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Jean-Pierre Changeux, François L'Yvonnet

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Jean-Pierre Changeux

François L'Yvonnet

# The Beauty and the Splendor of Truth

*Interviews on autobiographical  
recollections  
recollections*



**THE BEAUTY AND THE SPLENDOR OF  
TRUTH**



Jean-Pierre Changeux  
François L'Yvonnet

THE BEAUTY AND THE  
SPLENDOR OF TRUTH

Interviews on autobiographical recollections



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## Foreword

What is immediately apparent from Jean-Pierre Changeux's intellectual itinerary is the continuous unfolding of an insatiable curiosity open to virtually every facet of the human phenomenon. With the possible exception of literature. His positive spirit loves reality too much to wander in that direction. A sense of wonder coupled with a desire to understand. This is undoubtedly one of the keys to the way his mind works. Reason in the sciences is never cut off from the beauty of the world. Rationality and imagination go hand in hand, without ever merging. Even as a child, he collected insects, observing and classifying them, seeking to read an order behind their diversity, while contemplating their great beauty. It's a kind of first-hand experience. The knowledge of causes, correlations and ramifications is at the same time an aesthetic experience. Beauty doesn't come as a bonus. The title of this book, "The Beauty and the Splendor of Truth", sums up this singular alliance. Plato is credited with the phrase: "The Beauty *is* the Splendor of Truth"; substituting the "*and*" for the "*is*" is a way of focusing the coordinating conjunction on the « and » what's problematic about this alliance, which reaches its maximum intensity with artistic creation: from beauty in general to beauty itself.

Jean-Pierre Changeux is first and foremost a great scientist, trained at the best schools, with an international reputation. He spent his entire life as a researcher at the Pasteur Institute and

for many years held a chair at the Collège de France. All these prestigious marks of undisputed scientific and academic recognition, were recognized by numerous awards. He is one of the founders of what we now call the Neuroscience, which often occupies the front pages of magazines, for better or for worse. Knowledge of the brain has developed spectacularly over the last fifty years. We're only just beginning to understand how this somewhat mysterious organ works. Jean-Pierre Changeux has made a major contribution in this respect. Suffice it to mention, among many others, his work on allostery, the nicotinic receptor and epigenesis. Biochemical studies of the brain owe him a great deal.

Fundamental work which, for a mind like his, with its encyclopedic culture, could not fail to engage a certain vision of man as part of the whole of life, his history and the world. The humanist does not take over from the scientist, but crowns his approach. Here we find the Pastorian touch. Science must be turned towards the human, towards the well-being of mankind. We know that science, left to blind logic, can have catastrophic consequences. We also know that art can be used to serve deadly ideologies. Jean-Pierre Changeux's words are anything but angelic. We have to take reality as it is, and not pay lip service to it.

Spinoza, a philosopher he is very fond of, said: "Neither laugh, nor cry, nor hate, but understand." This could be the title of this book of interviews. We have everything to gain by understanding. It's up to the mind enlightened by science and the arts to advance man's knowledge of man and his environment.

To want to explain, as he does, the workings of our mind from its neuronal foundations is not a scientific or reductionist bias, a way of dehumanizing the human being, but on the contrary the best way of freeing man from that which

alienates him most surely and threatens his very survival: ignorance of who he is and of the moral responsibilities incumbent upon him.

Given the difficulty of the subject under consideration, Jean-Pierre Changeux's talk cannot avoid going into the technical details of research and discoveries, while always ensuring that it is addressed to the honest man who takes "care to use his leisure for honest and useful things" (Descartes).

François L'Yvonnet



## I.

### **Origins and early work**

#### **1- FAMILY ENVIRONMENT AND TRAINING**

François L'Yvonnet - *Let's start at the beginning, with your family origins...*

Jean-Pierre Changeux - I've rarely mentioned them. However, my family origins, alongside more obvious influences linked to particular teachers or colleagues, have certainly played a role in my training, in the broadest sense of the term. My ancestors were very simple people, from France "deep", as they say. My origins are rural. Winegrowers for the most part, who were ruined by phylloxera. My paternal grandparents came from Burgundy and Berry. My paternal grandfather, whom I never knew, came from Cher. The name "Changeux" comes from this region of central France. Near Châteauneuf-sur-Cher, where the family had ties. My grandfather had gone up to Paris to find a means of support.

Among other tasks, he helped transport for the construction of the Eiffel Tower. Having inherited, *via* his wife, a building and land in Châteauneuf, he returned to the country, setting up an oil mill where walnuts were pressed. Quite a profitable business. But he died when my father was eight. My grandmother tried to keep the oil mill going, but lacking any experience - she was a seamstress by trade - she soon had to give up. She left Berry with her children, including my father, and settled in Argenteuil, where she opened a small haberdashery store. My paternal grandfather's mother's family came from Clissé, in Burgundy. Vineyards there too, also ruined by phylloxera. My father, who was born in 1897, had no formal training whatsoever, and tried his hand at various secretarial jobs in bank collections. In 1916, when he learned that he was to be drafted in August, and not knowing whether he would return from the war, he decided to embark on a bicycle tour of France, a sort of "voyage terminal", as he put it. Until the armistice, he served in an artillery regiment. Once demobilized, he resumed his secretarial activities before being hired by Gaz de Paris. He spent the rest of his working life inspecting gas installations. Not a very intellectual job.

*What about your mother?*

My mother's family came from the Rouergue region, from Sainte-Juliette, between Rodez and Albi. Her father was the village schoolteacher, where he spent his entire career. He taught around fifty pupils of all levels in the same class. He had long Clemenceau-style moustaches. He was very authoritarian. I never had much affection for him. But he was very attentive to his daughters' education, and they all attended religious boarding schools. My mother had tried unsuccessfully to enter the *École normale d'institutrice*. Like

many provincials of the time, she came to work in Paris. She joined the PTT and became a switchboard operator. An activity that rather amused her. She met my father at the Auvergnats ball. They married and had three children, my two sisters and me. I'm the youngest. They looked for a place to live in Paris, to be as close as possible to the great Parisian lycées and the Sorbonne. So, in 1939, they moved to rue du Four, in the 6th arrondissement of Paris, where I still live. At the time, this district was populated by small-town people, as was Saint-Germain-des-Prés. Alongside the famous clubs that made the place famous, there were all kinds of food shops that have now disappeared: butchers, bakers, delicatessens, four-season shops. There were also antique shops, bookshops and, later, record stores. The district's population was thus mixed, with employees rubbing shoulders with non-conformist intellectuals, who met up in now-famous cafés such as Café de Flore and Deux-Magots. It was a bit like pre-war Montparnasse. I went to the nursery and elementary school on rue Madame, then to the lycée Montaigne until the third year of secondary school, and to the lycée Louis-le-Grand until the bachelot. For preparatory classes, the lycée Saint-Louis. So much for my family curriculum.

*Were your parents very involved in your studies? Did they encourage your curiosity?*

You can't say that. I had a close emotional relationship with my mother, who was always very warm, encouraging me every step of the way. She was interested in my work, even if she soon ceased to understand its true nature. My father, on the other hand, was busy with his own business. We had little contact.

*What kind of future did your parents imagine for you?*

My mother, who had failed at the École normale, imagined a career as a high school teacher for me, which would have been a clear step up the social ladder. My parents were convinced that education was the key to social advancement. Both of them had experienced the difficulty of finding a job without any real qualifications. My mother, for example, took a long time to become a switchboard operator.

*Your early youth was marked by war...*

Born in 1936, I was four years old at the time of the defeat. So I experienced the exodus. I remember it vividly. Fleeing by train, we ended up in Brittany, in Redon. I'm not sure why my parents chose to head in that direction. Perhaps, quite simply, because it was away from the front line. I remember German planes flying over the train, terrorizing the passengers. We rushed out onto the platform. The next day, in the same place, a train was machine-gunned. Several people were killed. We slept in barns, on straw. Back in Paris, I still remember the food cards and my mother queuing in front of the stores. Throughout the Occupation, she struggled to feed her three children, which took a lot of energy. My maternal grandfather had bought, at his retirement, a small house in Domont, near Montmorency, where I was born. We gleaned in the surrounding fields. My mother managed to accumulate enough grain to provide the daily soup. And this lasted throughout the war. Wheat was our staple diet. As far as I can remember, I wasn't really hungry. My mother spared us the difficulties she encountered on a daily basis.

*Do you have any other memories of the war?*

In 1944, at my paternal grandmother's home in



Châteauneuf-sur-Cher, an event had a profound effect on me. I was eight years old. It was during the retreat of the German army. The whole family was quietly gathered in the house when there was a knock at the door. It was three German officers! Need I tell you that it wasn't our family's custom to have contact with Germans! We'd been taught never to talk to or receive anything from the occupiers. The three soldiers asked for something to eat and drink. They put aside their weapons and sat down to eat. Without a hitch. Then they left. I was terrified. So much so that, for several days, it was as if I were frozen. Much later, after the war, when I was invited to Germany to talk about allostery, I couldn't stand the sight of German officer's caps, like those worn by train station masters. I even came close to turning back.

*So you've had a very close family circle...*

I spent my youth in a very warm environment. In a harmonious family. This enabled me, very early on, to have personal interests, to be able to isolate myself, to start a stamp collection, for example, like many children of the time. And to spend long hours consulting the Larousse dictionary, looking at its illustrations. Almost every weekend, we went to visit my grandfather in Domont, and I took the opportunity to explore the nearby Montmorency forest. That's how I became interested in animals, especially insects, and started collecting them.

*Was your family traditionally secular?*

My family was Catholic. There was even a nun on my mother's side! I had a religious upbringing. I went to Sunday school and took my First Communion.

*A very French family... a schoolteacher and a nun. The only thing missing is the military!*

My maternal grandfather was a Hussar of the Republic. In his village, along with the parish priest and the mayor, he was one of three important figures. He taught in a secular school. This task occupied his entire life. I don't know if he was religious himself. Where I come from, as everywhere else in France, religion was mainly passed on by women. Because of my family origins, I belong to rural, Catholic France. A Catholicism that was in no way fundamentalist or restrictive, even on a moral level. On the contrary, I grew up in a Catholic environment that was, if not "progressive", at least very open-minded.

*Did your parents go to mass regularly?*

Every Sunday, we went to mass at Saint-Sulpice church. It was there that I discovered the organ, an instrument that was to play a major role in my musical education, thanks to Marcel Dupré, a great organist and the church's organist. It was he who inspired me to learn to play the instrument. I remember going up to the tribune to see him play. I came back fascinated. My interest in music was born in church.

*Insects and music are the two main interests of your youth.*

Absolutely. My interest in insects was my own. It was my own private domain. It gave rise to a kind of enthusiasm in me: the joy of discovery. It was the same pleasure of discovery that I derived from consulting the dictionary. I was accessing new worlds, new objects, new ideas, new faces. I was very attracted by novelty. So, at the age of eleven or twelve, I started collecting insects. At first, beetles, etc., then

gradually, for what I'd call aesthetic reasons - this is where beauty comes in - I became interested, not in butterflies, insects that are all too familiar, but in diptera, flies, which often land on flowers. I started collecting them. I had little books *La Faune de France* by Rémy Perrier - which enabled me to identify the different species of Diptera. My parents gave me a little money to buy glass boxes where I could pin the results of my hunts.

In 5th grade, at the Lycée Montaigne, my natural science teacher was a highly original character, Jean Bathellier, who was nearing at the end of his career. He had previously undertaken scientific research on termites, which had taken him to Indochina. Health and family problems cut short his stay. It was for this reason that he became a high school teacher. He was the author of important studies, recognized by the entomological community, on termite castes. He had retained a taste for research. His 5th natural science class was entirely devoted to crustaceans! It was fascinating. He meticulously described each species: Daphnia, Cyclops, Copepods, Decapods and so on. Real monographs. He tried to extract from particular cases general ideas on the unity of the plan of organization, on larval development and on evolution. This had a profound effect on me. I was fascinated by his teaching. It has to be said that his lecture, which was very thorough, was only received by a tiny fraction of the class. Few students took part. My contact with him was very warm. My family, interested in the portrait I'd painted of him, invited him to dinner at our house. He was very touched by my parents' interest in his teaching. It was he who convinced them to prepare the *École Normale Supérieure*.

*An idea that had no reason to occur to them spontaneously. The École Normale might have seemed socially inaccessible...*

My father threatened to get me into the Gaz de Paris, like him! Which was out of the question for me. I showed my fly collection to Jean Bathellier. He introduced me to one of his acquaintances, Eugène Séguy, a leading Diptera specialist. He was an old gentleman who ran the entomology laboratory at the Muséum d'Histoire naturelle. The walls were lined with boxes of insects. He himself was at his microscope, making watercolor drawings of extraordinary quality. He had written several illustrated books in his own hand. For Eugène Séguy, insects were both the object of meticulous scientific work - they belonged to a well-defined, scientifically identifiable species - and, at the same time, the source of colored graphic representations of great beauty. At the time, it was said that to be a biologist, you had to know how to draw. I myself drew a lot. Eugène Séguy was both warm to children and at the same time rather rigid. He wanted everything to be done rigorously. When we talked about a species, we had to know what we were talking about, what criteria led us to decide to give it such and such a name. He was very attached to nomenclature, which is binominal (genus, species). He wanted us, young as we were, to fit into this classification system.

*Have you ever heard of Ernst Jünger's entomological work? The great German writer was also an insect collector. He dedicated a book to this activity: Chasses subtiles. Some species of carabid beetles and tiger beetles have been named after him...*

I'm not familiar with his work, but the parallel is amusing. I continued my collection, which I soon extended to include plants. I built up a herbarium. I was fascinated by biology in general. After the baccalauréat, I entered a preparatory class,

called NSE ("Normale sciences expérimentales"), at the Lycée Saint-Louis, to prepare for the École Normale Supérieure. As my parents had planned, I stayed in the local school circuit. The two years of preparatory school were a very difficult time in my life. My math teacher was extremely authoritarian, intransigent and violent, very "castrating". Although I wasn't bad at maths, he succeeded in blocking me, as I often told Jacques Monod. He was so violent and humiliating that I couldn't do mathematics anymore. I kept up my flots thanks to physics-chemistry and biology. The written exam was bad. I got mediocre marks in maths and physics. Very good in chemistry. Fortunately, they were good enough to get me through to the oral. And there, I got 20 out of 20 in practical biology. The runner-up, I believe, got 12. So the oral went very smoothly, and I entered the school in good standing.

*Let's move on to your second area of interest: music.*

It's an interest in art in general, both music and the visual arts. The discovery of music is associated with Gregorian chant and the organ at the 11 a.m. Sunday mass at Saint-Sulpice. It was a sung mass in which the organ parts played an important role. My mother wanted me to have a musical education from an early age. I started by taking music theory lessons. It worked very well. Then I moved on to learning the piano. It was a lot more difficult, because my teacher, here too, had rather brutal methods. She was flapping my fingers with a ruler when I made wrong notes. So I gave up the piano.

Later, when I was around twelve-thirteen, I went with my parents to visit one of their acquaintances, Camille Bruneteau, who was principal at the Lycée François premier in Fontainebleau. After lunch, he treated us to a little harmonium recital in an adjoining room. That was the catalyst that got me

interested in music again. As I said, I wanted to learn to play the organ. But the break had been too long for me to claim to be a good performer. I also benefited from the lessons of Noëlie Pierront, organist at Saint-Pierre-du-Gros-Caillou, a pupil of André Marchal. Her teaching focused on the correct way to play the music of the 17th and 18th centuries. She was a "baroqueist", very attentive to the execution of works in the style of the period. She taught me to play Bach and French music of the 17th and 18th centuries, such as Couperin. I really enjoyed deciphering, more than performing. She also took the opportunity to teach me to decipher contemporary music, in particular pieces by Olivier Messiaen.

I became a passionate fan of Messiaen's music, even if I remained a mediocre performer. I was lucky enough to meet him personally at the church La Trinité, where he was in charge of the organ. I listened to him play his works with great emotion and, when I got up to the podium, asked him for some advice on how to play his *Nativité du Seigneur*. His interpretation of Bach didn't fully satisfy me... As chance would have it, we met again much later, in 1982, in Jerusalem, to receive the Wolf Prize together, he for music, I for medicine. At the award ceremony, his wife, Yvonne Loriot, had played his *Catalogue d'oiseaux* on the piano. Dazzling.

As for my interest in the visual arts, that's another matter. It wasn't Delacroix's three monumental paintings in the Chapel of the Holy Angels in Saint Sulpice that caught my attention, but a trip to Italy organized by my older sister, who was studying philosophy, when I was twelve or thirteen. We went to Venice and Florence. A visit to the Uffizi Museum was my first aesthetic shock. A real discovery. I knew nothing about the Trecento and Quattrocento. It was there that my taste for painting was born.

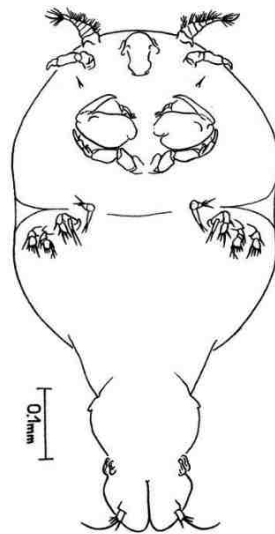
## 2- INITIAL WORK ON MARINE BIOLOGY

*At the same time, you were continuing your naturalist apprenticeship...*

During my first year of "classe préparatoire", I wanted to reinforce my biological knowledge by doing a summer internship in a marine biology laboratory. First in Arcachon, then in Banyuls-sur-Mer. It was in these two laboratories that I began to work on my own. In Arcachon, I took part in boat collections of marine species, which were then studied in the lab, group by group. It was there that I first heard of an eminent researcher, David Nachmansohn, who had worked in the Arcachon lab on the Torpedo fish. From Berlin, fleeing anti-semitic persecution, he had taught in France between 1934 and 1939, before taking refuge in the United States and finding a position at Columbia University. I was later to do an internship in his New York laboratory. More on that later. These "marine" internships allowed me to broaden my knowledge of animal species, taking into account their distribution and marine ecology. Alongside the "collection" aspect, there was the possibility of a rigorous scientific approach, in the spirit of Bathellier and Séguy. This reinforced my belief that there was research to be done.

In Banyuls, at the Arago laboratory, I briefly took some summer courses and, above all, asked for a place to work under the microscope. For a month, I dissected everything I could lay my hands on: cicadas, millipedes, sea cucumbers, crabs... I had compiled the results of my observations, accompanied by precise drawings, which I interpreted with the help of Pierre- Paul Grassé's *Traité de zoologie*, a very popular

work at the time. Each group was described from the point of view of physiological anatomy, in the spirit of the 19th century. I presented my work to the deputy director of the Banuyls laboratory, Claude Delamare-Deboutteville. A very interesting and distinguished character. His father had been one of the pioneers of the automobile. He was interested not only in the description of animal species, but also in their distribution in the field, their particular environment. He decided to take me into his laboratory for the last two months of the summer vacations. And since I was interested in parasites, he encouraged me to work on Holothurians, organisms of the Echinoderm class, more commonly known as "sea cucumbers ».



1. *Allantogynus delamarei* - a new species of copepod parasite of Holothurians. (After Jean-Pierre Changeux, 19551.)

I set out to study everything that could cohabit or live inside sea cucumbers. This led to the discovery of a new animal



species, a sea cucumber parasite (*Allantogynus delamarei Changeux*), to whom I dedicated my first publication, in 1955<sup>1</sup>. All the drawings illustrating this work are my own pen-and-ink work.

I completed these studies with a few observations on Protists, the Gregarines, parasites of Holothurians, of which I described a new species (*Cystobia grassei Changeux*). This work, the subject of a monograph published by Éditions Hermann<sup>2</sup>, served as my post-graduate diploma. It was also my first "link" with André Lwoff, who had himself worked on Protists at Banyuls in the 1930s, with Édouard Chatton, the Laboratory's director at the time.

