideal if genes themselves could diffuse, but that we know they cannot; and the second, that diffusion requires the elimination of cellular membranes, otherwise the problem is complicated.
- 23 Reading this article I was struck by the correspondence between his model and our hypothesis. Homeoproteins' "*wall-crossing*" properties do indeed remove, so to speak, the membranes. Moreover, when the boundaries of the different territories and parts of the brain are being established, the homeoproteins expressed on each boundary side in the neuro-epithelium are most often, if not always, self-activating and mutually inhibiting. The genes obviously do not diffuse; but if the diffusion of the product activates the transcription of its own gene, then everything happens "as if" the gene diffused.
- 24 I was especially struck by this convergence, as we had known for a long time, since the work of Christiane Nüsslein-Volhard³, that the homeoprotein of the bicoid family,

expressed in a gradient in the drosophila embryo, is a diffusing morphogen that regulates both transcription and – significantly – translation. But this was not a problem because, in the embryo at the syncytial stage, the nuclei are not separated by membranes; there are no membranes. Our assumption could be reformulated as follows: because homeoproteins cross through membranes, the neuro-epithelium is a functional syncytium for homeoproteins.

- 25 Lewis Wolpert became well known in 1969 for an article published in the *Journal of Theoretical Biology*⁴, in which he developed his model known as the “French flag problem”. Wolpert explained how a morphogen, synthesized by a “source” and degraded by a “sink”, forms a gradient through a pluricellular field. Adding threshold effects to this gradient expression, we can understand that between concentrations of 100 and 66, the traversed cells express a blue, and then white and red characters, respectively, between the values of 66 and 33, then 33 and 0. Thus ensues the French flag problem, which nevertheless encounters the difficulty that, in the nervous system, and probably elsewhere as well, diffusion is very limited. This was a difficulty that we endeavoured to solve with the experimental model formulated by David Holcman.⁵
- 26 If followed by the induction of its own synthesis in the receiving cell, the protein’s crossing gradually marks out a territory as if the protein were diffusing, whereas it is simply “infectious” – the infection is blocked by another protein inhibiting its production. This is consistent with Turing’s prediction and with many experiments demonstrating that a boundary forms where two homeoproteins meet. If the effectiveness of the infection varies over time, a gradient of expression will then form, reflected at the surface by the exportation of the protein and its maintenance in the extra-cellular matrix by way of bonding to complex sugars. This mechanism enables a cell to express its position at its surface, and then allows for other cells to interpret that position as they migrate or differentiate. I will not go into this further here. Anyone who would like to know more may refer to the published work and/or attend the lectures this year on the nature and mode of action of morphogens.
- 27 I would now like to discuss the insertion of our hypothesis in the 1980s landscape. The intercellular movement of homeoproteins enables two cells to compare their positions. This transfer of positional information by proteins that are morphogens, both in Turing’s sense and in the sense that they regulate the expression of developmental programmes, provided a possible answer to the question of the link between cell position and the initiation of a differentiation programme. The answer differed from those proposed until then, in so far as it is the same family of molecules that acts as morphogens and as transcription or even translation factors. Hence, it is an extremely parsimonious mechanism, even if this initial recognition is followed by the recruitment of other signals regulating the robustness of the process. Remember that even if robustness is a crucial feature of development, too much robustness can impede evolvability or even the physiological plasticity that may accompany signal transduction.
- 28 From an evolutionary perspective, this mechanism preceded classical modes of signalling. Homeoproteins exist in plants and animals, two realms which use very different signalling systems. By pursuing this idea, Alain Joliot and his colleagues showed that the mechanisms of intercellular transfer of homeoproteins between the two realms of nature are maintained⁶. This evolutionary dimension is found in the fact that this direct morphogenetic function of homeoproteins offers original pathways of reflection on the evolution of morphogenetic fields. It is also a practical tool in experimental evolution.

Need I emphasize what a revolution the recent intrusion of evolution into the field of the experimental sciences has been?