*Your first publications were supported by Claude Delamarre-Deboutteville...*

He was a very generous and honest man. He wanted me to be the only person to sign the publication, being the sole author of the discovery. These are not common practices. Claude Delamarre-Deboutteville was interested in interstitial fauna, which he had co-discovered. These are microscopic animals found between grains of sand. When you make a hole in the sand at the edge of the sea, which fills up with water, a very special fauna lives there, called interstitial fauna. He was also very interested in the distribution of various species of parasites, particularly fish parasites. I was enthusiastic about his work. It was a moment of real scientific happiness. I could have both an "aesthetic" and a scientific activity, both practical and theoretical. In the practical part, the "drawing" component was very important, the graphic re-transcription, as faithful as possible, of the observation.

Still, I was not satisfied. At the end of my stay, I wondered what my next step might be. I spoke to a colleague I'd met in the corridors of the Arago laboratory, who suggested I read the works of Jean Brachet, one of the founders of experimental and chemical embryology, who taught at the Université Libre de Bruxelles. I was offered an internship in his laboratory. That was at the start of the 1958 academic year. Brachet was one of the pioneers in the study of gene transcription. He pioneered work on RNA (not messenger RNA, which came later with François Jacob and Jacques Monod). We didn't want to think of him as a molecular biologist, even though he played an essential role in this field. At the time, we were talking more about cell biology. I also met another talented Belgian, Christian de Duve, who came from Louvain. He would later work at the Rockefeller Institute. Some of his lectures were of great interest. He had discovered lysosomes, intracellular organelles containing various enzymes (proteases, phosphatases, etc.) in very compact form, which play a role in cell metabolism, particularly in the elimination of certain molecules.

### **3- MEETING JACQUES MONOD**

*Then came the time to "germinate" your own theoretical hypotheses...*

During my stay of a few weeks in Brussels, I had worked out a brief theory on cell differentiation, which seemed to hold the rail. My thesis would echo it. I thought that the first stages of fertilization, the activation of the egg, the activation reaction of the oocyte, could be explained by a rupture of the lysosomes caused by the penetration of the spermatozoon. A

whole series of chemical transformations would follow, triggering cell division. Back in Paris - at the Institut de Biologie Physico-chimique, where I had taken up residence - I wanted to put my theory to the test on the sea urchin egg. Unfortunately, I hadn't mastered the enzyme assay. I'd done histochemistry and various assays, but not enzyme activity measurements.

*At the same time, you were a "caïman" and an "agrégé-préparateur" at the ENS.*

I was in charge of preparatory courses for the agrégation in natural sciences, with a particular focus on experimental work. I carried out both activities simultaneously. At the Institut de Biologie Physico-chimique, I was able to train in chemistry. I had received a high-level education in zoology and physiology, but not at all in biochemistry. A colleague, Jeannine Yon, who was working in an adjoining room, pointed out to me that, as far as she knew, the only French laboratory working on fundamental biological problems involving enzymology was Jacques Monod's at the Pasteur Institute. An unknown name at the ENS.

So I wanted to meet him. Chance brought me face to face with him in a corridor of the Institut de Biologie. He had come to visit René Wurmser, his director, to seek his support for an appointment to a vacant chair in the Faculty of Science. I approached him and told him my problem straight away, asking him if he could teach me how to assay an enzyme, a phosphatase, at the same time as I gave him a brief summary of my research project. He invited me to come and present my work publicly at the Institut Pasteur. At the end of my talk, on a Saturday morning, in front of a partly perplexed audience, Monod asked me to follow him into his office. He presented

me with a delicate choice: either I left for the United States to continue my studies in a good chemical embryology laboratory, as no one in France was working in this field; or I stayed in Paris and he took me into his laboratory. But then, I had to "change my game", learn enzymology, genetics, immunology, everything that made up the nascent field of molecular biology. He gave me two months' reflexion. In the meantime, he had given me François Jacob's thesis to read, with whom, he thought, I might eventually work. Gérard Butin, a former student at the Ecole Normale Supérieure, then a collaborator of Monod's, had presented me with some bacterial cultures. It smelled terrible. No aesthetic interest! No affinity with them! But on reflection, after several weeks, I accepted anyway. I joined the Pasteur Institute...

*What was the state of French research at the time? We're in the post-war period. Were the marine biology laboratories (Arcachon, Banyuls, Roscoff), for example, at the cutting edge of research?*

The teaching I received at the Sorbonne and the École Normale was based on a very traditional vision of biology, which was subdivided into zoology, botany, physiology and geology. These were the titles of the certificates I took for my natural science degree. It was a vision inherited from the 19th century, which was nevertheless the great century of biology, with Charles Darwin, Claude Bernard, Louis Pasteur, Johann Gregor Mendel... The teaching I received took little account of evolution, genetics and DNA. I did take a course on Darwinian evolution by Charles Devillers, but it was isolated. The bachelor's degree in natural sciences did not include biochemistry or the then nascent field of molecular biology. The descriptive aspect of things prevailed. The main

originality lay in the marine and terrestrial biology labs, where students went out into the field. My experiences in Arcachon and Banyuls were decisive for me. But all this was done within the framework of the tradition inherited from the previous century. Pierre-Paul Grassé, Maurice Caullery, Étienne Rabaud, Lucien Cuénot and others were simply repeating old intellectual patterns well established in French universities. This tradition of thought was still rooted in the conceptions of Jean-Baptiste de Lamarck (1744-1829) and the heredity of acquired traits, without showing any major interest in Darwinian evolution. This I'm still surprised, but Mendelian genetics, and above all Darwin - apart from a few works, such as Cuénot's on the mouse or Devillers' on vertebrate evolution - did not attract the attention of French research. It flourished in Anglo-Saxon countries, particularly in America.

*Does it make sense to speak of a French school of biology at that time, with a certain style?*

There was a very traditional French school, as I said. At the École Normale, for example, people of my ilk were given the nickname "coquillard" (shell-addict), because naturalists were supposed to spend their time identifying shells. This was the way my physicist and mathematician colleagues saw biology. Putting names to shells, like I used to do when I was a kid. Admittedly, there was a brilliant French school of descriptive zoology, exemplified by the Muséum d'Histoire Naturelle, but it seemed to have exhausted its resources. This wasn't entirely the case, however, as it was to be revived by ecology. We realized that, to protect animal species, we needed to be able to draw up as complete an inventory as possible. In this respect, Claude Delamare-Deboutteville was ahead of his time.

*Wasn't the Pasteurian tradition a bit of an exception?*

At the Institut Pasteur, we also described the micro-organism species that cause disease, but we didn't stop there. Pasteur was a chemist. The chemical vein was illustrated in the mid-twentieth century by Ernest Fourneau, Jacques Tréfouël and, above all, Daniel Bovet, who gave birth to therapeutic chemistry. Molecular biology grew out of the encounter between biological chemistry and the naturalistic vision of Monod and Lwoff.

*Was the disciplinary compartmentalization inherited from classical naturalism an obstacle to the development of biology ?*

It certainly was. Science teaching at the École Normale had remained static. The Department of Natural Sciences was headed by Maxime Lamotte, an eminent traveler-naturalist and discoverer of the high-altitude fauna of Mount Nimba in Guinea. He was a pioneer in population genetics and scientific ecology, but had no interest in the chemistry of life. It was a momentous - and heartbreaking - decision for me to leave the École and join Jacques Monod's laboratory. After welcoming me, he insisted that I leave my two positions: agrégé-préparateur at rue d'Ulm and visiting researcher at the Institut de Biologie. I remember pointing out to him that I would then lose my pension rights. He let out a Homeric laugh that echoed throughout the laboratory, telling me: "If at your age you're worried about retirement, it's over!" I reassured him. In any case, I had to break with the tradition of ecological zoology to devote myself exclusively to molecular biology.

*Monod himself was not a graduate of the Ecole Normale Supérieure. Nor were Lwoff or Jacob...*

Monod didn't think much of the Normaliens. He summed them up in one good word: "Moi Je, y'a qu'à" (Me I, Just to do). But the title of "normalien" still allowed me to enter his laboratory.

*What kind of man was Jacques Monod? We'll have more to say about the researcher, but what about the personality of this extraordinary scientific?*

My first impression had not been very good. It was at the thesis defense of a colleague from the Ecole Normale Supérieure, from a year before mine. The jury was presided over by a haughty, intransigent, even harsh and scathing figure. Nothing that particularly appealed to me. I later learned that the candidate, who had worked in his laboratory, had been accused of falsification. Jacques Monod, the chairman of the jury, had been particularly demanding about the quality of the experimental data presented to him. This rigor didn't displease me *a priori*. All of which didn't stop me, a few months later, from turning to him and asking for his help. The way he invited me, without even knowing me, to give a talk at the Institut Pasteur, was a sign of great open-mindedness and a rare ability to listen to what a young researcher he'd met by chance might have to say. His simplicity was matched by an aristocratic elegance. Despite his short stature and the after-effects of poliomyelitis, everything about him gave an impression of authority and charm, from the regularity and intelligence of his face to the distinctiveness of his language, in both French and English. He could refer, albeit rarely, to his Genevan origins and the twenty-six members, at least, of this

great bourgeois family born of the Reformation who, for some, would become pastors or theologians, explorers, for others, like Theodore Monod or artist, like Lucien Monod, Symbolist painter, pupil of Puvis de Chavannes, and father of Jacques.

*The word "aristocracy" evokes a court, an etiquette, uncontested lineages and shared convictions.*

That's right. It was out of the question, for example, to talk favorably to him and his immediate entourage about the events of May 1968, or to refer to "Chairman Mao". I never felt comfortable in this circle, nor was I tempted to join it, perhaps because of my family background, but also because I wanted to remain free in my convictions. This in no way altered my relationship with Monod. Our intellectual closeness accommodated our differences of opinion.

*We also like to talk about his seductive side....*

He liked to seduce. This aspect of his personality didn't concern me directly, but it could affect those around him. Although I never had to defend myself against it, I sometimes had to soothe the wounds of people close to me.

*How would you qualify his form of intelligence?*

Jacques Monod aroused an admiration in me that I have never denied. His intellectual power was extraordinary. François Jacob described him as a "formidable mécanique". His capacity for integration and rationality surpassed our own. He also possessed an extraordinary will - obsessive, one might say - to bring to light the organization of the living world he



was working on, and to build a universal truth out of it. Following in André Lwoff's footsteps, he had a rightful place in the great Pastorian tradition. He was fond of repeating that "what's true for the colibacillus is true for the elephant", which means that it's also true for mankind, for all of us, even if it's not entirely accurate. The conclusions of his reasoning were often unequivocal, falling like a cleaver. I adapted in the moment, saving a possible reply for the following day. Our dialogue, particularly right up to the end of my thesis, was of a consistently high quality, even if, of course, many other interlocutors tried to monopolize his attention. Strangely enough, his imagination didn't always seem to match his "sovereign rationality". Perhaps this explains the productive collaborations he established with more intuitive minds, such as André Lwoff, but also Melvin Cohn, François Jacob and, dare I say it, myself.

*Was he as "generous" as Claude Delamarre-Deboutteville had been with you?*

André Lwoff, in his autobiography<sup>3</sup>, notes Monod's habit of not mentioning the authors who prejudged him, or those who accompanied and frequented him. I experienced this myself. Often, at the end of the morning, he would tell me that he had discovered during the night what I had mentioned to him the day before. Again, I was used to it. It didn't seem to me that there was any intention of appropriation, but rather a form of identification with the new idea: he was invested in its future development, without worrying about its origin. I've often seen this trait in my collaborators among the most brilliant. Our dialogue was above those conflicts of ego, often oversized among scientists. It was accompanied by a mutual trust and

esteem such that any obstacle, as long as it was scientific, fell by the wayside before the fruitfulness of the debate. We shared, and had always shared, the same love - if I dare use the term - for the progress of knowledge, which is not to say that we never had disagreements.

*A research laboratory is a small community of complex human relationships...*

On the occasion of very pleasant lunches, taken in community under the glass roof near the library of the Cellular Biochemistry Department, differences of opinion often arose. The long table was usually presided over by André Lwoff, with his wife Marguerite on one side and Élie Wollman on the other. Everyone had their place and placed their plate and cutlery on it. Jacques Monod sat close to Marguerite. The younger members of the group made their way to the other end of the table. The conversation might turn to politics, national or international, or to the already "complicated" relationship with Pasteur's administration. It became livelier when the subject touched on philosophy or art. One day, as I was talking about Malraux and *Les Voix du Silence*, Monod suddenly asked me to sum up the author's thoughts in a few words. I stammered out some general comments on a work he obviously didn't like, only to be rudely rebuffed in front of the whole table. On another occasion, I ventured to mention the name of Teilhard de Chardin and his *Phénomène humain*... What did I say? In Monod's eyes, I had become a papist, snob and Germanopratin (frequenting Saint-Germain des Prés), who couldn't read Darwin. Fortunately, the evocation of Plato or Aristotle usually calmed the spirits, offering the table the opportunity for a calmer reflection. Once lunch was over, everyone returned to their workbenches, pipettes and

spectrometers.

*Jacques Monod was also a public man, an uncompromising citizen...*

First of all, it's important to remember that Monod was a highly cultured man. He played the cello and had practiced conducting. As you rightly point out, he also had a remarkable sense of civic responsibility and boundless dedication. He was firmly committed to social issues that were close to his heart. His role in the Resistance is well known. Later, at the Caen symposium (1966), he called for a "genuine research policy". At the Bobigny trial (1972), he defended abortion. At the Royaumont colloquium (1972), on "L'Unité de l'Homme", alongside Edgar Morin, he promoted a fundamental anthropology that would link data from the theory of evolution, ethology and brain studies to the humanities. When he was director of the Institut Pasteur, he was able to project its scientific orientation several decades ahead of schedule, supporting in particular the creation of a molecular neurobiology laboratory!



## II.

### **Early molecular biology: many keys for a single lock**

#### **1- LIFE AND ENVIRONMENT**

*Before getting to the heart of the matter, it might be useful to give an overview of what living beings are in their relationship with the environment...*

As I said, my youthful passion for the richness and diversity of animal species was accompanied by a strong aesthetic component that has never left me. It also aroused my curiosity about the origins of living things. It was my interest in the chemistry of development that led me to Brussels. The ancient Greeks and Latins, Aristotle, Pliny the Elder, etc., already noted that living beings, from man to insects, are characterized by their ability to maintain an autonomous form and to possess a behavior specific to each particular species. No one would dispute that there are differences between a fly and a bee, or a chimpanzee and a human being. What's more, every living thing possesses the ability to reproduce - to perpetuate itself - and this is a key factor in its success which sets it apart from an inanimate object, such as a pebble or a pile of sand. As far

back as antiquity, the hypothesis was formulated that a mysterious vital force, or "energy", existed in every living being.

A "vital principle", in addition to and distinct from the laws of matter, would govern all life's phenomena. Henri Bergson, a professor at the Collège de France, defended this thesis in *L'Évolution créatrice* (1907), calling for an enigmatic "élan vital" to drive the evolution of living beings. This idea dovetailed with the biblical account that "God fashioned man from dust of the ground; he breathed into his nostrils the breath of life, so that he became a living being" (Gn 2, 7).

The pre-Socratic Democritus, Descartes and the philosophers of the Enlightenment, such as Diderot, opposed this vision with a naturalistic, or rationalist, conception, according to which life is the sum - the synthesis - of "mechanical" processes which, even if not fully understood, owe nothing to the immaterial or the supernatural. From my early years at the ENS, I'd been interested in old editions of science books, which is how I happily acquired the second edition, *in quarto*, of Descartes' *Traité de l'Homme*. This seminal text - one of the first attempts to model the brain, with its famous illustrations of the reflex arc - bowled me over. Its last sentence, on man, stipulates "that we must conceive", "in this machine", "no other principle of movement and life, than his blood and spirits, agitated by the heat of the fire which burns continually in his heart, and which is of no other nature than all the fires which are in inanimate bodies".

*With the physiologist Claude Bernard, knowledge of living organisms was enriched by new concepts...*

I had read Claude Bernard, of course, who was particularly

interested in the characteristic autonomy of living beings. Although the idea of "vital force" was sometimes mentioned, he approached the question as a physiologist. He proposed the concept of the "milieu intérieur" or internal environment. He wrote: "This sort of independence of the organism from the external environment comes from the fact that, in the living being, the tissues are in reality withdrawn from direct external influences and are protected by a true internal environment, which is mainly constituted by the liquids that circulate in the body"<sup>1</sup>. Claude Bernard posited that the invariance of the internal environment, or homeostasis, was ensured by a global physiological regulation, which owed nothing to any vital force.

Since Claude Bernard's time, many cogs in the Cartesian clock have been unraveled. In the 1950s, it was discovered that deoxyribonucleic acid, or DNA, contains in its sequence the genetic heritage of the species, and that proteins (macromolecules made up of a chain of amino acids whose sequence is itself encoded in the DNA of our genes) perform the multiple "housekeeping" tasks necessary for the cell's survival and reproduction.

*So how do we think about the relationships between living organisms and their environment, especially when the latter is changing and evolving?*

As far back as Greek antiquity, two currents of thought emerged. The "innatist" or nativist tradition, inspired by Plato and taken up again by Descartes, and now found in genetics, states that everything that characterizes living beings is written in our genes, and in our genes alone. Spontaneous variations in the genome will be followed by the natural selection of those best able to survive variations in the environment

(Darwin). The empiricist or constructivist tradition, originating with Aristotle, then John Locke or Condillac, argues in contrast for the decisive contribution of interaction with the environment in the construction of the organism. An enigmatic "instruction" would sculpt a kind of inner statue that would make it possible to explain, for example, the elongation of the giraffe's neck and its hereditary transmission (Lamarck).

Closer to home, our understanding of living beings will be profoundly renewed by comparison with artificial machines. As early as 1948<sup>2</sup>, Norbert Wiener introduced the notion of cybernetics (from the Greek "κυβερνητική", used by Plato to designate the piloting of a ship), whose purpose is the science of communications and their regulation in both natural and artificial systems. One of his major contributions, very popular in the 1950s, was to demonstrate the critical importance of *feedback* regulation - especially negative *feedback*. This enables an organism to maintain its stability and invariance when its environment changes. This is a fundamental mechanism that supports Claude Bernard's homeostasis.

The proposal was quickly put to the test in 1954<sup>3</sup> by biologist Aaron Novick and physicist Leo Szilard on the bacterial cell. They used a chemostat, a kind of bioreactor, in which the *E. coli* multiplied at constant volume, and showed that the internal synthesis of a tryptophan precursor is rapidly inhibited if tryptophan is added from the outside. This suggests that an early enzyme of the tryptophan metabolic pathway is retro-inhibited by the chain's final product. Autoregulation takes place at the level of the cell's biochemical map. Bacteriologist Edwin Umberger discovered that a specific regulatory protein was involved in this "intracellular *feedback*" (1956)<sup>4</sup>. So how does the key to this lock work?



## 2- LEARN BIOCHEMISTRY AND CHOOSE YOUR THESIS TOPIC

*You chose to stay in France and work at the Pasteur Institute with Jacques Monod and François Jacob...*

Warned by my readings on the chemistry of life and its regulations, I chose to abandon higher organisms in favor of bacteria, which seemed to me - at the time - repulsive and devoid of any aesthetic appeal.

The Institut Pasteur was recognized as a world center for microbiology, and Monod and Jacob's reputation was already high internationally, even if their working conditions didn't seem optimal to me. Jacques Monod had his laboratory on the first floor of the Chemistry building, while François Jacob had his in what was known as the "Grenier", the attic, on the last floor of the same building, under the roof. Monod's working conditions were more pleasant and comfortable. When I arrived in his department to prepare my thesis, Monod immediately warned me that he already had students, whereas François Jacob had none, and that it was therefore preferable for him to become my thesis supervisor. So I joined Jacob in the attic.

It was a small laboratory, comprising two rooms, one occupied by the technician, the other being his office. The only equipment was a vat in which bacterial cultures, mostly Petri dishes covered with agar gel, formed a small halo of bacterial clones in flacons. These are known as bacterial colonies. François Jacob's work involved the genetic engineering of bacteria, crossing males and females, and observing the recombinant bacteria produced by their cross-breeding. To identify the biochemical status of the altered

bacteria, he used Petri dishes containing dyes to identify the physiological function of the bacterial colony. During the day, he prepared stacks of dishes, which he placed in the oven in the evening, to observe and count the results the following morning. Around 11 a.m., he would go downstairs to report to Monod. The results were obtained with the lactose system, its key enzyme,  $\beta$ -galactosidase, and its induction or repression under genetic control. François Jacob, to his credit, had perfected the dissection of the genetic mechanisms underlying the regulation of  $\beta$ -galactosidase biosynthesis, in the presence or absence of the substrate, lactose, or its analogues. These genetic experiments were carried out in a very simple manner, with no "tools" other than Petri dishes and a trained eye for spotting colonies... He proceeded very rapidly. It was spectacular. Once the result was obtained, he transferred the clone to Jacques Monod, whose approach was mainly biochemical. Monod *measured* enzyme activity and kinetics *in vitro*, and assessed their specificity.

*You had not yet been trained in molecular biology; what might your job have been with François Jacob?*

He had asked me to create an infection curve for a bacterial culture using a bacteriophage - a virus that kills bacteria. One can follow the progression of such a culture, the division of bacterial cells, and at the same time observe the effects of the killer virus. It was the first job he'd asked me to do. I was ignorant. On his advice, I used "broth", i.e. a culture broth based on a variety of organic extracts on which the cells "grow" easily, rather than a synthetic medium composed of defined elements, such as salts, sugar, etc. I was able to observe that the bacterial cells were able to divide and divide easily. I observed that the bacteriophage used did indeed kill

the bacteria, and that the growth curve stopped.

One day, Monod - a rare occurrence - came up to visit Jacob in his laboratory. He asked me what I was doing. I opened my notebook and showed him the "broth" growth curve. He immediately lost his temper, reproaching me for not having carried out a quantitative measurement of growth, using the data systems he had himself introduced in his thesis (devoted to the study of bacterial growth kinetics). Then, addressing Jacob, he asked: "How could you agree to have an initial growth curve made in a complex medium, when you know full well that no serious quantitative study is possible when bacteria are grown in broth?" Addressing me: "How much sugar did you add to see if the growth continued, and that it wasn't simply the lack of sugar that caused it to stop?" I replied that I had put five drops of sucrose solution... Immediate reaction: "What does that mean? How many micromoles per liter?" Monod's irritation, very controlled all the same, resulted in me leaving François Jacob's laboratory and joining his own.

*That can't have helped your relationship with François Jacob...*

I maintained cordial relations with François Jacob, but it's certain that this brief stay at his side didn't make our relationship any easier. A certain bitterness followed, as I did not pursue my thesis work under his direction. At Jacques Monod's behest, I went down to the first floor. Monod found me a place in a lab close to his own. He told me I had to learn the basics of biochemistry. That was my wish! I reminded him that I had approached him at the Institute of Biology specifically to learn how to measure enzymes. He asked me to

study a new bacterial construct obtained by François Jacob: it was a pioneering work in genetic engineering. Jacob had succeeded in transmitting the "Lac" segment (lactose operon) of the colibacillus *E.coli* in *Salmonella typhimurium*, a human pathogen found in certain cheeses. Jacob provided me with the bacterial strain. Subsequently, I learned to cultivate strains of this type on my own in synthetic media, not in "broth". *Salmonella* is lac-negative. It does not respond to lactose. It's not a lactose-adapting bacterium, unlike *E. coli*. In the classification of bacteria, this is precisely what distinguishes them. The new bacterial construct was a kind of interspecific chimera, a bacterial monster of sorts.

It was very interesting to study how the *E.coli* operon was expressed in another bacterial species. I had to measure  $\beta$ -galactosidase, the enzyme of the Lac system, but also permease, which is a transporter of lactose, i.e. sugar, inside the bacteria, and which had been discovered at the Pasteur Institute by Georges Cohen. I set out to understand how this synthesis was coordinated, and to discover in this chimera, at the regulatory level, what had been observed in the *E.coli*, all of which enabled me to learn the basics of enzyme chemistry, enzymatic reactions and enzymatic kinetics, while at the same time understanding how, in the case of this chimera, we could follow the co-regulation of the two protein systems. It took me two or three months. Jacques Monod came to see me every morning, looked at my notebook and checked that everything was done correctly. These were essential moments in my learning of molecular biology. I could never have received such training from François Jacob, who had only a fragmentary knowledge of chemistry. For example, I'd never seen him measure an enzyme in his laboratory.

*This first work in Monod's laboratory was the subject of a note in the Comptes rendus de l'Académie des Sciences<sup>5</sup>, which demonstrated the identity between the colibacillus enzyme and the enzyme synthesized by hybrid salmonella...*

This note in the *Comptes Rendus*<sup>5</sup> was the occasion of a rather painful and, at the same time, instructive experience. Monod, in his own way, could sometimes be a little "castrator". The first version I proposed to him was violently rejected. I was, however, the only signatory. He found the style lax, the length excessive and the lack of scientific rigor flagrant. A note in the *Comptes Rendus* had to be written, in his opinion, with extreme care, more inspired by the style of a sonnet than that of a Proust novel.

"As in a classical tragedy, everything had to contribute to the action", were his words. Subsequent versions suffered the same fate. By the fifth, I could no longer construct a sentence, and by the sixth, I was losing my vocabulary. The ninth version finally received the *imprimatur* and was sent to Jacques Tréfouël, who was to present it to the Académie. For Monod, it wasn't enough to experiment or even invent, you had to know how to write. The written expression of ideas was as important as the ideas themselves. He made Boileau's rule his own: "What is well understood is clearly stated...". I've even heard him say that an idea only exists when it's set out in written form.

*What was your relationship with André Lwoff, who had his lab next door to François Jacob's?*

It was a small laboratory in the attic, where his wife Marguerite also worked. André Lwoff showed a great deal of interest in what I was doing, which didn't displease me, and

encouraged me at the highest level. He was a charming and highly cultured man, and a painter in his spare time. But we didn't really work together, just studied the same protozoa thirty years apart in Banyuls...

### 3- THE WORK OF THESIS

*There was also your thesis...*

Jacques Monod once brought François Jacob and I together in his office to discuss a number of possible thesis topics. This was in 1959, before the publication of Jacob and Monod's "model", which dates back to 1961. Monod had asked me if I was interested in "constitutive" mutations in the lactose operon, those that had lost regulation. There was also talk of positive (not negative) regulation. All of these subjects were related to the regulation of protein biosynthesis, which Jacob and Monod were particularly interested in at the time. None of these subjects appealed to me! I wanted to embark on a project that was truly different from those already at an advanced stage, where I would only have served as a substitute.

Monod then told us about physicist Leo Szilard's research into the existence of internal metabolic regulation, possible *feedback*, according to a cybernetic vision, à la Norbert Wiener, of the metabolism of living cells. François Jacob, for his part, mentioned the recent results obtained by Edwin Umberger<sup>4</sup>, which confirmed that there were indeed negative *feedback* systems on certain bacterial enzymes. Monod had also mentioned the name of Arthur Pardee, who had collaborated with him and Jacob at the Pasteur Institute on the

lactose operon, and who had made an observation comparable to Umberger's on another system. The problem of regulating the activity of bacterial enzymes immediately brought to mind my first theoretical model on the activation of the enzymes of the egg during fertilization, developed on my return from Belgium.

On the other hand, having read Claude Bernard, and being aware of his concept of invariance of the internal environment, I sensed - intuitively - the general importance that understanding this regulatory mechanism could have. I therefore chose to devote my thesis to this area of research. Several approaches were possible. One was to create mutants, genetic modifications that could be used to dissect a biological mechanism, as both had done to demonstrate the "Jacob and Monod model". François Jacob had mutants with a high requirement for the amino acid valine. Moreover, the *E. coli* was sensitive to this amino acid, and valine-resistant mutants had already been selected. For Jacob, the best way to tackle the problem was to isolate mutants of the regulatory enzymes threonine deaminase and acetolactate synthase. With regard to the latter enzyme, I was able to discover that certain mutants were indeed disrupted in their valine retroaction and therefore produced, or "spit out", valine. In all likelihood, the retro-inhibition system had been altered. With Georges Cohen, we tried to measure acetolactate synthase. It turned out that the assay was very difficult to perform, as a cofactor came into play that we couldn't control. That's why we didn't publish this work. Nevertheless, it was the first time that such a result was achieved.

I abandoned this first approach to focus on the biochemistry of threonine deaminase, the first enzyme in the isoleucine biosynthetic chain, a simpler regulatory enzyme. Repeating Umberger's experiment, I confirmed that threonine deaminase

biosynthesis is inhibited *in vitro* by isoleucine, with cooperative kinetics similar to those observed with oxygen binding to hemoglobin. I also resumed the isolation of mutants and found with threonine deaminase what I had already obtained with acetolactate synthase. At the same time, I noticed that the properties of threonine deaminase, in the enzyme preparation I was using as a control, were changing over time: the enzyme's sensitivity to isoleucine was progressively diminishing. It became clear to me that what I was looking for with a mutant, I could find *in vitro* with the right treatment.

*Did Monod keep a close eye on your research?*

Monod and Jacob were surprised that I didn't want to work on their model, which at the time was still in development. They were convinced that my project was secondary to their own work. This in no way dissuaded me, but on the contrary reinforced my conviction that what I was doing was of interest and of general significance. I then found myself in a difficult situation, because although Jacques Monod had been very present up until then, as soon as my thesis subject, which didn't come from him, was decided, he let me down a little. He left me free to manage my own adventure as I saw fit. Except for the publication of our "model" in 1965, he was never a co-author of my experimental work. The three articles published prior to the publication of my thesis were under my signature alone. This attitude - rare among laboratory directors, who generally co-sign their students' articles - can be interpreted as a form of respect for my own research. It can also be seen as a refusal to endorse work he hadn't initiated himself. And, since I hadn't pursued my study of mutants, my ties with Jacob were definitely weakened.

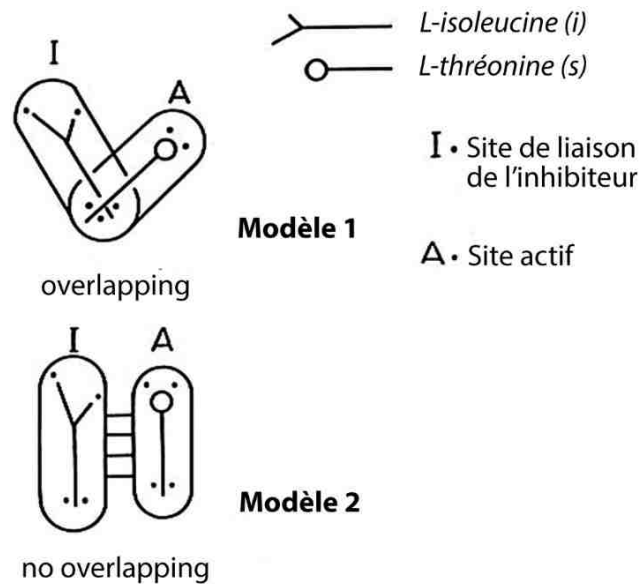


*So you continued your research work "on your own »...*

To a certain extent. I set out to define *in vitro* conditions that would selectively and reproducibly abolish the regulatory properties of threonine deaminase without causing it to lose its enzymatic activity. I began by using a thermal procedure, heating the enzyme to a certain temperature and for a certain time, so as to observe a complete loss of sensitivity to isoleucine, without any appreciable loss of activity. Versene (the common chemical name for ethylene diamine tetra-acetic acid) blocked this effect. A heavy metal, such as mercury for example, had to be involved in this process by binding to a thiol group (-SH). Hence the idea of obtaining, by chemical means, the same result without heat treatment. For the first time, I used the term "desensitization" (today, I prefer "decoupling") to describe this phenomenon. I also noted that the "decoupling" phenomenon was not limited to a loss of isoleucine control, but was accompanied by the abolition of cooperative substrate kinetics.

Jacques Monod was interested in these results. He arranged for me to make a brief presentation as a student at the Cold Spring Harbour Symposium in the USA in July 1961, devoted that year to *Cellular Regulatory Mechanisms*. It was my first visit to America, in the auditorium of famous laboratories located in the heart of the United States countryside, far from the skyscrapers of Manhattan. I spoke for twenty minutes. It was an opportunity for me to question the two models that come to mind to account for the seemingly "competitive" antagonism established between two structurally different compounds such as isoleucine and threonine. According to the first model, the interaction is of the classic competitive type:

the binding surfaces of the substrates and the regulatory inhibitor *overlap*. According to the second, there is *no overlapping*: the interaction is established between distinct sites. Two "keys" for the same receiver. I decided in favor of the second model <sup>6</sup>.



2. Two modes of regulation of an enzyme's catalytic activity by its feedback inhibitor. Substrate (threonine); regulatory inhibitor (isoleucine). 1 - with overlapping sites (steric interaction) and 2 - with non-overlapping sites (allosteric interaction). (Adapted from Jean-Pierre Changeux, 1961)<sup>6</sup>.

After my presentation, the eminent bacteriologist Bernard Davis took the floor to underline the analogy between my work and that done with hemoglobin. A premonitory sign if ever there was one! During the Symposium's final discussion, Monod cited my results, including the idea of two distinct sites, and integrated them into the general

framework of the regulation of cell metabolism.

Concomitantly and independently, Arthur Pardee and his student John Gerhart, who were working on another bacterial regulatory enzyme, aspartate trans-carbamylase, mentioned a comparable, as yet unpublished result with a purified enzyme. Neither had attended the symposium, but Monod was aware of their work. On the strength of these two results, back in Paris, Monod proposed in the written discussion the term "allosteric", to qualify what I, for my part, had called the "*no overlapping sites*". It was an amazing success of the new word as an efficient vehicle of the concept...

The question then arised: what is the mechanism that allowed these two sites to be linked together at the level of the protein molecule? The idea was that this link resulted from a change in the conformation of the molecule. Instead of being direct, the interaction was transmitted via a reorganization of the protein's spatial structure. Daniel Koshland had proposed an "instructive" model for enzymes, with the concept of "*induced fit*"<sup>7</sup>. It is the actual binding of the substrate that *instructs* the change of shape of the protein molecule.

*It's apparently a very original concept...*

As I said in the preamble, the instructive thesis is already present in Aristotle, unlike Plato, who thinks that everything pre-exists. The remainder of my research will decide between these two possibilities. In my thesis work I accumulated a wealth of data concerning the effect of a variety of ligands on threonine desaminase : the occurrence of cooperative effects between identical sites, such as those observed with oxygen and hemoglobin<sup>8</sup> and the effect of

heterotropic ligands like the feed-back inhibitor isoleucine and homologs, some of which like valine, could activate the enzyme. In October 1963, I submitted the first version of my thesis to Jacques Monod, together with other experiments I had carried out in parallel. He was very interested. A sort of "conversion" seemed to have occurred, like a transition between the 1963 model, with Jacob<sup>9</sup>, which succeeded to that of 1961, and another model to come, that of 1965, which was to conclude my thesis and of which I was to be a co-signer. The question arose as to the nature of these conformational changes or allosteric transitions. We had to understand the underlying mechanism. It took place step by step. Back in 1963, I already had a minor disagreement with Monod: we agreed on the distinct sites, but not on the conformational change. Most regulatory proteins known at the time, such as hemoglobin or glycogen phosphorylase, have a complex structure resulting from the stable association of a defined number of subunits. This assembly is called an "oligomer": for example, the assembly of 2 subunits forms a dimer, 4 subunits a tetramer, 6 subunits a hexamer... The isolated subunit has no symmetry, and its assembly with itself (or another homologous protein) creates a stable symmetrical molecule. In certain circumstances, the oligomer can dissociate into its subunits and then re-associate reversibly, and when this aggregation transition takes place, the biological activity of the molecule can change.

A simple model for conformational change was then that the allosteric effector changes the protein's aggregation state. For example, if the monomer is inactive, the activating ligand will stabilize the oligomeric aggregated and active state of the protein. I tested this hypothesis on threonine deaminase, measuring its sedimentation coefficient - an

indicator of the enzyme's aggregation state - in the presence (and absence) of the *feedback* inhibitor isoleucine. There was no effect, a finding that ran counter to what Jacques Monod was suggesting at the time. There was a more discreet conformational change that we had to try to understand. If it wasn't aggregation-disaggregation, what was it?

At that point, I made an observation that surprised me: when I added urea - a molecule that tends to disorganize proteins - to a solution of threonine deaminase, I observed that, at low doses, the enzyme reversibly inactivated itself. I proposed the hypothesis that this was a dissociation-association. That the enzyme, in fact, split into its inactive subunits. The inhibitor isoleucine, in the presence of urea, caused - surprisingly - a reactivation, and hence an aggregation of the enzyme, while the activators (valine, norleucine, and the substrate analogue allothreonine) favored its inactivation, and hence its dissociation. In the paper I presented at the 1963 Cold Spring Harbour symposium<sup>10</sup>, I interpreted this fact as a demonstration that, in the absence of urea, the allosteric transition of threonine deaminase was manifested by a change in the interaction strength between subunits, yet without leading to any dissociation: a discreet conformational transition of protein structure.

The allosteric inhibitor would stabilize a strongly associated or "constrained" state of the oligomer; the substrate or allosteric activators, a "relaxed" state, susceptible to dissociation by urea. These facts and observations were confirmed several years later by Burns and colleagues, using threonine deaminase purified from *Salmonella typhimurium*.

#### 4- FORMULATION OF THE MODEL

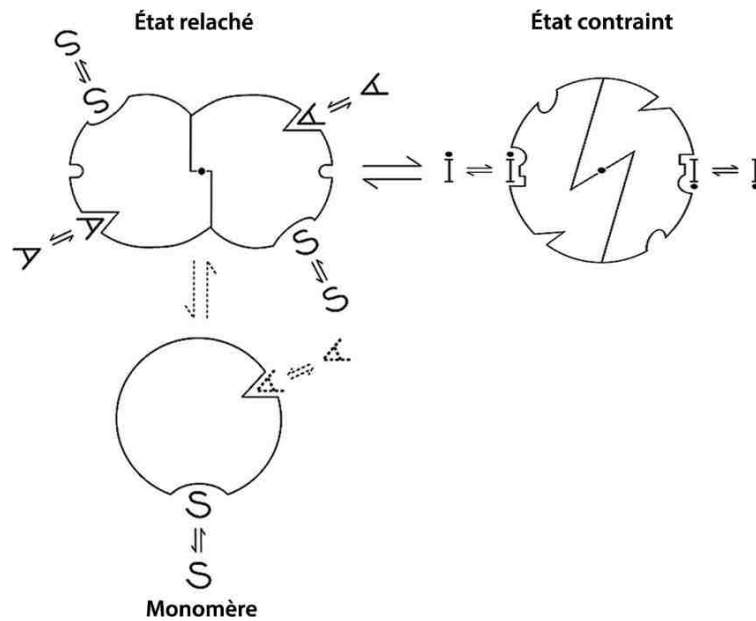
*This aspect of your work must have been of great interest to Jacques Monod...*

That was when I was finishing my thesis work. I was presenting this urea experiment to Jacques Monod. He asked me how I interpreted this discovery. I told him that we had to assume at least three states: a state in which nothing happens; a state in which the activator is present; and a state in which the inhibitor is present. "No" he said, "always make the minimum of hypotheses "two should be enough!" I replied, "I'm afraid you're right." Illumination! At this remark, my imagination exploded, and I instantly realized that two states were enough to explain many things. These complicated relationships between heterotropic and homotropic interactions could be solved very easily by postulating just two states, but these had to pre-exist ligand binding: a "constrained" state and a "relaxed" state. The affinities of each state for the various ligands would be different, and the ligands would shift the equilibrium in one direction or the other, depending on whether it was activating or inhibiting. A kind of "*molecular switch*" between the two states would be present in the absence of ligand and play a critical role in mediating signal transduction. This is the origin of the "Monod-Wyman-Changeux"<sup>11</sup> model (1965).