- 29 But we now need to move one step up to propose that through this merging between genetics, development and evolution, triggered by the discovery of developmental genes, a theory of life forms is now asserting itself. It is independent of theories imported from other disciplines, especially the theory of information which, via cybernetics, structured the major breakthroughs in biology in the immediate post-WWII period. This new theory accomplishes the Bernardian prediction that a scientific zoology would be capable of scientifically producing new biological forms “like the chemist produces bodies which are potentially there but did not exist in the natural state of things”. This possibility of producing biological technological objects through the reasoned manipulation of genomes is of crucial importance. Through these new tools, spawned by concepts specific to biology, we witness the convergence, in facts – those that move in animal houses or grow in fermenters and fields –, of the reproduction, the development and the evolution of organic forms, the three disciplines that are at the heart of the specific nature of life forms.
- 30 Without forgetting physiology, given that the genetics of development, of that which is continued in adults, and which is Claude Bernard’s silent embryogenesis, is reviving the physiological concept of *milieu intérieur* and of regulation. In recent years, primarily owing to functional genomics, it has appeared that genes work in networks and that many elements of regulation – most of the genome in many species – maintain this polygenic activity within windows compatible with physiology. This is a contemporary view of the *milieu intérieur* and of the constraint that it imposes to maintain living systems within precise limits of variation, and to channel them from the point of view of both their physiology and their development or evolution. It is not possible to create just any organic form nor to leave an organic form to drift towards just any physiological absurdity. That is the role of genetic networks, within which development genes play the important role of monitoring this regulation, even in adults. Let us revert to our hypothesis of “messenger” proteins and take stock of the neurobiological and endocrinal dimension of their diffusion. In short, through the mechanism that we propose, the genetic network with intracellular activity could shift towards a supracellular level engaging the unity of the organism.
- 31 To revert to this one last time, we can say that the highly surprising properties of these transcription factors must be interpreted within the framework of this theoretical crystallization. This means that, over and above the remaining grey areas, they play their part in its practical modalities, for example by proposing a plausible mechanism for the establishment and evolution of cerebral territories, compatible with experimental data and developmental theories. They also enrich, still in practical terms, the wide range of mechanisms of epigenetic individuation, especially during the formation of neuronal circuits, and the definition of the critical period, as we have shown with the German, British and Japanese colleagues cited above.
- 32 This proposition may seem daring. But I cannot see why, in the name of what anti-intellectual puritanism with trendy worker-power overtones, biologists should deprive themselves of contributing to the theoretical development of their discipline. Why should they restrict themselves to using technological progress to make increasingly precise or colourful observations whose beauty prevails and creates the illusion of understanding? Like everyone, I love these novelties; yet it seems contrary to experience that one can see

something other than that which can be conceptualized theoretically. Briefly, demonstration must often precede display; it is when “things do not look right” that they become interesting. But this requires knowing how not to reject the unexpected. Even if there is an element of truth in the old saying “to see is to understand”, the fact remains that “to stare wide-eyed is not to see”.

- 33 It is true that my idea of a theory in biology is rather distant from theoretical biology which puts observed or photographed phenomena into equations. I understand it in simpler, more concrete terms: not as the mathematical description of what is seen, but as an evolving model, a tool that has been adapted, with mathematics perhaps, but also natural language. Above all, theory serves to understand what we cannot see, to guess, beneath the visible, the invisible of the living, its underlying “logic”, with nothing indicating that it pertains to mathematical logic. In fact, my intuition is that the mathematics of the living – which remains to be invented – would more likely lie with geometry.
- 34 I wish to point out immediately that the existence of an independent biology – master of its theory and capable of producing technical objects based on this theory, mostly genetically modified organisms – does not mean that its interactions with other disciplines are obsolete on either a theoretical or a practical level, that of instrumentation for instance. But for physiologists, these interactions must be carried out from the point of view of physiology. By thus asserting this independence, biology has no reason to see itself as a field of application of concepts articulated in other disciplinary fields. Conversely, with this self-confidence, biology has no reason to pretend to be a hegemonic meta-theory which would be inclined to legislate outside its field of validity, particularly in the humanities.
- 35 To avoid any possible ambiguity, may I stress that I resolutely support a naturalization of the mind, understood as the study of the cerebral mechanisms (and of the way in which they develop and have evolved) necessary for exercising a human specificity that is reflected in our social organizations and cultural practices. I here focus on *sapiens* only, not because I do not see us as animals, but because the changes that have taken place in the *Homo* species have extracted us, so to speak, from nature. I will take as evidence the exceptionally high ratio, in *sapiens*, of brain volume to body mass. Compared to chimpanzees, we have an excess 900cm³ of brain. Out of 1400cm³, that is not insignificant. And size is not everything. The boundaries between territories have shifted to the benefit of an unprecedented development of cognitive areas, including those of language. So, we do indeed have 98% of genetic proximity with chimpanzees and 80% with mice. But these are only quantitative estimations that ignore qualitative differences, in particular those attached to the regulatory sequences that determine the place and the duration of gene expression, two variables which are obviously decisive in morphological and psychological evolution. This is why I here take the liberty of excluding other animals, including chimpanzees, even if I have no contempt whatsoever for these distant cousins and their cultural practices: cleaning potatoes and using a twig to eat termites.
- 36 To come back to humans and the role of biology for studying them, it is not because we share the study of humans as research objects with other disciplinary communities that we necessarily propound identical theories, or group theories and independent disciplinary fields under the iron rule of a single discipline, be it neurobiology. For a scientific object is not only the material object, but rather both the material object and the theory that serves to conceive of it. It is not because we are made of atoms that the