The model includes not only the idea of two pre-existing states, but also the cooperative effects already noted by Umbarger, explaining it on the basis of the cooperative properties of the protein oligomers and the symmetry of their subunits assembly.

The transition would take place in a concerted fashion, en bloc, for all subunits at once. As if between two symmetrical mini- crystalline states. This accounted for the threshold effect, the molecular switch common to many regulatory proteins. The reference to the symmetry of the hemoglobin molecule had already been suggested by Jeffries Wyman, as early as 1948, which seems to have justified Monod's inclusion of his name as a co- author. It had also been observed by the Anglo-Austrian chemist Max Ferdinand Perutz, with the three-dimensional crystallographic structure of hemoglobin<sup>12</sup>. The model was initially intended to complete my thesis<sup>13</sup>, and I published a first version, based essentially on the experimental data in the Annals of the 1964 Brookhaven Symposium dedicated to the subunit structure of proteins (where I first met John Gerhart<sup>14</sup>).

An interesting philosophical point: the model here is selective, "Darwinian" if you like. The ligand binds differentially to one of the two pre-existing states, shifting the equilibrium in one direction or the other. This is a signal transduction mechanism, transferring a chemical signal into biological activity. Moreover, the same conformational transition accounts for both the interaction between different ligands (ie the effect of the feedback inhibitor) and identical ligands (ie the cooperative threshold effect). A simultaneous change in all the binding properties of various ligands takes place at once. We have a lock which may be open or closed but in addition we have "many keys for the same lock".



### 3. Model of the allosteric transition between two conformational states.

(After Jean-Pierre Changeux, original doctoral thesis, 1964)<sup>11</sup>.

We therefore have evolutionarily selected regulatory proteins in our genes, whose pre-existing regulatory function is influenced by the environment. It's not a question of "instructing", but of modulating a regulation already predetermined by the genome, within a framework that is not "instructive", but "Darwinian" or, if you prefer, selectionist. This notion, central to the Monod-Wyman-Changeux model, represents an authentic intellectual revolution. In the 1963 model with Jacob, credit was given to Koshland and his instructive scheme. From then on, a selectionist schema prevailed, bringing about a real conceptual break in the biophysics of proteins.



*This is the second aspect of allostery...*

The first aspect, which quickly won unanimous support in the scientific community, was the idea of separate allosteric sites. The second was still open to debate. It was the idea of a spontaneous commutation between protein conformations *in the absence* of ligand. The debate between "instructive" and "selectionist" was not just ideological, it was primarily experimental.

Before I left for the USA, the eminent biophysicist Manfred Eigen had come to Pasteur to present initial support for the selectionist model, based on rapid kinetic measurements with glyceraldehyde-3-phosphate dehydrogenase.

During a first post-doctoral position at Berkeley, in the laboratories of John Gerhart and Howard Schachman (who were working on aspartate transcarbamylase), we were able to compare protein conformation and ligand binding as a function of the concentration of ligand. We established that the hypothesis of pre-existing states was, with this system, largely validated by experiment<sup>15</sup>. This was soon to be confirmed and extended in Pasteur by Henri Buc to rabbit muscle phosphorylase b and bacterial phosphofructokinase; by Joël Janin and Georges Cohen to homoserine dehydrogenase from *E. coli*; and by numerous other researchers with other enzymes. To date, the MWC model has been cited more than 10,000 times, which is a very high figure for a theoretical article in biology.

In any case, from a philosophical point of view, the molecular approach to the regulation of protein activity that I adopted for my thesis was in line with the naturalist, or rationalist, perspective of Democritus, Descartes and the

Enlightenment, mentioned at the beginning of this chapter. Jacques Monod referred to it as the "second secret of life". I've never ventured to adopt such a formulation, without denying, of course, the generality of the concept and the total absence of reference to any "vital principle".

## 5- WHERE DOES LIFE BEGIN ?

*Didn't your scientific work and its results go against some of your convictions, leading you to revise them from top to bottom?*

My thesis was nearing completion, when in 1963, responding to an invitation from Jacques Polonovski, a brilliant and sympathetic colleague, I had given a lecture on Rue Madame, organized by the Catholic Union of French Scientists, on the theme: "Where does life begin?" Even though my religious convictions had already been seriously shaken by my own research and the reflexions it had given rise to, and also by my discussions with Jacques Monod, I had agreed to speak before this audience. I gave as faithful and honest a presentation as possible of the laboratory's work, of Jacob and Monod's work on the operon, and of my thesis work.

I concluded: "The living organism thus appears as a set of elementary machines, the cells possessing both individual automatic regulation and collective regulation... at several different 'levels of organization'...". There was no deliberate ideological bias in what I said, but a great deal of frankness and sincerity. My family was there. I wasn't as successful as I'd hoped. For one thing, few questions were asked, but one in particular disarmed me. From the back of the room, an

elderly man stood up, a religious man of very Teilhard de Chardin distinction, and told me that I hadn't understood anything about Life. For him, "Life was spontaneity and immanence", and nothing I had said had answered his questions! Even if the misunderstanding was obvious, the dialogue was broken... definitively.



### **III.**

#### **Discovering a New World**

##### **1- A BRIEF HISTORY OF THE NOTIONS OF PHARMACOLOGICAL AGENT AND RECEPTOR**

*We could start by giving a brief history of the concepts of pharmacological agent and receptor, which will help us to better understand your own scientific contribution in these fields...*

It's a good idea to address this issue, as there are still ambiguities surrounding the division between traditional (and alternative) medicine and scientific medicine. Traditional medicines are still alive and well - just think of homeopathy. We'll come back to this point when we discuss the application of allostery to drug development. But right now, we must remember that there is a very ancient medical tradition, with its roots in the distant past, present in societies without writing, which we call shamanism. The shaman, as part of a social group, resorts to ecstasy, which puts us into a state of trance, during which, says Mircea Eliade, "His soul is supposed to leave the body to undertake celestial ascents or infernal descents"<sup>1</sup>. The shaman is both an intercessor between humans and "spirits", and a healer.

His extraordinary abilities give him the power to heal illnesses. To this end, he uses plants that both induce ecstasy (hallucinogenic effect) and expel evil spirits from the patient's body. This led to the establishment of an initial repertoire of active plants.

In a tomb in Shavidor, Iraq, dating from the Upper Paleolithic (60,000 years ago), the pollens of eight medicinal plants with powerful pharmacological action have been found. Interestingly, people under the influence of hallucinogenic drugs, like shamans, are able to distinguish between hallucinations and reality. The cheetah, for example, can be both a totemic animal with a positive social function and, at the same time, a wildcat that is hunted because it kills animals serving for food. Closer to home, numerous Mesopotamian documents written in cuneiform between 3,000 and 1,000 BC attest to medical practices akin to shamanism. Illness is a divine punishment, and healing a purification-remission of a fault, a transgression. A cathartic process...

*A purification-purgation, as it were...*

The Greeks coined the word "*pharmakon*", meaning both "remedy" and "poison", to designate the magical action exerted by plants to heal (or poison). Two hundred and fifty names of medicinal plants are inscribed on the tablets from the library of Assurbanipal (7th century BC), including mandrake, hellebore, poppy and cannabis. The repertoire expanded with the Egyptians, but it was with the Greeks that genuinely rational medicine developed. This had to do with the cultural context, the birth of the City, and the promotion of public and adversarial debate, which gradually broke with

the cult of secrecy and mystery. The professional doctor differs from the priest. The distinction between diagnosis and treatment, and the critical examination of its effects, gradually freed medicine from irrationality. Hippocrates' *The Sacred Disease* (5th century B.C.) is an illuminating work in this respect. He contrasts rational medicine with "magical" medicine, or shamanism as we would say today. Epilepsy, for example, traditionally seen as a divine sanction (hence its name "sacred disease"), is seen by Hippocrates as any other disease, neither divine nor sacred. His argument is physiological. The evil comes from the brain. He concludes that, to remedy it, "we must distinguish the appropriateness of useful means, without purifications, magic tricks and all that charlatanism"<sup>2</sup>.

*Arab and Persian physicians of the Middle Ages inherited Greek knowledge and passed it on to the West...*

In this respect, two great figures stand out: Razi (or Rhazes), author of a *Treatise on Medicine* in the 9th century AD, and Avicenna, two centuries later, who left a famous medical encyclopedia... Each of them demonstrated a desire to develop rational medicine. With the Renaissance, and the scientific revolution that accompanied it, rationality in medical therapeutics made a definitive name for itself in our part of the world. Paracelsus (first half of the 16th century) introduced the notion of "active principle" and "active dose". In the 18th century, Von Haller recommended that all drugs be tested on healthy subjects before being included in the pharmacopeia. Lavoisier, his near-contemporary, increased the identification of chemical species. The pharmacological agent is now a "defined chemical substance with a toxic or medicinal action, which precisely

modifies the state of the organism, whether healthy or ill".

## **2- CLAUDE BERNARD AND THE PHARMACOLOGICAL RECEPTOR CONCEPT**

In the following century, Claude Bernard, based on experiments on the effects of curare, a substance extracted from certain Amazonian lianas used by Amerindians to coat their arrows, demonstrated that it paralyzes skeletal muscles without interfering with the heartbeat, and that it blocks neither the motor nerve nor the muscle, but the action of the nerve on the muscle<sup>3</sup>. It has no effect on the sensory system. It affects the peripheral parts of the nervous system, but not the central ones. Claude Bernard thus experimentally sought to localize the toxic effects of certain substances in the body. He likened these pharmacological agents to "chemical lancets". And although he was mistaken in believing that curare acts via the motor endings up to the spinal cord, i.e. on the side of the nerve and not the muscle, his work represents a great advance in understanding the mode of action of pharmaceutical agents.

Later, in 1905, the work of John Newport Langley<sup>4</sup>, building on Claude Bernard's experiments, showed that curare acts at the muscle level, and that the action of nicotine opposes the effect of curare. Nicotine causes muscle contraction, while curare blocks it. He then proposed the concept of a "receptive substance" or "receptor", which recognizes a signal coming from the nerve and transmit it to the muscle fiber.

This receptor concept is also the fruit of a reflection stemming from the work of Pasteur who, following his experiments on tartrates, stressed the importance of "molecular dissymmetry", a characteristic of living beings<sup>5</sup>. Meanwhile, in 1898, Emil Fischer synthesized sixteen isomers



of glucose and showed that only four of them were fermentable and stereo-chemically related: "The enzyme and the glucoside must fit together like a *key* to a *lock* if they are to perform a chemical action on each other<sup>6</sup>". At the same time, the physiologist Thomas R. Elliott puts forward the idea of chemical transmission with the adrenergic system<sup>7</sup>. He suggested that it is a "stimulatory secretion" released by the nerve that causes the muscle to contract. This is called a "neurotransmitter". Several hundred of these substances have been identified in the brain, acting as intermediaries in chemical communication between neurons and muscular or glandular targets, and between neurons themselves. The best known are acetylcholine, adrenalin, dopamine...

### **3- TOWARDS A MOLECULAR BIOLOGY OF THE PHARMACOLOGICAL RECEPTOR**

*This allows us to consider that the nervous network is in fact a chemical network...*

The brain is a chemical communication system. A chemical machine, if you like. The concepts of pharmacological agent and receptor take on their full meaning when associated with a third, complementary concept, that of chemical neurotransmission. The neurotransmitter is a chemical substance. This is an essential step towards understanding how the brain works. Conceiving of the brain as a chemical machine - a point of view I firmly defend - is therefore nothing new.

*As knowledge of the nervous system expands, new disciplines will emerge...*

For a long time, the anatomical approach to the brain was predominantly macroscopic (Vesalius, for example, had already described cerebral convolutions in detail in the 16th century), then microscopic, starting in the late 17th century, which led to the study of nervous tissue in the 18th and especially 19th centuries. Descartes had already spoken of nerve fibers and cell bodies, but the relationship between the two was unknown to him. It wasn't until the work of the Spaniard Santiago Ramón y Cajal (1852-1934) that the notion of the neuron or nerve cell took hold. He distinguishes a cell body and several extensions: including a long axon on which the signals circulate from the cell body to the periphery and multiple dendrites that collect information from other neurons to the cell body. Neurons form an immense network, but one that is not continuous. The fundamental hypothesis proposed by Cajal as early as 1888<sup>8</sup> is that neurons establish discontinuous contacts with each other, known as "synapses". At synapses, cell membranes are juxtaposed, leaving a gap between them, a synaptic cleft. The discontinuity of the nervous network was definitively demonstrated, much later<sup>9</sup>, with the use of electron microscopy, which allows magnifications 1,000 times greater than optical microscopy. At the synapse, the membranes of the cells in contact remain separated by a distance of around 20 nanometers. The synapses themselves are small: the size of a bacterium. There are around 100 billion neuronal cell bodies and around 10,000 times that number of synapses in the *Homo sapiens* brain. Information therefore circulates mainly through a system of interconnected neurons, the famous "*neural networks*" that computer scientists try to simulate, without referring, unfortunately, to the fact that much of the rapid

communication at the synapse level is « chemical ».

*What signals circulate in the nervous system ?*

It is not chemical signals that travel along the axons, but an electrical wave called the "Action potential" (or "nerve impulse"), which results from a selective change in membrane permeability to sodium and potassium ions<sup>10</sup>. There is a difference in ion concentration between inside and outside the cell. Sodium, for example, a depolarizing agent, is in short supply inside the cell and rich on the outside. The opposite is true of potassium, which is a polarizing agent. The propagation of nerve impulse along axons occurs at a speed that is less than that of sound, far from the speed of light, as is the case in computers. Sound travels at 36 km/s, light at 300,000 km/s. We now know that the molecules acting as ion channels are "allosteric" proteins, and that their molecular transitions impose an irremediable time constraint. We'll come back to this later. It may come as a surprise, but that's why the brain is so slow!

At the synapse, when the nerve impulse arrives at the nerve ending, the electrical wave does not directly cross the synaptic space (except for so-called electrical synapses). Chemistry takes over from electricity. In the classic case of a chemical synapse, a neurotransmitter is involved. Electrical invasion of the terminal leads to rapid release of the neurotransmitter, whose concentration rises rapidly and transiently in the synaptic space. This brief burst of neurotransmitter spreads to the membrane of the next cell, reaches the receptor and triggers a new electrical response. All this happens in less than a few thousandths of a second.

The synaptic response can mobilize a transport of positively

charged Na<sup>+</sup> K<sup>+</sup> cations and create a transient depolarization that will result in the start of a new propagated nerve impulse. The synapse is said to be excitatory. This is the classic mechanism proposed by Henry Dale<sup>11</sup> and then Bernard Katz<sup>12</sup> with the neuromuscular junction. Acetylcholine or glutamate are excitatory neurotransmitters.

But our brain knows about inhibition, and a specialized process comes into play. As first shown by John Eccles<sup>13</sup>, in the case of inhibitory neurons or synapses, the electrical response of the synaptic membrane is a hyperpolarization that blocks the departure of nervous influx. Gamma aminobutyric acid or glycine are highly abundant inhibitory neurotransmitters.

Most of what we know about communication in the nervous network has been acquired through electrophysiological methods. Some people speak of a "dry" neuroscience, which would be distinguished from a "wet" neuroscience. Electrophysiologists, with their electrodes, make "clean" recordings, but don't get their hands wet looking for the molecular mechanisms involved in producing the signals they record. An important commitment for me, right from the completion of my thesis, was to try to make the link between the two approaches, electrophysiological and biochemical, and not to pit them against each other. David Nachmansohn's research work was an important source of inspiration for me in this respect.

#### **4- DAVID NACHMANSOHN (1899-1983)**

*A figure you've already mentioned in connection with your stay at the Arcachon marine resort...*

In Arcachon, I'd only heard in the course of a few quotes of his works... It was in New York, later, that I met him. He looked a little like Erich von Stroheim in *La Grande Illusion*, with a certain stiffness of posture, a head carriage and the elegance of a Prussian officer. either in French or English. His family, of Russian-Jewish origin, had fled the pogroms and settled in Berlin, where he attended the Gymnasium. His knowledge of Greek was sufficiently advanced to enable him to read Homer, Sophocles or Plato in the text. He was also an avid reader of Spinoza's *Ethics*. He studied medicine at the University of Berlin, where he met those who were to discover the fundamentals of cellular chemistry: Hans Krebs (Krebs cycle), Ernst Chain (therapeutics and chemistry of penicillin) and Fritz Lipmann (coenzyme A). Then he joined Otto Meyerhof's laboratory at the Kaiser Wilhem Institute in Berlin-Dahlem (the equivalent of our CNRS, fifty years ahead of its time), which would decide his future direction. Otto Meyerhof is one of the representatives of the great Berlin physicalist tradition which, since Emil du Bois-Reymond and Hermann von Helmholtz, has striven to reconcile physics, chemistry and physiology, including thermodynamics, in order to understand the phenomena of life ("from the Helium atom to the flea"). Nachmansohn's spirited determination to demonstrate the chemical basis of animal electricity, illustrated in his seminal book *Chemical and molecular basis of nerve activity*<sup>14</sup>, was a direct descendant of this tradition.

*It was to this Berlin school that we owe the famous "physicalist oath »...*

Brücke, Helmholtz and Du Bois-Reymond had, in 1842, taken a solemn "oath": "[We pledge] to put in power this

truth: no other forces than the common physical chemical ones are active within the organism. In those cases which cannot at the time be explained by these forces one has either to find a specific way or form of their action by means of physical mathematical method, or to assume new forces equal in dignity to the chemical-physical forces inherent in matter, reducible to the force of attraction and repulsion”, “the only way the scientist could learn about these forces was through experimentation and observation.” I share this point of view.

Like many scientists of Jewish descent, Nachmansohn left Germany when Hitler came to power in 1933, and settled in Paris, where the Sorbonne offered him a professorship. In London, he attended meetings of the British Physiological Society, where he met Henry Dale, an emulator of John Newport Langley, who would prove decisive for his career. He learned of his theoretical model, much debated at the time, according to which acetylcholine acts as a neurotransmitter at the nerve-muscle synapse. Having chosen to pursue this line of research, Nachmansohn made an original contribution to the theoretical project by working on the enzyme acetylcholine terase, which hydrolyzes acetylcholine and rapidly eliminates it from the synapse. In particular, he shows with the French anatomist René Couteaux, in agreement with Dale's model, that acetylcholinesterase is present at much higher concentrations at the neuromuscular junction than in the rest of the muscle or motor nerve.

In the tradition of Du Bois-Reymond, he focused on the electrical organs of the Torpedo ray (*Torpedo*) and the Gymnote (*Electrophorus*), fish that produce electrical discharges of up to 20-60 volts, 50 amperes in the case of

the Torpedo, or 250 volts, 0.5 amperes in the case of the Gymnote. In Paris in 1936, he discovered the extreme richness of acetyl-cholinesterase<sup>15</sup> in the electric organ. This prompted him to carry out a seminal experiment with this organ in June 1939, at the Arcachon marine biology station. Together with Wilhelm Feldberg (pharmacologist in Dale's group) and Alfred Fessard (electrophysiologist at the Sorbonne), Nachmansohn demonstrated that injection of acetyl-choline into the artery supplying the Torpedo's electrical organ resulted in a major change in electrical potential between the ventral and dorsal sides of the organ. This was the first demonstration of the electrogenic effect of acetylcholine. The results were published in the midst of the war, in 1940, in the *Journal of Physiology*<sup>16</sup>.

The rise of Nazism forced Nachmansohn and his family to leave France in 1939. He joined John Fulton at Yale (a researcher who did not believe in chemical synaptic transmission), before settling permanently in 1942 at Columbia University, College of Physicians and Surgeons, New York. It was here that he made his major discoveries: the identification of the first enzyme for the biosynthesis of a neurotransmitter (acetylcholine), choline acetyltransferase; the chemical dissection of the catalytic site of acetylcholinesterase; the development of the isolated electroplaque the basic component of the electric eel electric organ; the purification of acetylcholinesterase...

*When do you meet David Nachmansohn?*

I first met him at Columbia in October 1965. Very quickly, a deep bond developed between us, which continued without the slightest hitch until his death. Perhaps I aroused in him a hint of nostalgia for those happy scientific and family moments he had experienced in Paris?

Even after my visit to Columbia, he never ceased to support me, helping me to set up my molecular neurobiology laboratory at the Institut Pasteur, and to equip it with the electroplate recording system. And our frequent visits to each other, in Paris and New York, were always warm and rewarding.

In spite of this, there was a single serious intellectual disagreement between us, which remained unspoken right up to the end, and which concerned the mechanism of synaptic transmission. While working in Paris, not only did he agree with Dale's model, but his research had provided further evidence in its favor. During his time at Yale, his ideas changed completely. The model now put forward by Nachmansohn, a very heterodox one, was the complete opposite of Dale's: the neurotransmitter, in this case acetylcholine, would be involved in the propagation of action potential along the axon, but not in the transmission of the nervous impulse at the synapse! Acetylcholine would lose its status as a synaptic neurotransmitter. This idea, surprising if ever there was one, was so dear to his heart that he constantly presented it in public.

*A curious theoretical about-turn, which is difficult to explain...*

His thesis earned him very tenacious hostility, which I wouldn't hesitate to describe as ferocious, from some of the biggest names in electrophysiology at the time, such as Bernard Katz and Steven Kuffler. And, in turn, this backfired on me, being one of his close friends... In fact, he would often take me aside, and without witnesses, to explain the scientific arguments which, according to him, justified his theory. I always listened with attention, patience and - perhaps surprisingly - affection. He never questioned me



directly about what I thought. For my part, I never asked him to explain his change of position in the 1940s...

At all costs to avoid offending him, I never admitted to him that I didn't share his views...

## **5- FIRST WORK ON THE NERVOUS SYSTEM AT THE INSTITUT PASTEUR**

*Does it make sense to extend the allosteric model to the study of the brain?*

As I was finishing my thesis in 1964, immobilized at home by the consequences of a skiing accident, I wondered what field of research I could now devote myself to. At the time, I was reading two fundamental books: David Nachmansohn's one on bioelectricity, *Chemical and Molecular Basis of Nerve Activity* (1959), and John Eccles' *The Physiology of Synapses* (1964). These readings convinced me that I'd get nowhere by following the pure electrophysiology route, "à la Eccles", but that Nachmansohn's approach was more appealing.

At the end of my thesis, I explicitly stated that "we should one day try to recognize, in the membrane phenomena that give rise to both the recognition of stereospecific metabolic signals and their transmission, the synaptic transmission, for example, mechanisms analogous to those described in connection with allosteric proteins". I took the risk of writing these words. After the defense, I reflected on a possible postdoctoral position. There were two possibilities: either to pursue the "Monod-Wyman-Changeux" model and go to Berkeley, California, to seek to demonstrate some

important propositions of the two-state model; or to orientate myself towards the study of the nervous system and join David Nachmansohn's laboratory.

*Did you move to the United States immediately after submitting your thesis?*

I stayed on at the Institut Pasteur for a few more months, during my military service, and set myself the task of trying to identify the acetylcholine receptor in the electric organ of the Torpedo fish, which I knew, from my first stay in Arcachon, to be extremely rich in cholinergic synapses, all identical to each other - a veritable "culture" of synapses. Several attempts at its identification were underway, mainly in South America, for a simple reason: the main electric fish known for its powerful discharges, the electric eel *Electrophorus electricus*, lives in the waters of the Amazon and Orinoco rivers. However, these attempts were unsuccessful, as were those of Nachmansohn, due to a lack of suitable labelings. Aware of these initial failures, I wondered whether acetylcholinesterase might not be a potential acetylcholine receptor target. It had been demonstrated, in David's laboratory among others, that the chemical specificity of acetylcholinesterase was different from that of the receptor. Could an allosteric site on the esterase serve as a receptor? On this basis, and taking advantage of my assignment at the Institut Pasteur, I continued my research work. It was on this occasion that I met France Tazieff-Depierre, a pupil of Daniel Bovet and herself under contract to the army...

*The wife of vulcanologist Haroun Tazieff! What's the army doing here?*

Because chemical weapons - "nerve" gases such as sarin or soman - whose toxic effects are well known, have been used for decades are powerful inhibitors of acetylcholinesterase, the enzyme that destroys acetylcholine at the synapse. The search for an antidote was (and still is) an important issue for national defense. France Tazieff-Depierre, a close collaborator of Daniel Bovet, gave me a rich collection of cholinergic derivatives synthesized by Bovet and Ernest Fourneau, including flaxedil (the first synthetic curariform used in surgical anesthesia). Working on the electrical organ of the Torpedo fish, I discovered in 1965-1966 that flaxedil had an effect on acetylcholinesterase, at a site that was not the catalytic site, but a kind of allosteric site, which I named at the time peripheral anionic site. "I was not convinced that I had discovered the receptor, but I'd my first hint of taste of the cholinergic system<sup>17</sup>.

## **6- STAYS IN THE UNITED STATES (1965-1967)**

*It was then that you left the Pasteur Institute for a long stay in the United States...*

After a short stay in Buffalo, in the summer of 1965, with Harold Segal, where I had been able to confirm my work at Pasteur, and before going to California, to Berkeley, to Gerhart and Schachman's laboratory, I went to visit David Nachmansohn in New York. It was, as I said, our first meeting. I also met up with my wife and son, who had

arrived from France by boat. In front of his team, I gave an initial, very informal talk on the state of my research and, in particular, the extension of the allosteric model to the acetylcholine receptor. Among the listeners was Arthur Karlin, who was particularly interested. He was working on the electroplaque, the basic cell of the Torpedo fish's electrical organ. The idea of doing an internship with him crossed my mind, and I approached him. He refused, as it was his project and not mine, and he also wanted to work on receptor allostery. As it happened, we met again later, on the occasion of a prize awarded to me by the National Academy of Sciences in Washington, D.C., when he told me that, in refusing my request, he had made the mistake of his life. Nevertheless, Nachmansohn agreed to welcome me to his lab on my return from Berkeley.

*What profit did you gain from your Californian postdoctorate?*

My stay at Berkeley, from October 1965 to March 1967, in the Molecular Biology Department, had gone very well, but I wanted to move away from the study of bacteria and focus on higher organisms.

An unexpected meeting with the famous physicist Max Delbrück led to my decision. In 1966, during my post-doctoral position at Berkeley, he invited me to give four lectures on allostery at the California Institute of Technology (Caltech). He was an eminent researcher who, along with other physicists such as Schrödinger, had initiated the first attempt to find an answer to the question "What is life ?

At my first lecture, he gave me a surprising introduction. The title of Peter Weiss's play, which was much talked

about at the time, *The Persecution and Assassination of Jean-Paul Marat by the Inmates of the Asylum of Charenton Under the Direction of the Marquis de Sade*, had become, revisited by Max Delbrück: *The Persecution and Assassination of Jean-Pierre Changeux by the Inmates of the Institut Pasteur Under the Direction of the Marquis de Monod* - a humorous way of highlighting the conditions of my thesis work. At the fourth conference, I suggested extending the concept of allostery to synaptic transmission in the nervous system. On that occasion, I evoked my experiments on acetylcholinesterase, pointing out that we could imagine, at the level of the synaptic membrane, receptor organizations larger than a simple symmetrical oligomer. He reflected this idea with a German postdoctoral fellow.

Delbrück recommended that I meet Charles Kittel, who taught solid state physics at UC Berkeley. He was a great Francophile - all the furniture in his apartment was of French origin - and every year he invited all the French post-docs on campus, to a dinner with Parisian baguette and fine wines. We established a very fruitful collaboration, which led to a theory based on the idea that a receptor, such as that for acetylcholine, could associate with itself and form a two-dimensional cooperative network, a kind of micro-crystal in the plane of the post-synaptic membrane. This would make possible a cooperative transition between receptor molecules, with all-or-nothing effects - or phase transitions - that could be described on the basis of a classical model of statistical physics called "spin glasses". The paper published<sup>18</sup> met with some success, except that no cooperative effects between receptors have yet been observed in the brain! Only in bacteria. Thirty years later, cooperative receptor networks were identified by Dennis

Bray<sup>19</sup>, in the case of the tropism of bacterial cells to certain chemical stimulants, and interpreted as follows on the basis of our model... The observation of non-linear effects of this nature in living beings remains an interesting possibility...

*But it didn't work for the brain!*

As far as synaptic transmission is concerned, this can't work. If it were to "work", it would only be once, because then the whole synapse would be blocked for a long time by a hysteresis effect. Additional energy would have to be supplied to quickly return it to physiological time. This was my first work with physicists. They taught me that, to fully understand any phenomenon, you first need to produce a mathematical model of it. Not a common idea in the life sciences.

*Then you return to New York...*

This highly instructive experience with Charles Kittel and Max Delbrück encouraged me to pursue my research towards higher levels of organization than the bacterial cell, and strengthened my desire to work on the nervous system. David Nachmansohn hosted me at Columbia University from March to October 1967. I wanted to take part in the identification of the acetylcholine receptor, using the electric organ I knew so well. At the same time, I wanted to familiarize myself with the electrophysiology of the basic cell of the electrical organ, the electroplaque, and thus understand the *in vivo* pharmacology of this receptor, before considering *in vitro* studies. The idea was to work from the cellular to the molecular system. It was a wonderful six months, spent to dissect the electrical organ and make

electrophysiological recordings using my own hands. With another researcher, Thomas Podleski<sup>20</sup>, we carried out electrophysiological dose-response experiments. This led to the publication of a first electrophysiology paper devoted to the allosteric properties of the acetylcholine receptor. In California, at the Salk Institute in San Diego, I met Jon Singer, who offered me a sample of an "affinity marker", TDF, which he had previously used with antibodies. This molecule shares a trimethylammonium group with acetylcholine, together with a reactive diazonium group. The mechanism postulated was that TDF would bind to the receptor site and once bound establish an irreversible covalent bond with the protein. TDF behaved with the electroplaque as expected. There was thus the possibility of affinity labelling of the receptor<sup>21</sup>.

## **7- RETURN TO PARIS AND DISCOVERY OF A SNAKE VENOM TOXIN AND PURIFICATION OF THE RECEPTOR**

*Back from the United States, you're back at the Institut Pasteur...*

Back in Paris, in the small laboratory generously made available to me by Jacques Monod, I continued the study of electroplating with Thomas Podleski, who had joined me, and a young researcher I had recruited Jean-Claude Meunier. I had difficulties in trying to extract the TDF-labelled protein. For his part, Arthur Karlin, in 1968, inspired by early work on allosteric enzymes, established that the electroplaque is sensitive to agents that reduce -S-S- disulfide bridges to -SH- thiol residues<sup>22</sup>. He synthesized a homologous derivative of TDF (MPTA), as it possessed a reactive group which covalently bound to the thiol groups<sup>23</sup>.

But even if ameliorated the selectivity of the technique soon proved insufficient to isolate the receptor in an active form from crude extracts of electrical organs.

*Competition between laboratories, which can be fierce, also has beneficial effects on scientific research...*

First, there's validation. What has been demonstrated by one team can be reproduced by another, and is therefore transmissible. Secondly, there is intellectual emulation and an enrichment of knowledge, through a diversification effect. This is sometimes difficult for researchers who, to withstand the competition, have to constantly test new ideas. Several teams of researchers were therefore in competition. I felt we had to do things differently, to come up with an original idea. As it happened, Monod had taken on a Japanese post-doctoral fellow, the physicist Michiki Kasai, whom he didn't quite know what to do with. He generously put him at my disposal. We both demonstrated (1971) that membrane fragments purified from the electric organ are capable of closing in on themselves in closed vesicles, or "microsacs", from which it becomes possible to measure fluxes of radioactive Na<sup>+</sup> (or K<sup>+</sup>) ions by a simple filtration method. Better still, the microsacs responded by increasing ionic flux to "nicotinic" cholinergic effectors with a specificity very close to that observed with the electroplaque and the neuromuscular junction. This made it possible to study the "chemistry" of the physiological acetyl-choline response *in vitro*<sup>24</sup>.

A second discovery, just as decisive, was linked to a chance encounter. In the spring of 1970, France Tazieff-Lapierre told me over the phone that a Taiwanese pharmacologist, Chen-Yuan Lee, who was presently in her



laboratory, wanted to see me. I received him. He had read a recent article on acetylcholinesterase in which I suggested that the receptor site, although distinct from the active site of the enzyme, could be an allosteric site of a protein complex common to the esterase and the receptor molecule. He had, he told me, the means to verify or invalidate this hypothesis. He had been working for years on a snake venom toxin (from Bungarus, a type of Taiwanese cobra),  $\alpha$ -bungarotoxin, which he had isolated and purified and which, he claimed, blocked neuromuscular transmission in higher vertebrates, at the postsynaptic level. The toxin is active at very low doses and is virtually irreversible. It was an illumination, for this was exactly the "chemical lancet" I was looking for. At my request, he provided me with a sample of the toxin, which I immediately tried out. The results were remarkable, and I was soon able to demonstrate that bungarotoxin blocks both *in vivo* the electrical response of electroplating and *in vitro* the ionic flux response of microsacs to nicotinic agonists. It also blocks *in vitro* the binding of a nicotinic agonist, decamethonium, to a macromolecule I had previously solubilized from a microsacs preparation, using a mild detergent. The receptor protein had thus been identified! I wrote a paper (1970) and sent it to Jacques Monod, who enthusiastically forwarded it to the *Proceedings of the National Academy of Sciences*, the prestigious American scientific journal<sup>25</sup>. We were the first to demonstrate, on the one hand, the effect of the toxin on the receptor of the electrical organ and, on the other, to find in organ extracts a temperature-sensitive molecule, destroyed by proteolytic enzymes and distinct from acetylcholinesterase. The idea of an allosteric site for acetylcholinesterase was thus abandoned. *In vitro* and *in*

*in vivo* analysis yielded a single protein tagged with both nicotinic ligands and snake venom toxin.

It had to be purified under solution conditions with a non-denaturing detergent. The toxin played an essential role in quantifying the receptor protein being purified and, better still, in purifying it. The first method I used involved coupling the toxin to microbeads of sepharose (a polysaccharide extracted from algae), on which it is immobilized but still active. By mixing these beads with crude extracts of electrical tissue, we found that 75-100% of the receptor protein binds to the beads, while 85-100% of the acetylcholinesterase remains in the supernatant<sup>26</sup>. These results confirmed Chen-Yuan Lee's original intuition concerning the distinction between the two proteins, but they also introduce a new purification method: affinity chromatography<sup>27</sup>. Many groups are contributing to this field of research<sup>28</sup>. The affinity column we use with immobilized quaternary ammonium enables us to purify the receptor in large quantities and with a high level of purity<sup>29,30</sup>.

*The publication of this work must have had a major impact on the world of neurobiology...*

It has had considerable repercussions... worldwide.

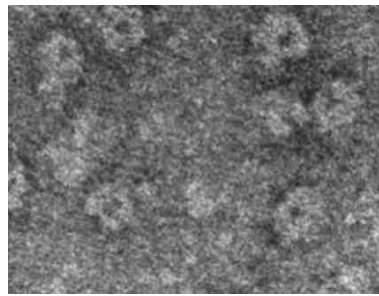
However, first we had to confirm that the purified protein was indeed the physiological receptor *in vivo*, but also, and, above all, to relate it all to man. In humans, there is a very disabling disease, autoimmune myasthenia *gravis*, which manifests itself as paralysis of the neuromuscular junction. Patients are very tired, flaccid and unable to open their eyes. A rival team in California at the Salk Institute, co-directed by one of my former postdocs, James Patrick, had also succeeded in purifying the receptor from the electric organ

and injected it into rabbits. He was looking for anti-receptor antibodies and eventually use them to localize the receptor *in vivo*. His team found that the rabbits became flaccid, that their ears fell off. They showed the clinical signs of myasthenia. Anti-electrical fish receptor antibodies blocked receptors at the nerve-muscle junction in rabbits<sup>30</sup>. This provided both a brilliant demonstration of the purified protein's intervention at the nerve-muscle junction *in vivo*, and an animal model of the human disease<sup>31</sup>. This experiment provided further proof of the value of basic research. Working on the electric organ of the *Torpedo* fish or of the electric eel leads directly to practical applications in public health, in this case, to the understanding of a human disease. It was the discovery of the receptor that enabled us to understand this disease!

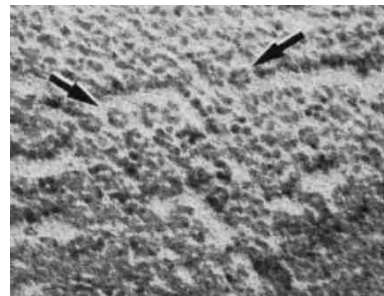
## 8- THE RECEPTOR MOLECULE

*Now you can start visualizing the receptor...*

Once the receptor had been purified, we attempted to "see" it directly by examining the purified preparation under the electron microscope with a high resolution giving access to the molecular level. Backed by Jean Cartaud's expertise, we reveal an unexpected image: a homogeneous sowing of multiple particles around nine nanometers in diameter, in the shape of doughnuts. They are circular with a central depression of around 1.5 nanometers (millionths of a meter). If we look at them in detail, we can see that they are made up of subunits, 5 (or 6) in number (see arrow), suggesting that the molecule is an oligomer<sup>32</sup>.



*Electrophorus*



*Torpedo*

4. First images of the acetylcholine receptor after purification from the electrical organ of the electric eel (left), in place in the Torpedo sub-synaptic membrane (right). (Adapted from Cartaud *et al.* 1973)<sup>32</sup>.

Previously used allosteric proteins, such as *threonine deaminase* or *aspartate transcarbamylase*, were globular (or spherical). They were perfectly symmetrical. Here, we were dealing with a new category of molecules, highly interesting because they were inserted into a biological membrane. Because it's integrated into the synaptic membrane, the receptor is exposed to the synaptic cleft and the cytoplasm. In between, it interacts with membrane lipids (which the detergent disperses during the release in solution). We therefore expect an oligomer with a *sui generis* organization, whose symmetry properties may differ in several respects from those of classical globular proteins. A first step in elucidating this problem was to evaluate the size of the molecule and its possible forms. This was achieved by electrophoresis, in which molecules are caused to migrate through an agar gel by the application of an electric field that moves them more or less far, depending on their size. A molecule with a high molecular mass moves very little, and vice versa if its mass is low. If the molecule splits into

subunits of low molecular weight<sup>33</sup>, it is an oligomer made up of several subunits. But what about the receptor?