biologist is *ipso facto* a physicist, or a physicist a biologist. Likewise, a biologist who studies the human brain is not, by right, metamorphosed into an anthropologist or a philosopher; that would require him or her to appropriate the theories of these disciplines, which is indeed possible. This does not however mean that the effects of new knowledge do not resonate beyond disciplinary boundaries, to the point of sometimes shifting them. Theories are not dogmas; they evolve.

- 37 It is inevitable that the terms so often used, joining the prefix neuro- to a variable suffix – philosophy, economics, ethics, aesthetics, etc. –, sometimes seem to imply that these disciplines, by the very fact of “scientific and technical progress” (as they used to say in the USSR) become the fields of application of the neurosciences. Of course no one claims this openly, and everyone will agree that, when Philippe Descola expressed himself in his most recent book *Par-delà nature et culture*⁷ on the proximity between humans and animals, it had nothing to do with a biological distance which we are able to assess by comparing both the structure and the expression of their genomes. Even though the fact of bringing nature into a relationship of anthropological connectedness with *sapiens* – “this panther is my sister” – is necessarily the work of the human brain.
- 38 While many philosophers strive to take into account what we now know, albeit very incompletely, about the brain’s functioning, others, sometimes amongst the most renowned ones, are studying categories of thinking independently of any organic reference. The same thing can be argued with respect to all disciplines, from the supposedly softest ones to the so-called hardest ones, including mathematics. I cannot see in the name of what naive materialism anyone would question that right. Hence there is no doubt that, when a great physiologist draws on his work to declare that Descartes was wrong and Spinoza was right, it is essentially jokingly that he does so.
- 39 But, you will say, a neurobiologist, even one who is more “morphogeneticist” than “neuroscientist”, cannot escape this question of the relationship between the mind and its substratum, nor cleverly side-step it. I agree, and that is why I believe that we have to remain very attentive to the eminently polysemic nature of the word *thinking*. If a biologist wants to express himself rightfully on thinking, he has to do so from his own discipline and, if he is a materialist, without resorting to a dualistic position. In short, we need a biological definition of thinking which is distinguished from the question of its localization, otherwise dualism, which has gone out at the door, will come back in through the window.
- 40 I am therefore going to venture such a definition: “thinking is the adaptive relationship between life forms and their environment”. And, in the term *life forms*, I include individuals and species. Let us consider for a moment the consequences of this definition. The first is that a relationship is not a substance; which means that it has no base. It follows that Cabanis’ fine expression, “the brain secretes thought like the liver secretes bile”, though useful in its time, is no longer valid as a materialist standard. A second consequence is that the term *thinking*, in its biological definition, applies to all organisms and species. And since this is a matter of evolution, selection will take place at two levels, that of the individual, as Charles Darwin taught us, and that of species, as Stephen J. Gould proposes in *The Structure of Evolutionary Theory*.⁸ We could then say that bacteria and plants think – as do all living beings that reproduce, develop and evolve. This relationship is indeed rich to some extent, and no one can doubt that it is richer in *sapiens* than in any other species, due to its exceptional brain. But thinking thus defined needs a God no more than it does a structure in which to embody itself, whether a brain or a

genome. Neither transcendence nor immanence, we think that we are perceiving the imposing imprisoned silhouette of the great philosopher of nature, the one who dared say “neither God, nor nature”, a veritable “precipice in the middle of the salon”, that of the Enlightenment philosophers, to use Annie Le Brun’s expression.