*In view of the allostery model...*

An initial study carried out in my laboratory by Ferdinand Hucho<sup>34</sup>, a German postdoctoral fellow, and others in parallel by several research groups in the USA, including Arthur Karlin<sup>35</sup> and Michael Raftery<sup>36</sup>, showed that in the presence of denaturing detergent, the receptor dissociates into smaller subunits. It is therefore an oligomer. But, first surprise, these subunits appeared to be different from one another. In fact, there are four types of subunit of slightly different sizes:  $\alpha$   $\beta$   $\gamma$   $\delta$ . Secondly, by differentially and covalently linking these subunits together in the native oligomer, Hucho separated five bands suggesting a five-subunit - pentamer - organization of the oligomer. One of the four subunits was repeated twice. The result was an incredibly baroque structure  $2\alpha$   $\beta$   $\gamma$   $\delta$  with a total molecular weight of 250,000 daltons. Karlin and Raftery, who hadn't fully assimilated the concepts of allostery - even though one of them had written a paper on the subject<sup>37</sup> - didn't react. But for me, this raised at least two major difficulties...

In classical allosteric oligomers, the symmetry axes are of order two, and possibly of order three. Jacques Monod - driven by his Platonic inclination - was convinced that allosteric proteins should preferably be dimers or tetramers with even-order symmetries. Here, however, we were confronted with a first paradox: five bands, five subunits. A pentamer! What's more, this curious oligomer appeared incredibly baroque... assembling four different types of subunit in a jumble. The question then arose: was this bizarre object totally lacking in symmetry? Or did it possess some

kind of hidden symmetry? The answer came with the development of a new technology.

*How can such a problem be solved, given that, as we've seen, competition between groups is very intense?*

Faced with fierce competition between laboratories, we tried to solve the problem by applying a new technology, developed in Donny Strosberg's laboratory, to identify the precise sequence of amino acids making up a protein chain. This was done in my laboratory, in 1979, by Anne Devillers-Thiéry<sup>38</sup>. The sequence of the first twenty N-terminal amino acids of the  $\alpha$ -subunit was established. This was the first "identity card" for the nicotinic receptor. Other cards will subsequently be established, with receptors of the same pentameric family, or with other receptors. This identity card was the gateway to deciphering the receptor's biochemical structure. A race against time: Raftery, in his Californian laboratory, with more advanced technological resources than in Europe, confirmed our results on the  $\alpha$  subunit and then revealed the N-terminal sequences of the other three subunits<sup>39</sup>. A thunderbolt. It shows that significant sequence homologies exist between the four subunits. The receptor molecule might not be so baroque after all. Could symmetry have been resurrected?

I land on my feet. I'm delighted with this result: the receptor molecule can now be considered to possess fifth-order "pseudo-symmetry", with its axis of rotation perpendicular to the plane of the membrane. For me, this is an important step towards understanding the structure of the molecule. The receptor is indeed an allosteric oligomer, but with a very new symmetry. We didn't stop there, of course. The next step was to establish the complete sequence of all the sub-units. A new

technique had just been developed, involving two steps: cloning the complementary DNA and then sequencing it. At the time, this was highly sophisticated genetic engineering for a neurobiology laboratory!

*Had other neurotransmitter receptors already been cloned and sequenced?*

This was the first attempt to clone and fully sequence a neurotransmitter receptor. Initially, this method requires the messenger RNA of each subunit present in the electrical tissue to construct a complementary DNA (cDNA) by reverse transcription. We rapidly obtained the first cDNA clones<sup>40</sup> in parallel with James Patrick and Stephen Heinemann's group<sup>41</sup>. After establishing their complete nucleotide sequence, we deduced the total amino acid sequence of the subunit.

Sequencing of the cDNAs of the four subunits was carried out by several groups worldwide, almost simultaneously: Shosaku Numa from Japan, a pioneer in this field<sup>42</sup>, Patrick-Heinemann and Barnard. At the same time, in my laboratory, Anne Devillers-Thiéry and Jérôme Giraudat<sup>43</sup> obtained the complete sequence of the  $\alpha$  subunit of the European Torpedo receptor (*Torpedo marmorata*), which is known to contribute to the receptor site.

Comparison of the amino acid sequences of the four aligned subunits confirmed the significant homologies already noted between subunits, and was therefore consistent with a pseudo-symmetry of the receptor. At this stage, however, these sequences are only one-dimensional. To make progress in understanding the spatial organization of the oligomer, we need to move from one dimension to three. For proteins in general, this poses a very difficult problem. Along with

Numa<sup>44</sup> and others, we have been content to propose a first - intermediate - two-dimensional model. It will prove extremely useful. It is based on an organization of the receptor that reflects the fact that it crosses the synaptic membrane from one side to the other and has transmembrane polarity. A novelty compared with the globular structure of classic allosteric proteins! The model distinguishes between several domains: a large N-terminal hydrophilic domain, four highly hydrophobic stretches and a small hydrophilic domain. Functionally, we demonstrate that the large domain is exposed to the synaptic space and carries the active site, that the four hydrophobic segments cross the membrane - one of them delimiting the ion channel - and finally that the small hydrophobic domain is exposed to the cytoplasm and can be modulated by signals from the cytoplasm.

*Is this model valid for other neuronal receptors?*

It will soon be shown that this model of trans-membrane organization of the nicotinic receptor applies to other pentameric receptors. The teams of Patrick and Heinemann, in the USA, and Marc Ballivet and Daniel Bertrand, in Geneva, have demonstrated this with the identification of new nicotinic receptors species present in the nervous system and the brain, in particular. These neuronal receptors are made up of several novel subunit types, including  $\alpha$ -4,  $\beta$ -2 and  $\alpha$ -7, with the  $\alpha$  subunit always engaged in the active site. These oligomers resemble the muscle oligomer, albeit with a perfectly symmetrical neuronal receptor,  $\alpha$ -7. A total of 16 nicotinic genes have been identified in the human genome, and the subunits they encode can associate with each other to form a considerable number of oligomers.



The majority of nicotinic receptors are found in the nervous system, but some are also found in other parts of the body (skin, digestive tract, immune cells, lungs...). Each combination of subunits has its own pharmacology and can be targeted by a particular drug. This diversity creates both an advantage (a wealth of different targets for drugs) and a difficulty (how to distinguish between them?). For this, we can draw on the two-dimensional organization model proposed for the Torpedo receptor, which appears to be very general. It applies to neuronal receptors as well as to all pentameric receptors<sup>45</sup>.

*It is therefore a first to have succeeded in identifying this muscle receptor...*

Other pentameric receptors were subsequently isolated and biochemically identified: those for GABA ( $\gamma$  - aminobutyric acid) and glycine, which are inhibitory receptors. Inhibitory receptors have a chlorine-permeable ion channel, whereas the ion channel of excitatory receptors lets cations through. These receptors have their own pharmacology. The GABAA receptor is the target of benzodiazepines, one of the most widely prescribed psychotropic drugs (to relieve anxiety, stress and insomnia), and of general anesthetics. The glycine receptor is the target of strychnine, a highly toxic alkaloid extracted from the vomiting nut, which in low concentrations is used for its stimulant properties. Finally, the 5-HT<sub>3</sub> receptor is excitatory and the target of serotonin and anti-nausea drugs.

Following the nicotinic and pentameric receptors, several other major classes of neurotransmitter receptors were identified several years later, which are also the target of many drugs. These include G-protein receptors by Lefkowitz (1986),

which include olfactory receptors, and tyrosine kinases by Schlessinger (1984) sensitive to growth factors and involved in cancer, and also pain receptor channels by Julius (TRP, 1997), which are channel receptors, structurally different from the nicotinic receptor, but functionally close. Myriads of receptors have now been identified in all living organisms.

This major set of biochemical discoveries has opened up a field of research that has become gigantic in just a few decades. It is profoundly renewing our understanding of the chemistry, pharmacology and pathology of our brains, as well as that of our organism as a whole<sup>46</sup> ... It is indeed the discovery of a new world!

## IV.

### Designing a drug

#### 1- WHAT IS A DRUG ?

*Why take an interest in drugs?*

The discovery and exploration of the "new world" of receptors is expected to be accompanied by important developments in the understanding of the fundamental processes of cellular life and higher brain functions. Since my early work on allostery, I've always been concerned with the general question of the impact of scientific progress on society, even if my work has remained essentially devoted to fundamental research... Among these consequences for society, the design and development of new drugs hold a particularly important place. The brain, as we know, is the victim of such crippling diseases as Alzheimer's, schizophrenia, autism and depression. The burden on society is considerable. As a conservative estimate, in Europe in 2010, around 165 million people suffered from Alzheimer's, schizophrenia, autism and depression.

The total cost is estimated at 800 billion euros. The launch of new treatments is urgently awaited, even if it often gives

rise to heated debate. These interviews provide me with the opportunity for a new personal experience: that of trying to assess, retrospectively, whether reference to receptor allostery opens up original perspectives in drug design.

*We've seen that a pharmacological agent can be both a poison and a remedy. But what is the precise definition of a medicine?*

Medicines are the opposite of both toxic agents and ineffective procedures. The notion of medicine is precisely defined by the French Public Health Code (art. L5111-1): "A medicine is any substance or composition represented as having curative or preventive properties with respect to human [or animal] diseases..." A drug can therefore be used to combat a disease, or to anticipate (or prevent) its development. This also applies to genetic diseases, such as those predisposing to certain cancers, for which pharmacological treatments can be designed to interfere with genetic alterations. This requires a great deal of scientific knowledge. The Code's definition continues: "... as well as any substance or composition which may be used in or administered to human beings [or animals] with a view to making a medical diagnosis or to restoring, correcting or modifying their physiological functions by exerting a pharmacological, immunological or metabolic action". Consequently, there is not only the treatment, but also the prevention and, with it, the search for a diagnosis of the disease that enables a target to be identified.

*How do you determine a drug's target?*

We need to define the target, in fact, and ensure that a molecule falls within the definition of a medicine, as laid down in

the French Public Health Code. There are two stages, from the design of a new active substance, a scientific and technological process, to its marketing authorization, or MA, and thus its widespread use by patients. Marketing gives immediate access to care, but it is also a commercial venture which, as we shall see, raises major ethical issues.

The drug development process comprises several stages. First, there is the search for a candidate drug substance. In the case of the nicotinic receptor and its homologues, for example, we know from the work of John Newport Langley that this receptor, at the neuromuscular junction, is sensitive to nicotine and curare. It is therefore a proven fact that drugs act on these receptors (Claude Bernard had already suggested the action of curare at the nerve-muscle junction). There are therefore possible candidates here. Others may come from traditional medicines that use certain plants. And let's not forget the role of chance: products used to reach one particular target may be more effective on another. This is a kind of *drug repurposing*. It may happen that a candidate molecule is already patented, which poses an ethical problem we'll discuss later. Furthermore, the molecule identified as candidate will not be used directly on humans. This brings us back to Claude Bernard and the idea of animal experimentation. The Nazis didn't bother with this precaution: they injected bacteria or viruses into human guinea pigs without prior warning. Some extreme defenders of the animal cause would rather protect the animal than man.

*This was to some extent the position of Claude Bernard's wife and especially his daughters, who, after his death, welcomed all kinds of animals into their house in compensation for those sacrificed by their father and husband.*

There are two complementary aspects to this first test on a living model, both of which are essential for assessing benefits and risks. The substance is usually first tested *in vitro* on micro-organisms or cell cultures, then *ex vivo* on isolated organs. Finally, it is tested *in vivo* on live laboratory animals. The main animals are the mouse, the hamster in a pinch, and the monkey, which is the closest to man. This is the pre-clinical stage. Once a molecule has been identified that is non-toxic on cell cultures, that does not kill mice or monkeys, and that has an observed and measured therapeutic effect, a clinical trial on humans can begin. This involves three phases:

- Phase I, or safety testing: carried out on healthy volunteers, this phase aims to establish the minimum active dose and, above all, the maximum tolerable dose.
- Phase II, which consists of bioavailability and efficacy tests on volunteer patients. Its aim is to establish the relationship between dose and response.
- In Phase III, the drug, whose pharmacological activity has been confirmed in the previous phase, is tested to assess its real clinical benefit. The aim is to establish the balance between benefits and risks. After all, with any drug, there are always side effects. The drug candidate is compared with a reference drug and a placebo (a therapeutic procedure that has no specific efficacy of its own, but acts on the patient through psychological or physiological mechanisms). Randomization is carried out by randomly distributing the placebo and the drug substance being tested. Randomization is most often used for studies conducted according to the "double-blind" procedure: neither the patient nor the doctor knows whether it's a drug, a placebo, or the reference that's being administered. This statistical method is a guarantee of rigor and quality. Once these three stages have been completed, the drug can be marketed.

There may be very long-term side effects. In this case, we can talk about a Phase IV, which, once the treatment has been approved for sale, should make it possible to detect rare side-effects or late complications.

*It is the anticipation of this phase IV that has fueled a number of more or less fantasized reservations about RNA vaccines against Covid 19...*

We can never be sure that there will be no long-term side effects. The only thing to do is to scrupulously follow the steps involved in designing and marketing a product, taking into account possible side-effects. A drug may not act on just one target, but on others, not intended as such. This is the case, for example, with anti-cancer products, which can be accompanied by various discomforts such as fatigue and nausea. When it comes to the nervous system, side-effects are fairly easy to detect: they can include sleep disorders, headaches, various cognitive deficits, etc. These should be avoided at all costs.

*With this in mind, what can we say about "non-conventional" medicines, to which you have alluded on several occasions?*

We've already talked about traditional medicines. The WHO defines traditional medicine as the health practices, methods, knowledge and beliefs that involve the use of plants, animal parts and minerals, spiritual therapies, techniques and manual exercises - separately or in combination - to treat, diagnose and prevent disease or maintain health. In Africa, for example, 80% of the population uses traditional medicine. Between 30% and

50% in China... The question is whether these populations should abandon traditional medicine in favor of rational pharmacology. Many practices, such as massages and dietetics, can have beneficial effects, at least in terms of therapeutic support. On the other hand, substances used in parallel are objectively ineffective (such as those extracted from rhinoceros horn, which, moreover, threaten the survival of the species). Chinese pharmacopeia even offers immortality elixirs! Numerous scientific studies have demonstrated the ineffectiveness of traditional medicine.

Chinese medicine, with the exception of a few herbal remedies now integrated into modern medicine (such as artemisinin, a highly active antimalarial). Colleagues at the Institut Pasteur (Anne Dejean-Assémat and Hugues de Thé) have demonstrated that certain products of traditional Chinese medicine, such as arsenic, combined with retinoic acid, can cure acute promyelocytic leukemia<sup>1</sup>.

In short, we need to be very careful with traditional medicines. They are largely ineffective, but there are good exceptions which prove that not everything can be rejected, and that further studies are needed. Nor can I forget that rational pharmacology, which I defend, includes molecules from traditional cultures, such as curare and nicotine from Central and South America.

*What can we say about homeopathy? A pseudoscientific practice that is both unconventional and non-traditional...*

Homeopathy was invented by German physician Samuel Hahnemann in 1796. It's an ancient practice based on the belief that it's possible to treat a patient by diluting substances to a very high concentration which, if concentrated, would cause negative symptoms. When we



examine the dilutions used, we see that the sugar pills sold commercially under the name of homeopathic medicines most often contain no active molecules at all, and this is because there is a finite number of molecules in a mole of matter<sup>2</sup>. This limits not the quantity of the substance itself, but the number of molecules that go to make up the product, diluted to the supposedly active dose. The end result is a pill that contains no active molecules at all.

It has long been proven that homeopathy does not have the desired effect of a genuine medicine. There have been attempts to establish the contrary, such as that of Jacques Benveniste, with his highly controversial theory of the "water memory" which was totally invalidated in 1993, but recently revived by Luc Montagnier, until his death. Large-scale clinical studies have shown that homeopathy is no more effective than the placebo effect. Not to mention the danger of such a pseudo-medicine: certain infectious bacterial diseases could have been treated if scientific medicine and antibiotics had been used. Examples abound. When I was Chairman of INSERM's Scientific Advisory Board, between 1983 and 1987, I pleaded for the lack of efficacy of these treatments to be made public. Nothing happened. For its part, the French Academy of Medicine took a stand in 2004, calling for an end to the reimbursement of homeopathic preparations. But it wasn't until 2018 that Health Minister Agnès Buzyn asked the Haute autorité de santé to issue an opinion on the efficacy of homeopathy and the justification for its reimbursement by the Assurance maladie. French President Emmanuel Macron finally opted for a total end to reimbursement in 2020.

### *Why so much hesitation?*

It turned out that some homeopathic "medicines" could still have some effect. I have already mentioned the placebo effect. Substances containing no active ingredients can improve a patient's state of health. In healthy patients, the placebo effect has been proven to be up to 30% - and sometimes even 50% - effective against pain, and even higher for migraines and depression. I remember that, when I was chairman of the French National Consultative Ethics Committee, we had to deal with the following question: how do you measure the scientific efficacy of a drug against depression? Given that the placebo effect is very high, and that the risk of suicide is high, should we favor the drug over the placebo, thereby putting the patient at risk?

The placebo effect is well documented and studied in several neuroscience laboratories. Brain imaging shows that the placebo effect has both psychological and physiological effects<sup>3</sup>. It must therefore be taken into account in research and rational drug design.

## **2- THE ULTIMATE TARGET OF A DRUG: ITS CONNECTION TO A RECEPTOR?**

### *What is the ultimate target of a drug?*

As we've just seen, designing a drug comes up against considerable scientific, financial, ethical and even political difficulties. It is out of the question to tackle them all in this interview<sup>4</sup>. I will deliberately restrict my comments to the very first steps in the identification of a drug candidate, a pre-clinical stage which is necessary if ever there was one,

but obviously not sufficient. Thousands of receptors have already been identified, and many of them are known as potential drug targets.

To select a candidate molecule, it's not enough to identify the target receptor protein. We also need to understand how these new molecules bind to their receptors and what effects they have on the protein carrying their binding site, particularly in relation to their allosteric properties. The nicotinic receptor and its homologues will continue to offer a model of choice for identifying the ultimate target of a potential drug and knowing how it acts.

*How can we identify the sites carried by these receptor molecules?*

Following the discovery of the nicotinic receptor and its basic properties, a major step was the chemical identification of binding sites likely to interact with the neurotransmitter and various pharmacological agents. For several decades, work has focused on the labeling and identification of these sites with the nicotinic receptor and its pentameric homologues. There are three main categories of sites: the active site, the ion channel and the allosteric modulator sites. These three categories of sites are all drug targets.

There's the *active site*, where curare and nicotine bind, the affinity marker with TDF, and then MPTA. By using these affinity markers, we were able to identify the amino acids present at this site. The problem with MPTA is that it only marks thiol-SH groups. We do have an initial label on the site, but we don't yet know much about its structure<sup>5</sup>. What we do know is that these initial markings indicate that the site belongs to the extracellular, synaptic domain. This is a

first confirmation. Using a radioactive toxin, Robert Oswald and I<sup>6</sup> were able to show that, when the toxin is covalently labelled and attached to the receptor, the  $\alpha$  chain is labelled, but so are other sub- units ( $\gamma$   $\delta$ ). This means that the active site straddles two subunits,  $\alpha$   $\gamma$  and  $\alpha$   $\delta$ , which are also labelled by the toxin. The site therefore lies at the interface between subunits.