- 41 If I now compare bacteria and humans, to consider extremes only, I see that the adaptive strategies obviously differ, since bacteria adapt primarily through a genetic mechanism of clone selection, whereas the human brain is an extraordinary instrument of adaptation which plays on two interdependent levels, that of culture and that of individuation. The properties of the nervous system – primarily its physiological and morphological adaptability which remains at work throughout an individual’s life, as “silent embryogenesis” – do indeed allow for an individual evolution. This individuation finds its extreme expression in the human brain, not only in its natural brain but also (especially?) in its brain extended through culture and techniques. We should bear in mind that, since its origins, *sapiens* has survived only by virtue of its ability to develop and to use tools. Today the computer extends its brain just as the bicycle extended its legs. And the invention of reflective consciousness, above all, enables the individual to think of him- or herself as coherent, despite having a brain that stops evolving only with death: we “never bathe in the same man twice”, even if culture – techniques being one of its fully-fledged facets – affords an extension of the historical adaptation of the species way beyond an individual’s death.
- 42 The last consequence of our definition is that it leaves room for distinct definitions provided by various disciplinary fields: philosophy, anthropology, literature, in short, all the paths of knowledge that shed their specific light on the human phenomenon. Which in no way means that there are no relations between these fields, or that these relations do not also evolve, just as our theories evolve – otherwise they would become rigid dogmas. Briefly, this definition respects the diversity of fields of knowledge. Interdisciplinarity no longer leaves open hegemonic temptations, irrespective of their origins, for it is not only biology that can give in to hegemonic temptations. And this will be my last development on this theme, for just as defending one language means defending all languages, so too defending the independence of a field of knowledge means defending that of all fields of knowledge, biology included.
- 43 This defence of biology against outside incursions is a quintessentially Bernardian theme. The incursion of physics first, which the great physiologist refuted by inventing the *milieu intérieur* – as Canguilhem taught us, the equivalent in physiology of the ether of post-Newtonian physicists. Life is no longer “all the forces opposing death” – that is, Bichat’s purely thermodynamic conception, inherited from Carnot and Lavoisier – but a dual movement of creation and destruction of organic forms, a ceaseless creation of forms, to use Darwin’s expression. Next, it is a philosophical incursion, that we see in *An Introduction to the Study of Experimental Medicine*⁹, where we find the constant refusal to be dragged into the Comtian classification of scientific disciplines. Biology – and beyond it, any scientific discipline – cannot agree to philosophies controlling it, under the pretext that they declare themselves to be scientific. That is their business.
- 44 I have no hostility whatsoever towards any discipline or towards inter-disciplinarity. Earlier in this lecture I mentioned the close ties that my team has fostered with chemists (Gérard Chassaing’s team), mathematicians (David Holcman’s team) and physicists of soft matter (through collaborations with the teams of the Physics Department of the École normale supérieure: those of David Bensimon and Vincent Croquette, Maxime Dahan and

Éric Perez). As far as we are concerned, the conceptual and technical assistance that these ties have afforded us has served to answer questions of a physiological nature. The same applies, reciprocally, to our colleagues who have often used our models to study questions concerning their own discipline. This does not mean that the boundaries have not shifted or quivered – sciences are living objects – but that everyone has derived benefits for their own field, which is the condition of a successful collaboration. Thus we are far away from those large, supposedly multidisciplinary institutions in which each discipline is organized as a fortress primarily concerned with knowing what the neighbours receive: solidarity resembling that of leeks in a field, except that leeks are not in the habit of devouring one another.

- 45 Apart from these collaborations, which are usually mainly of a technical nature even if theories are sometimes modified as a result, another space exists in which disciplines come into contact: that of musing. I think I have already pointed out that the practical conditions of scientific research leave little time for activities other than the rational, preferably new, production of knowledge. Reading the great authors of the past, some of whom I have cited above, venturing into the field of the history of science or of philosophy, even of literature, or collaborating with theatre directors like Jean-François Peyret, are activities often perceived as time taken away from serious scientific work. Worse still, it can appear to be a sign of weakness or superficiality, a fanciful way of continuing to exist when science escapes us. We are then rapidly relegated to the category of media scientist, a contemporary variation of the cultured doctor in a bow tie, or seen at all the dinner parties in town. I wish to assert here that these failures to match the image that science likes to convey are, to my mind, scientific activity. I have taken the risk of calling it “nocturnal science”.
- 46 I have been indulging in these nocturnal practices for a long time. This explains my interest in scientific authors who have already passed away, in some cases long ago. Claude Bernard, for example, whose Chair of Experimental Medicine, the most prestigious one for a physiologist, which Pierre Corvol, our Administrator, now holds. Reading this literature has been of valuable help to me in understanding the most specialized questions addressed by biology. If the sciences are defined not only by their research subjects but also (above all?) by their theories, and if these theories, once again, are evolving, it is easy to understand that reading old texts can but enlighten our more advanced research. The idea is not to replace the old with the new, but to hold a friendly conversation with the researchers who raised the questions and made them evolve; or who failed to do so due to obstacles that we must also understand, as they are sometimes still present. Drawing on my personal experience, the concepts of *milieu intérieur* and “silent embryogenesis” have been particularly helpful in tying up development with physiology or pharmacology. When, several years ago, I chose the title “Development *and* Neuropharmacology” – the italics on *and* emphasizing the dialectic relation between these two fields –, it was neither by whim nor by chance.
- 47 Incidentally – or is it incidental? –, this frequentation enables us to enter into the intimacy of human beings and to grasp the difficulties that they encountered, and which affected their lives, in the most prosaic sense. Whether we read Darwin’s correspondence, the letters of Claude Bernard to Madame Raffolovich, or writings on the lives of Lamarck, Turing or Galileo, how can we remain insensitive to these great scientists’ existential difficulties and to their questions, their way of making us know, not their methods for finding – if any did exist we would know –, but their questions such as “how did I find it?”

or even “did I find it”? In short, practising the Masters, right down into their intimacy, not only puts us in our right and modest place, it also enables us to grasp the humanity of science, and the prevalence and importance of the doubt inherent to all human life, especially that of scientists.

- 48 But it can happen that we really do leave the field of science, or of the history of science and scholars, and wander into more literary approaches to explore a no-man’s land where nothing is concluded but where correspondences between different fields of knowledge or culture can emerge. This is the very definition of what I call literature, that chaotic area where thought is in search of itself and invents, reverie or promenade, with words; when logic has not yet been in a position to ensure its ascendancy with the help of objective facts and structured theories. It is here, literature requires, that I wish to risk reflecting on the place of the language of the subject of science in scientific invention.
- 49 Rest assured, I am certainly not trying to advocate French as a scientific language. I am perfectly comfortable with the fact that English is the language of scientific communication and will be so for the foreseeable future, in conferences, seminars, articles and patents alike. I have no taste for the pathetic rear-guard battles being waged here and there. On the other hand, I am convinced that when it comes to imagining, to moving about in the chaotic space I have just mentioned, one’s own language remains literally an invaluable poetic instrument. By “one’s own language” I am referring above all to one’s mother tongue, although I can conceive that one can make a foreign language one’s own, by working on it from the inside, by appropriating it and making it evolve singularly, as rappers do. There are the scientists of the inner city, who are not necessarily any less inventive than those living in the better-off neighbourhoods.
- 50 While this is of course true of such sciences as biology which are conceptualized in natural language, it is perhaps less so for those which have the good fortune of creating their own poetic value through a rich universal and scientific language, as seems to be the case of mathematics or certain branches of physics. But the two can merge into a singular idiom which belongs to both. Through this claim to idiosyncratic bricolage of a language as an “instrument of scientific creation”, I am clearly seeking to defend the right of the subjects of science to exist. I am aware that this goes against a conception of science as the “discourse of truth”, in which the scientist is a sort of contemporary seer, paranoid in the sense of President Schreber. This activity consisting of shaping a language that is also a theoretical tool, even a theoretical bricolage, could perhaps quite simply be called “thinking for oneself”. It is in any case an idea worth exploring.
- 51 Putting the subject back at the centre means acknowledging that this living brain, the victim of continuous accidents, sometimes tried by excesses – or the lack thereof –, devastated by grief or confused by joy, can produce theories to build bridges that hold and rockets that land on the Moon or Mars, even if accidents can happen. How can we not be concerned about the strange power of this object which, to cite Turing, “has the consistency of lukewarm porridge”? This helps to explain why even in science there are believers in the Immaculate Conception. But whether it distresses or delights us – and whether Saint Teresa likes it or not, Bernini’s one of course –, life forms are not immaculate. To convince ourselves, we need only dip our fingers into a brain or even, more simply and pleasantly, go and have a look at *L’Origine du monde* [Gustave Courbet’s painting *The Origin of the World*]. This necessity to refer to the real object does not exclude a stream of research based on the merging of life forms and machines which, by articulating two logics, will facilitate our understanding of the brain’s functioning.

Several paths can thus be opened by these chimaeras. Some are plainly pragmatic, as in the struggle against disabilities. Others are eminently futuristic, when it comes to working on future developments, through what seems to be a form of partial denaturalization of the living.