We continued our research work with a TDF derivative, developed by chemist friends from Strasbourg<sup>7</sup> (Christian Hirth and Maurice Goeldner), who had prepared markers for us. Together, we were able to demonstrate that there were amino acids belonging to the  $\alpha$  chain and also to the  $\gamma$  and  $\delta$  chain in Torpedo<sup>8</sup>. There are several loops that form a kind of "pocket" in which the acetylcholine molecule is housed<sup>9</sup>. In organic chemistry, this pocket is referred to as "aromatic", because aromatic amino acids have benzene-like rings, as tyrosine and tryptophan typically do. Others, such as glutamate and aspartate, with carbonated side chains, are also included. It is therefore a basket at the interface between several subunits, whose chemical organization enables recognition of acetylcholine, something Karlin could not achieve with his MPTA. This result also differs from the initial observations of Nigel Unwin who, unaware of our work, proposed that the acetylcholine site lies at the heart of the  $\alpha$  subunit ("*lies entirely within the alpha subunit*", 2000). The notion of sites localized at the interface between subunits took us a step further. Our discovery was confirmed for other receptors belonging to the nicotinic receptor family and many other allosteric proteins. The chemical nature of the association between receptor subunits intervenes. The very first electrophysiological recordings on the electric eel electroplaque, which I made at Columbia with Thomas Podleski, showed dose-response curves to

nicotinic agents with a characteristic sigmoidal shape. This was reminiscent of oxygen binding to hemoglobin and, of course, of the cooperative effects characteristic of allosteric proteins in general. The latter were confirmed by *in vitro* binding measurements. There is therefore positive cooperativity between several identical sites present at repeated interfaces between subunits of the allosteric oligomer... It goes without saying that these "threshold" (molecular switch) effects will have major consequences on the definition of the effective dose of a drug on a patient.

*Now consider the ion channel...*

How do you identify a hole? Because the *ion channel* is a hole. Here, too, we adopted a biochemical approach in contrast with the electrophysiological one. We looked for a means of marking the site using local anesthetics, such as those used by dentists. Studies with several of these proved interesting, as they block the ion channel - like a cork in the neck of a bottle. We understood, as was already known by electrophysiology, that these local anaesthetics penetrate the ion channel when it is open. The local anesthetic enters and blocks the canal. Nerve signal transmission is inhibited, and the painful sensation is no longer propagated: anesthesia is achieved.

General anesthetics have a different mode of action on the central nervous system. We therefore tried to select molecules that could enter the canal and, once inside, be photo-activated by irradiation with ultraviolet light, thereby binding irreversibly. Robert Oswald and I found that one of them worked very well, chlorpromazine<sup>10</sup>. This is a molecule that French researchers had identified as a neuroleptic, effective in the treatment of schizophrenia. But

here, with the purified receptor, it serves as a marker. We've shown that chlorpromazine marks all four subunits at the same time (in fact, all five, since one is repeated twice). And, if we add acetylcholine, the kinetics of access to this site are multiplied by one hundred<sup>11</sup>. In other words, when the channel is opened, chlorpromazine binding in the channel is increased a hundredfold. This effect is blocked by the toxin or curare. We therefore found the conditions for labelling the open ion channel. For us, this was an essential criterion for identifying the channel. We pushed the analysis to the level of the labelled amino acid. Jérôme Giraudat, in my laboratory, found that it was serine 262<sup>12</sup>. It is present in the particular M2 transmembrane (M) segment. This was the first time the word "M2" had been uttered. Other hypotheses had been formulated concerning M4, M1 or M3. There's a serine ring in the middle of the M2 segment, as well as other rings, leucines and threonines. There was a kind of equatorial marking of this transmembrane segment.

This result was extremely important to us. We were quickly reassured by the confirmation of this result, thanks to the work of my former postdoctoral fellow Ferdinand Hucho using a different blocker of the channel<sup>13</sup>. This was the first identification of a structure engaged in the ion channel of a pentameric receptor. This conclusion was supported by the discovery that mutation of several amino acids, including one located in a loop at the base of the MII segment<sup>14</sup>, critically converts the selectivity of the ion channel from cationic to anionic. This made it possible to transform an excitatory receptor into an inhibitory one.

Our competitors, Numa and Sakmann, mastered two techniques: genetic engineering and electrophysiology. Sakmann is known for having recorded, with Erwin Neher

(1976), the individual ion channels that correspond to the opening and closing of a single receptor molecule. This is a technique that has since been widely used to monitor the receptor's elementary properties. Both confirmed what had already been demonstrated by Barnard's group: that functional genetics can be performed on the frog egg by introducing genetic differences into the injected cDNA clone. A little after us, they showed that there are functional differences between the Torpedo and ox receptors, that the elementary conductances are different. They used a genetic argument to suggest a possible contribution from M2<sup>15</sup>. Taking their analysis a step further, the team introduced mutations along the entire length of the chain, and also found M2<sup>16</sup>. They observed, not the hydrophobic rings at the center, but rings of negatively charged amino acids, aspartate, glutamate, located on either side of the central core, at both ends of M2. They named them: "external", "intermediate" and "internal" hydrophilic rings. These results, both biochemical and electro-physiological, are in agreement with each other. The hydrophilic rings "frame" the central chlorpromazine-labeled hydrophobic core. Together, they represent the first irrefutable identification of an ion channel by both chemical labelling and molecular genetics. It also represents a breakthrough in demonstrating the allostery of these receptors. We can now mark the active site and the channel separately and, using fluorescence experiments, measure the distance between these sites and demonstrate that this is, in the case of the Torpedo receptor, 60 to 65 angstroms. The distance between active sites, for example on an  $\alpha$ -7 receptor, is of the order of 20 to 35 angstroms. Their interaction is therefore necessarily allosteric. The relationship between these distinct sites is indeed indirect... allosteric !

*Allosteric modulatory sites remain to be considered...*

There are the active sites, where curare and nicotine bind; the ion channel, with non-competitive blockers of the channel, illustrated by local anesthetics; and other distinct sites, the *allosteric sites*. As early as the 1950s, observations were made of newly synthesized molecules, the benzodiazepines, and their mode of action. These psychoactive compounds acted as powerful tranquilizers and sleeping pills, but their mode of action was not understood. As early as 1977, Hanns Mohler and colleagues had noted the unexpected activation of the GABA<sub>A</sub><sup>17</sup> receptor, one member of the nicotinic receptor family by benzodiazepines, and even used the term "allosteric" to describe them. An interesting but unexplained observation. It remained unexplained until Jean-Luc Galzi and I proposed in 1994, on the basis of sequence analysis, that benzodiazepines bind to sites that are homologous to the active sites, but normally inactive, because they are located at unsuitable interfaces between subunits<sup>18</sup>. This hypothesis has been extensively verified. This is a first type of "allosteric" site, but still close to the active site. With the  $\alpha$ -7 nicotinic receptor, we were able to establish that calcium ions could act as receptor activators. The site was localized, as yet only approximately, at the junction of the large extra-synaptic hydrophilic domain and the membrane domain, at a different site from the active site<sup>19</sup>.

The site of ivermectin, another allosteric modulator, is even more interesting. It's a compound identified, in 1974, by Satoshi Omura and William Campbell<sup>20</sup>. Omura isolated this rather complex molecule from bacteria. It is a kind of antibiotic produced by soil bacteria. Campbell, for his part, demonstrated its extremely powerful anthelmintic (worm-



fighting) effects. Both humans and domestic animals are parasitized by worms such as ascaris and other nematodes. Some species found in tropical countries, particularly in Africa, are carried by water, attach themselves to the eyes and cause blindness (*onchocerciasis*). Cows are treated with ivermectin to rid them of roundworms (as distinct from tapeworms). However, cows treated in this way polluted the fields, as their dung was not destroyed by coprophagous insects (dung beetles). Could ivermectin have an effect on insects? Insecticides are often found to act on the nervous system of insects at the level of their nicotinic receptors, hence the idea, developed with Daniel Bertrand, of investigating whether ivermectin acts on a central nicotinic receptor in vertebrates. And it worked! Using the  $\alpha$ -7 receptor, we were able to establish that ivermectin acts on this receptor as an extremely powerful allosteric activator. We're dealing with a positive allosteric modulator that stabilizes the active state (PAMs). Other allosteric modulators can be negative, i.e. stabilizing the resting state (NAMs). This initial work, published in 1998<sup>21</sup>, also showed that mutations in the transmembrane domain abolished the effect of ivermectin, while the receptor was still active. This led to the idea, later confirmed, that ivermectin acts on a site located in the transmembrane domain.

#### *How do general anesthetics work?*

General anesthetics, which are molecules generally administered in gaseous form, such as propofol or desfluran, also bind to an allosteric site in the trans-membrane domain<sup>22</sup>. There may therefore be other allosteric sites in the transmembrane domain which have a positive or negative effect depending on the receptor species and molecule concerned. Various biochemical and structural observations

suggest that these sites share the property of binding lipids to the transmembrane domain. These could act as physiological modulators, with general anaesthetic agents such as ivermectin taking the place of lipids.

The result is a new pharmacology: not only that of the active site and its cooperative effects, that of the ion channel, in the open and closed conformations, but also that of the allosteric modulatory sites. The compounds acting at each of these sites are very different from one another. Ivermectin has nothing to do with either the active site or chlorpromazine. We're dealing with a receptor molecule with a triple pharmacology! That's what we had to understand. A problem then arose how to explain the coupling between all these sites?

### **3- UNDERSTANDING THE EFFECT OF A DRUG ON ITS RECEPTOR**

*In short, we need to understand the receiver's allosteric transitions...*

We have already discussed the coupling between topographically distinct sites as the basis of allostery itself and its extension to synaptic transmission. Here, we return to the cholinergic synapse, to the release of acetylcholine into the synaptic space, and thus the opening of the ion channel by acetylcholine. It should be noted that this transition to the active state can simply be interpreted in terms of the two-state allosteric model, between the resting and the active states of the receptor. We also know that the active state can be obtained without the addition of acetylcholine. It can open

spontaneously, which eliminates *induced-fit*, but is consistent with the occurrence of preexisting states, a central proposition of the classical allosteric model (*cf.* chapter 2).

If we briefly expose the nicotinic receptor to nicotine or acetylcholine, we find that it doesn't remain active for very long - it's on the order of milliseconds - and if exposure to acetylcholine is prolonged, an inactive desensitized state of the receptor is stabilized - this takes a longer time span, from ten milliseconds to a second. We go from an inactive state to a slow desensitized state. When we compare the quantities of acetylcholine that lead to the active and slow states, we see that, to reach the active - transient - state, we need a very high local concentration of acetylcholine, consistent with the low affinity of the active state. On the contrary, at low concentrations of acetylcholine, the desensitized state, with its high affinity, is permanently stabilized. This result seems to contradict what we know about drugs. We have always sought, and are still seeking, to find a drug that acts at the lowest possible dose. In fact, at low concentrations, the receptor is in a desensitized state with high affinity for the drug, but inactive.

Resting state, active state, desensitized state: this proves that the two-state model is too simple.

*We therefore need to postulate a model with at least three states...*

This is another major difference from the classic allosteric model. With Thierry Heidmann<sup>23</sup>, from 1979 to 1983, we tried to obtain biochemical evidence of these three states. The groundwork had been laid by electrophysiologists Katz and Thesleff<sup>24</sup> as early as 1957. To do this, we used a molecule, dansyl-C6-choline, an analogue of acetylcholine, but

fluorescent<sup>25</sup>. In other words, it is a fluorescent nicotinic agonist. We rapidly mixed this molecule by means of an appropriate device, the "*stop flow*", which enables transitions of the order of a few milli-seconds to second to be tracked. Separate biophysical recordings were obtained for the activation and the desensitization transitions, thus bringing chemical evidence for the existence of distinct desensitized states and its transitions from "resting" to "active" states. The same result was obtained by Jonathan Cohen, one of my former post-docs at Harvard, with radioactive acetylcholine<sup>26</sup>.

Thierry Heidmann then tried, in collaboration with a German group, to establish the correlation between binding to the active site and channel opening, using the microsacs preparation. With these receptor rich membranes, we were able to monitor ion transport and binding simultaneously, and to demonstrate that, in the active state, the channel is open, whereas in the desensitized state, it is closed, as it is in the resting state. This result is consistent with the idea that the receptor that binds acetylcholine (or nicotine) stabilizes, at equilibrium, the high-affinity inactive state. Again, this confirms that high-affinity medicaments do not bind to the active states - quite the contrary. This may explain the behavior of smokers who inhale a puff of tobacco, activate the receptors and then, as exposure is prolonged, desensitize them. Reactivation takes some time, hence the notion of successive puffs. Finally, Thierry Heidmann discovered that a non-negligible fraction (around 20%) of the receptor was spontaneously in the high-affinity desensitized state. For his part, Meyer Jackson had observed spontaneous opening of the muscle receptor of acetylcholine<sup>27</sup> (1984). These data are in clear agreement with the allosteric model: the transition between low- and high- affinity states may take place, spontaneously, in *the absence of* acetylcholine.

A new version of the 1965 allosteric model, which took into account the specific features of the nicotinic receptor, was developed with the help of hemoglobin specialist Stuart Edelstein<sup>28</sup>, whom I met in Howard Schachmann's laboratory during my first postdoctoral position at Berkeley. It was subsequently adopted by the eminent electrophysiologist Anthony Auerbach<sup>29</sup>, among others.

Having carried out these biochemical experiments, it was time to sharpen the analysis down to the atomic level.

*So you started with the raw extract, the "donuts", which you sequenced, biochemically highlighting the three-dimensional organization of the molecule, identifying the sites, showing their differences...*

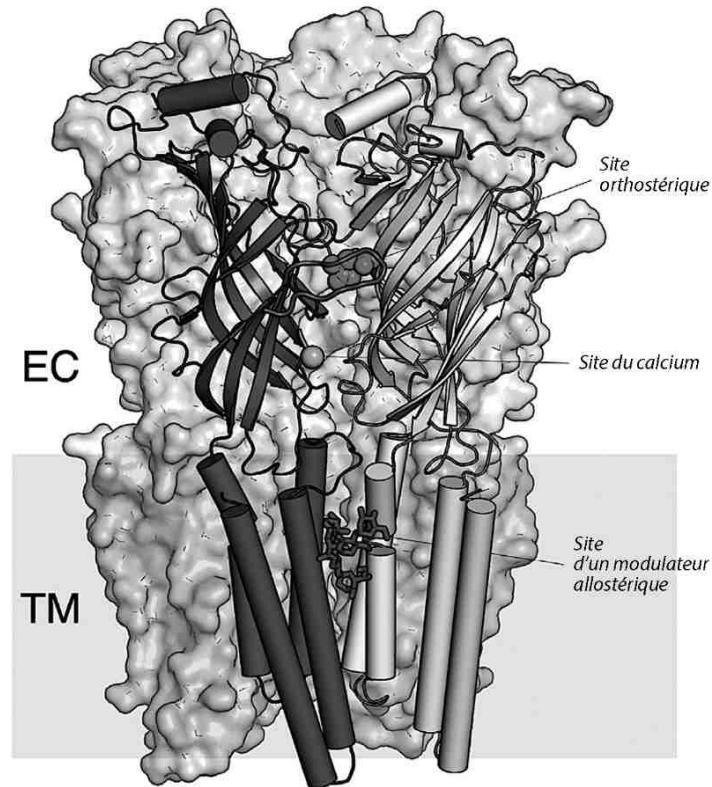
To move further, we needed a better resolved structure of the receptor, a three-dimensional structure, at the atomical level. To achieve this, as Perutz had done with hemoglobin, we needed crystals. We tried for years to crystallize the receptor. But without success. Then one day, in 2005, the editor of a scientific journal asked me to review work carried out by Tasneem's group<sup>30</sup>. This group had discovered homologous sequences of the nicotinic receptor in bacteria. This was an enlightenment for me, as it is well known that bacterial proteins are much easier to crystallize than the proteins of eukaryotes, especially those of humans. I realized that this was the key. I asked Pierre-Jean Corringer, who had worked alongside me and who succeeded me at the Pasteur Institute, if he was interested in the prospect of searching a bacterial receptor. He agreed. The collaboration continued for several years.

*You're back in the world of bacteria for which you had no great attraction...*

Using Tasneem data, Pierre-Jean Corringer and his team succeeded in purifying a "receptor" protein from a cyanobacterium that grows on the limestone rocks of the Swiss Alps<sup>31</sup>. This is a relatively primitive photosynthetic bacterium called "*Gloeobacter violaceus*". The Institut Pasteur has a rich library of bacterial clones and specimens were found which gave access to a cDNA, transcribe the protein, extract it, and show that it was a receptor-channel. Based on previous genetic data, this was the first demonstration of the occurrence of a channel receptor in bacteria. The depolarizing agent here is pH. Acidic pH activates the receptor. This is an important discovery. Bacteria contain molecules similar to the nicotinic receptor, which function like the channel receptors studied earlier.

Another group of researchers, led by Raimund Dutzler, had begun work on a receptor from another bacterium, ELIC<sup>32</sup>, in parallel, in 2008, after reading the same article. They also succeeded in purifying and crystallizing the protein, but without demonstrating its functionality - functionality which we had already demonstrated with *Gloeobacter violaceus*. Their X-ray structures revealed, at low resolution, a receptor with a closed channel. We did the same with an open channel receptor at pH 5, at high resolution<sup>33</sup>. With the help of Pierre-Jean Corringer, Marc Delarue and their team, we were thus able to establish, in parallel with Dutzler's work, the X-ray structure of the first channel receptor, one with the open channel, the other with the closed channel, with a resolution of 2.9 angstroms, i.e. at atomic level. The three-dimensional structure of the receptor molecule revealed a pentameric oligomer with rotational symmetry of order 5. The model of trans-membrane organization into three domains - synaptic,

cytoplasmic membrane - was fully confirmed, as the positions of the sites.



5. General diagram of the structure of a pentameric receptor-channel at the atomic level showing the distribution of the active site (orthosteric), at the extracellular domain (EC), and the ivermectin site (allosteric), at the transmembrane domain (TM).

(Adapted from Marco Cecchini and Jean-Pierre Changeux, 2015)

Subsequently, other channel receptors were crystallized, and the distribution of active sites, at the interfaces between subunits and channel in the axis of symmetry, fully confirmed. The first eukaryotic one was an anionic channel receptor from a worm (*Caenorhabditis elegans*) that responds to glutamate and is activated by ivermectin<sup>34</sup>. Ryan Hibbs

presented the first three-dimensional structure of a eukaryotic receptor, which they were able to compare with the prokaryotic structure we had established. The similarity was extraordinary! Although there are sequence differences, the three-dimensional structures are very similar. Other receptors followed, present in vertebrate and human brains: GABA<sub>A</sub>, glycine, 5HT<sub>3</sub>... then, in the hands of Ryan Hibbs, ganglionic and muscular nicotinic receptors and, most recently, the now famous alpha<sub>7</sub><sup>35</sup> receptor.

*Does this mean we have bacterial receptors in our brains?*

Rather, of bacterial origin. We have receptors in our brains, which are highly similar to the bacterial ones, which is quite extraordinary! These central receptors show allosteric transitions homologous to those of bacterial receptors. It's the "bacterial" dynamics of these receptors that possibly contribute to make our brain so slow, that it operates at the speed of sound... and not light, like a computer.

#### **4- THE ULTRA-FAST DYNAMICS OF A DRUG'S ACTION ON ITS RECEPTOR: AGONIST OR ANTAGONIST?**

As far as conformational dynamics are concerned, a number of hypotheses have been put forward as to how the various sites are assembled. Another aspect comes into play here: X-ray crystallography reveals a static structure, while computational methods, based on the same structures, seek to understand the dynamics. The discipline is known as molecular dynamics. Martin Karplus, who has worked at Harvard and Strasbourg, has been rewarded for this discovery.