- 52 The time has come, to conclude, to offer a glimpse of the teaching that will be imparted within the framework of the Chair that has been entrusted to me, and I would like to thank all my new colleagues. I know full well that our research is not complete and that many difficulties lie ahead. We have probably made mistakes, and these mistakes must be tracked down and if possible rectified. Teaching will be a tool for the critical work which must necessarily accompany any research that advances by trial and error. How is this to be done? Unfortunately, we can no longer bring along our rabbit or mouse to perform some experiments with the help of a lab assistant. On the other hand, we can always do thought experiments, and the most immediate way of proceeding is still to dissect scientific articles, including one's own. Dissecting here means explaining, resituating in a historical context, even reinterpreting the results and proposing perspectives; in short, through concrete work, identifying the context of a scientific question. This year we will embark on this exercise, based on articles on morphogens. We will effectively be doing science by trial and error, forgetting neither its diurnal component nor its nocturnal component.
- 53 Alongside this exercise, which is a scientific activity in its own right, one which leaves room for doubt and criticism, including self-criticism, I will illustrate a certain conception of science fit to make it part of culture. It is extraordinary that, while science has wormed its way into the minutest areas of our societies, it still oscillates in the public imaginary between Pantheon and mad scientist, Marie Curie and Mary Shelley's Frankenstein. Refusing the status for science of a poor relative of literary disciplines, from a cultural point of view, and opposing the idea that one has to choose between science and literature because of some destiny claimed to mark our belonging to one world or the other, means working towards the democratic re-appropriation of an object that many feel is foreign, at best, and threatening at worst. One of the facets of the work that I have carried out for over ten years now with Jean-François Peyret consists precisely in poetizing science onstage, and thus desacralizing it, turning it into the object of a culture that also speaks to the contemporary world.
- 54 This collaboration with a stage director, and a renowned one at that, is the latest form of the nocturnal activity that I have never neglected; not because it is an escape, but because I have evidence that it serves me in my everyday scientific preoccupations. I have spoken about Turing and how amazed I was reading his article on morphogens. I had already read the article, but at a time when it was of no use to me. It benefited me, in the scientific circumstances that are known, only when I had to reread it as part of my collaboration with Peyret, who was working on this extraordinary individual at the time. When a scientist is obsessed with a question that fails to find a solution, detours and unpredictable paths sometimes offer perspectives that are conducive to a positive reformulation. Making room for musing is increasing one's chances of finding a way out. Relatively speaking, of course, we know the role that Darwin's reading of Malthus and that his conversations about the law on the poor with his brother Erasmus, during his stays in London, had on the wording of the theory of natural selection.
- 55 But for this we need to restore science's vitality. This is an absolute priority if the doubt that I have often spoken about is not to grip citizens as well, with regard to the value of a

science that presents itself, all too often very seriously, as a discourse of truth. It ought to make us think that, over a hundred years after Darwin, in some of the most technologically advanced countries, *intelligent design* is still contrasted with evolutionary theory, like two contradictory truths and therefore of identical value. No! The creation of the world as related by the Old Testament has no scientific value, whether Captain Fitzroy likes it or not. And the sciences are not religions, and must at all cost refrain from presenting themselves as such. Contrary to religious dogma, scientific theories are not discourses of truth; they are human intellectual constructions, evolving truths, and therefore eminently rectifiable, sometimes dramatically so. And it is this activity of rectification, contrary to peremptory scientism, that makes us scholars, worthy of our small place as explorers of the paths opened by the great masters.

- 56 I am talking here for biology only – which is already a lot, and not all sciences function in the same way –, and will therefore seek to impart teaching that encourages us to appreciate the fragility of knowledge. Living objects, the result of endless evolution, are difficult to analyze. Hence, we need to admit that we risk stumbling at every moment. An inventive biological science has to accept the risk of making mistakes, and to progress it must both doubt – which is easy enough – and overcome its doubt – which is much harder. Coming back to the history of my laboratory, twenty years ago we were not in a position to know whether the path we were heading down was leading to a dead end or not. Do we even know that today?
- 57 But most importantly, I think, is that we did explore this path, compromising our convictions as little as possible, and refusing to apply a principle of intellectual precaution. I like to think that it is this that was recognized. I cannot tell you here and now whether we have reached our goal. In fact what goal? But morally we had no choice, and as we went along, work was accomplished – as my colleagues will perhaps confirm. And some results, which are I hope theoretically and practically significant, were gleaned, not to mention the daily intellectual pleasure, which is probably the most important thing. The only truth that holds is that we are always wrong; yet the important thing is not to not be wrong but, in being wrong, to try again, with only one ambition: to fail better.
- Beckett?
- Yes, Beckett.
- 58 Thank you.

NOTES

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