In my laboratory, Antoine Taly took the lead, using a simple



dynamics method, that of "normal modes" analysis. He proposed on the basis of this computational work, that during the activation transition a rotation takes place at the level of the synaptic domain, which is followed by another, in the opposite direction, at the transmembrane level<sup>36</sup>. This kind of torsion concerns the whole molecule: we called it a "*molecular twist*". This study was taken up again by Calimet *et al.*<sup>37</sup>, also in Strasbourg, under the direction of Marco Cecchini, a student of Martin Karplus, with whom I've been collaborating for several years<sup>38</sup>. We went a step further, adding to the *twist* another transition of the quaternary structure, which we called a "*bloom*". A detailed description of the conformational transition in the time domains of the millionth of second and at the atomic level by Marco Cecchini<sup>39</sup>, reveals the interplay between subunits, which are in themselves relatively rigid, like the hemoglobin subunits studied by Perutz. The molecular dynamics of twisting and blooming movements track the structural evolution of all pharmacological sites. It appears that these conformational changes affect the zones of interaction between subunits, which, as we have seen, contain the active site, the channel and the allosteric modulator sites (for ivermectin, among others). Marc Delarue's work at Pasteur, with the actual X-ray structure of the resting state (pH7) and active state (pH5) of the Gloeobacter receptor, is an important step in this direction, even if not everything has yet been resolved<sup>40</sup>. Recently, various groups have used high-resolution electron microscopy to identify the different conformations - resting, active and desensitized - in fair agreement with the original three-state model (*see* note 35). From the structure and molecular dynamics of each of these sites, at the atomic level, we can not only account for the specificity of binding, for example, of nicotine or ivermectin, to their site, but also highlight the differences between the

resting state, the active state and the desensitized state, and thus make rational predictions of the action of a drug on the three states of the receptor. Each state exhibits a different pharmacology: the active state is stabilized by agonists (nicotine) and the resting state by antagonists (curare or snake venom toxin). The active site is more closed in on itself in the active state than in the resting state. The same applies to allosteric modulators such as ivermectin. We can clearly see that, on the basis of fine differences in site structure, traceable between conformational states, we need to be able to predict rationally and computationally whether a drug candidate acts as an agonist, an antagonist or desensitizer.

*Can this work on the receptor be considered a pharmacological revolution?*

I think so. On the one hand, this work on the receptor establishes the existence of allosteric sites, different from the classical ones. An allosteric pharmacology will therefore develop, as we have seen. A new field of pharmacology is opening up, beyond classical competitive pharmacology. On the other hand, we can try to predict which receptor conformation it will preferentially bind to, and use computational methods to predict whether a product will act as an agonist, antagonist or desensitizer (steric or allosteric). Conformation specific pharmacology is developing. This is the second revolutionary aspect of this new pharmacology.

To illustrate this conclusion with the medical application of this research, I'll mention that around 80 allosteric modulators are in clinical use, half PAMs, half NAMs<sup>41</sup>. They include, for example: Aniracetam, a PAM of the glutamate receptor AMPA effective against stroke, Cinacalcet, a PAM recommended against hyperthyroidism, Maraviroc, a NAM

used against HIV, and also those multiple monoclonal antibodies effective against cancer that act as ultraspecific PAMs or NAMs of cellular receptors<sup>42</sup>. A Chinese allosteric database lists 82,070 substances as *potential* allosteric modulators and 538 as genuine allosteric drugs. The medical applications of the allosteric revolution are convincing...

## 5- ALLOSTERIC DISEASES... AND THEIR MEDICINES

*If there's an allosteric pharmacology, does that mean there are allosteric diseases?*

Along the way, we examined, in particular with Daniel Bertrand, the effects of various mutations in the nicotinic receptor gene, especially mutations in the channel. Our original idea was to mutate chlorpromazine-labelled amino acids in the channel; we expected to block the channel, to create an inactive receptor<sup>43</sup>. Daniel Bertrand, taken aback, tells me the news by phone. This is not the case. The receptor is in fact much more active than the normal receptor. I told him - enthusiastically - that the interpretation for me was clear: the mutation stabilizes the active state of the allosteric equilibrium (or a desensitized state with an open channel). It's an allosteric mutation. The kinetic model developed with Stuart Edelstein captures this. So, supposedly good ideas aren't always good, but they can lead to discoveries.

Since then, other mutations have been discovered in line with this interpretation, and the corresponding pharmacology. Some have been found, in the muscle receptor gene(s), that cause syndromes manifested by muscular weakness. The disease is called congenital myasthenia (different from that caused by an autoimmune block on the receptor). There are

two types of: constitutive mutations - gain of function - which stabilize the active state, and others - loss of function - which stabilize the resting state<sup>44</sup>. They have opposite pharmacology: to treat myasthenia that stabilizes the active state, we use nicotinic antagonists – like curare - that restore the normal state by counteracting the effect of the mutation; and for mutations that stabilize the resting state, one may use, on the opposite, agonists. So you have to be very careful when treating a myasthenic patient! If we don't know the type of allosteric effect of the mutation, we could be completely wrong about the right drug to administer...

Another type of disease was identified in Australia by Samuel Berkovic, targeting a neuronal receptor: "nocturnal autosomal dominant epilepsy of the frontal lobe"<sup>45</sup>. It manifests itself in children by seizure episodes during the night. But the cognitive capacities of the child are intact. It results from mutation of the amino acid homologous to that marked by chlorpromazine in the *Torpedo* receptor ion channel. The constitutive mutation will create nicotinic hyperactivity in the young patient's brain, triggering an epileptic seizure. Analogy with some myasthenic mutations it can be treated with nicotinic receptor antagonists.

A Chinese survey of allosteric diseases reported 5,983 of them! I don't know whether this figure should be taken literally, but it gives an idea of the number of diseases caused by allosteric mutations. This is not without problems. Often these diseases, are caused by constitutive mutations, which create hyperactivity. It's easy to compensate for a mutation causing a loss of function by adding the missing "product". To attenuate an hyperfunction that must be "extinguished" by an antagonist is a more difficult deal.

All this proves that there is not only a "pharmacological" revolution, but also a fundamental renewal in the

understanding of a number of important diseases and in the development of effective drugs against them. This opens up a new field for drug design.

**6- MULTI-DISCIPLINARITY, TEAM WORK, COLLABORATION:  
FROM BENCH TO BESIDE**

*You often speak of your "group", attesting that scientific work is always the work of a team. How many researchers were there in your laboratory at the Institut Pasteur?*

Twenty or so. A number that has not changed over the years. Around thirty, if you count students, researchers and administrative staff. In fact, at the Institut Pasteur, it's forbidden to have larger laboratories. There's an imposed surface area that can't be exceeded. A "young" group comprises five people. A larger group cannot exceed twenty scientists. This is an excellent thing. Research supervisors should be directly responsible for the research carried out in their laboratories. Nothing is more inefficient than having to go through an army of "Mexican generals", researchers who manage researchers, who manage researchers... The lab director organizes research around a project, a model, which he or she confronts with data collected by students, post-docs and possibly a few older researchers. Weekly laboratory meetings ensure the implementation of the project.

This is the place for a scientific debate of great freedom - sometimes violent - where facts, ideas and techniques are confronted, with a genuine multi-disciplinary approach to the same problem. As you may have noticed, the orientations of my laboratory have evolved considerably over the last few decades. Wherever possible, I have ensured that researchers

who have completed their thesis work have been replaced by other researchers with the necessary qualifications to tackle new fields.

An additional and very important contribution to this multi-disciplinary approach has been collaboration with other laboratories specializing in methods and techniques different from our own, from electrophysiology to bio-physics, and more recently molecular dynamics. The result is a kind of fusional interweaving of disciplines, giving rise to a common way of thinking that is effective in tackling the most difficult problems.

This imperative requirement for multi-disciplinarity is even more flagrant with drug design: from preclinical work to clinical trials and marketing, "*from bench to bed*". As we have just said, the first, preclinical stages already require a high degree of multidisciplinary convergence. The human clinical step requires additional expertise, which becomes particularly difficult when the patient is involved. Only doctors have access to it. Louis Pasteur - who was not a medical doctor - complained about this. He was unable to test his rabies vaccine himself... The result was many difficulties for him. The situation has hardly changed since Pasteur, and the link between researchers and clinicians is still very tenuous. Added to this are the financial aspects associated with human clinical trials, which far exceed the budgets of research laboratories. Hence the controversial role of "*big pharma*", whose main function is to ensure that such budgets are made available and grow. An alternative might be to bring clinicians and researchers together in an international, *non-profit* Foundation, bringing together scientific-and- clinical projects, solidly evaluated, and with the necessary funding to produce innovative drugs. We're not there yet.

In any case, the fundamental discoveries made about the structure of the nicotinic receptor and its conformational changes have led to a "pharmacological" revolution in the rational design of new drugs, but also to a new understanding of diseases of the nervous system and their treatment: a window wide open to the future...





## V.

### **Between nature and nurture: epigenesis**

#### **1- NATURE AND NURTURE**

*The debate between nature and nurture has long been part of our intellectual tradition...*

It's a debate that's both very old and very topical. It concerns the question of what is innate, linked to the species, to the individual, to "human nature", and what is acquired through our relationship with the environment, our interaction with the physical, social and cultural worlds. In short, we're trying to distinguish between what is "natural" and what is "cultural". It's a question that has been asked since antiquity, and not just in Europe. Sima Qian, a Chinese historian of the 2nd-1st century B.C., wondered, in connection with a call to war, whether "kings, generals and ministers are born as such", in other words, whether they have an innate predisposition to be what they are. Today, on an almost daily basis, we are led to wonder about the nature of man, about what it is in him, It's a debate that's still very much alive, and one that has seen opposing points of view clash over the course of history. It's a debate that's still very much alive, and one that has seen opposing points of view clash throughout history. From my earliest work in marine biology, at Banyuls, I had in mind the

two traditional philosophical positions: the innate position, which was Plato's first. Access to knowledge of truth, to intelligible reality, requires detachment from the "sensible" world. It's a real uprooting. We must "die to the sensible". All knowledge is reminiscence: "To know is to remember. To know is to know again.

*An "inneism" present in Descartes...*

For Descartes some of the ideas present in our minds are innate and provide the foundations for knowledge. Geometric truths are of this kind. Unlike Plato, Descartes does not disqualify sensible reality: it can and must be known through the mediation of our ideas. In his *Traité de l'Homme*<sup>1</sup>, the young Descartes describes the organization of the brain, albeit with anatomical errors, but with the idea that the brain is a kind of machine, comparable to a pipe organ, with several levels of organization. He doesn't rule out learning - he mentions it explicitly - which he imagines in the form of a kind of brush with spikes that pierce into a cloth or sheet of paper. The environment does leave an imprint.

*At the other end of the spectrum are the supporters of the acquired...*

This is the empiricist position, already present, it seems to me, in the Greek atomists Democritus and Epicurus. The latter defended it with his theory of simulacra that detach themselves from bodies and strike our senses - a radical sensualism. In the 17th century, the English philosopher John Locke took an extreme position: at birth, the brain is a "*tabula rasa*", a wax tablet on which nothing is written. Everything that constitutes the higher functions of our brain is acquired

through experience. He summed it up by saying: "There is nothing in the mind that was not first in the senses" (*An Essay Concerning Human Understanding* 1689). This point of view may seem rather idealistic, since it's hard to argue that if you teach a monkey to speak, it will start to talk. The image of the "clean slate", according to which the mind is born "virgin", has its limits. Locke, moreover, did not deny the existence of innate constraints, but the essential point for him was that "the soul is a blank sheet, empty of all characters, without any idea whatever". Sensory experience plays a fundamental role in setting up our cerebral functions.

Before Locke, Francis Bacon (1561-1626), who laid the foundations of modern science and its methods, deserves special attention: only sensible intuition is indubitably accessible and sharable. He was the first to conceive of scientific experimentation as an *active* relationship with experience. "We can only command nature by obeying it", he would say (*Novum Organum scientiarum*, 1620), and he gave us an outline of the experimental method, which was almost the one expounded by Claude Bernard.

*The Anglo-Saxon tradition is heavily influenced by empiricism...*

This was the case of David Hume, in the 18th century, who also defended the principle of economy, the combination of minimal ideas in the process of knowledge. It's a very useful principle that Jacques Monod reminded me of in his own way when he invited me to make a minimum of hypotheses. His recommendation had a highly creative impact on me. It is at the origin of the two-state model.

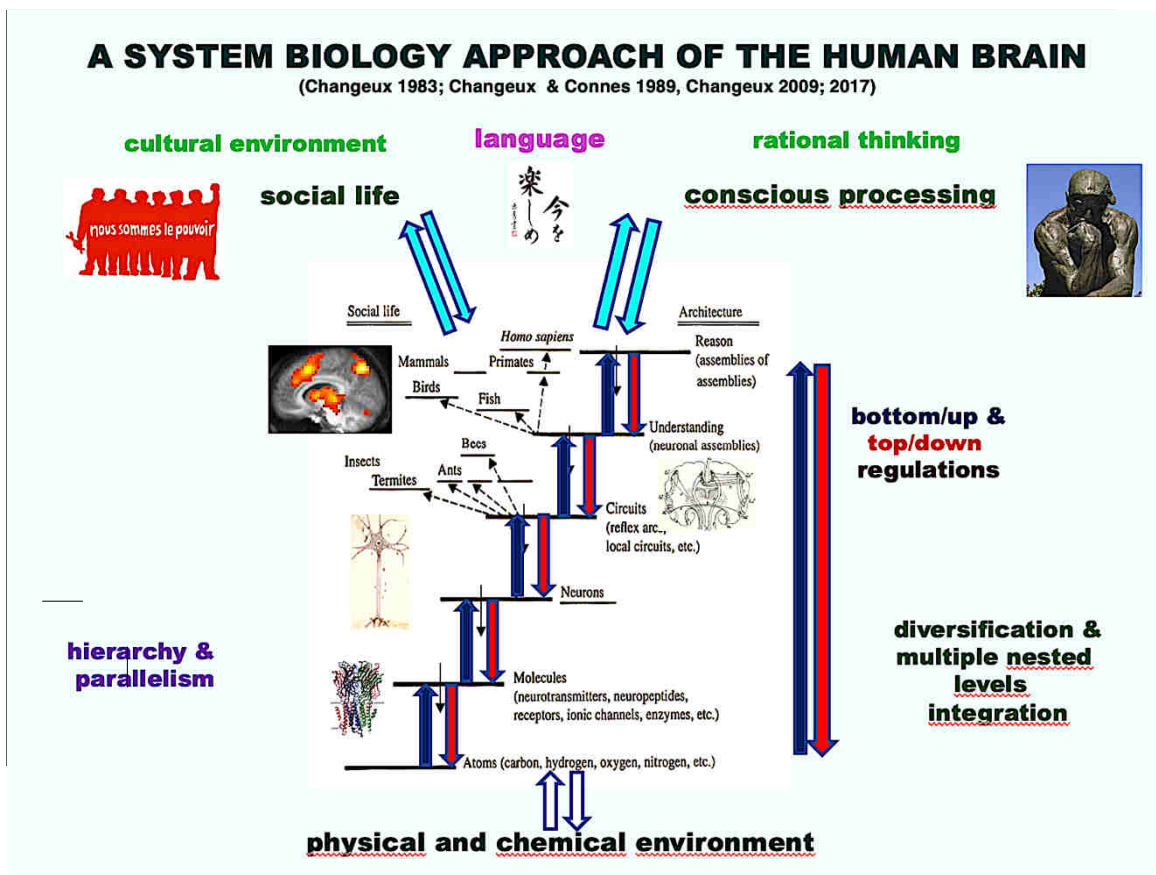
Empiricism is still very much alive, despite all kinds of objections, such as those raised by Diderot in his *Elements of*

*physiology* (1774). For him, the "fundamentalist" empiricist position was too simplistic. There are innate constraints that impose themselves on our relationship with the outside world. Canadian psychologist and learning theorist Donald Hebb (1904-1985) put it this way: when asked by a journalist, "What contributes more to personality, the innate or the acquired?", he replied, "What contributes more to the area of a rectangle, its length or its width? In other words, the two are closely intertwined.

*Have new developments changed your understanding of innate-acquired relationships?*

A number of scientific discoveries from the 19th century onwards have changed our perception of the relationship between nature and nurture, starting with the development of genetics, even if it has given rise to a number of aberrations (Francis Galton and his theory of eugenics, for example) and finally the discovery of brain connectivity and its complexity. I must mention here an important theoretical point, constantly present in all my reflections on the brain. It concerns two major principles of brain architecture: hierarchy and parallelism. First, parallelism: our brain is capable of analyzing signals from the physical or social environment via several parallel pathways. Thus, the architecture of the visual system is organized into a multitude of parallel pathways which, together with the auditory, olfactory and other pathways, enable the brain to analyze the world and form a global synthesis. Secondly, the hierarchical organization into levels of integration, from the atomic to the molecular, from the molecular to the neuronal. Neurons form a network that enables circuits to be established, which in turn form circuits and organize themselves with global architectures at the level

of higher functions, such as consciousness or social life. The brain's architecture is therefore both parallel and hierarchical. It's important to note that there are regulating relationships that go in both directions, between the "bottom" and the "top": all our functions are rooted, so to speak, in the physico-chemical, including social life and consciousness; and, reciprocally, conscious and social life can influence the physico-chemical level.



6. Hierarchy and parallelism in the organization of the brain  
(after Jean-Pierre Changeux, 1989).

What we call "bottom up" and "top down" regulation. The brain is slow, as we've said, but performing thanks to this

organization. Another essential point is that this hierarchical organization, which begins with the egg, the embryo, etc., is built up progressively over the course of an individual's life, until the adult state is reached, which in humans is around the age of fifteen-sixteen.

In short, there is not only hierarchy and parallelism, but also a gradual establishment of the cerebral organization. From birth to adulthood, the volume of the newborn's brain increases fivefold. Half of all synapses are built after birth, at a rate of around one million per second! The human brain is immature at birth, which is not the case with a chick, for example, which is immediately active and capable of feeding itself, without the intervention of any real learning process. This is also true of birds, with the distinction between nesting and nest-feeding species, between fledglings that remain in the nest for a long time, dependent on their parents (nest-feeders), and those that gambol around a few hours after birth (nest-feeders). Nidicoles acquire more behavioral performance than nidifuges. Man is an extreme case: he was selected by Darwinian evolution to spend half his life (when *Homo sapiens* appeared in Africa, his life expectancy was around thirty years) building his brain. He was selected to build himself progressively on the basis of his genetic heritage, and above all in relation to the outside world...

## **2- FIRST STEPS IN UNDERSTANDING INNATE- ACQUIRED RELATIONSHIPS**

When I returned from the USA in 1967, Jacques Monod made a small laboratory available to me so that my group and I could work independently, under his "protection", so to speak. At the same time, he appointed me deputy director of the molecular biology chair at the Collège de France. In 1972,

the first section of molecular biology is created at the Institut Pasteur. Within this entity, a neuroscience group emerged. At the time, I was something of a foreign insert in a research environment traditionally devoted to bacteriology, immunology and infectious diseases. Élie Wollman, whom I liked very much, once told me that I should better belong to the Salpêtrière. However, I always wanted to introduce and defend neuroscience at the Institute, convinced that a biological environment, including virology and bacteriology, in the spirit of Pasteur, would benefit my own work, and even more so neuroscience in general. Experience, I believe, has proved me right. The small neurobiology group that was to become the Molecular Neurobiology Unit was, at the outset, rather isolated. I therefore sought to establish contacts with the outside world, in order to maintain the originality of my research, by calling on physicists in particular. My general idea, was that, to fully understand a biological process, you need to produce beforehand a mathematical model of it.

*Your meeting with Ilya Prigogine was part of this process...*

I met Prigogine in Brussels, in 1968, after reading one of his articles given to me by Bernard Lavenda, who worked with him. "Structure, Dissipation and Life", published in 1967, dealt with the thermodynamics of systems out of equilibrium. An enzymatic reaction in a test tube or the dispersal of sand on a beach occur at equilibrium. Generally speaking, chemical reactions are divided into equilibrium and non-equilibrium chemistry. We know that systems that are thermodynamically at equilibrium are stable but Prigogine wondered, from a physical point of view, whether there might be stable non-equilibrium systems. He called them "dissipative structures". The out-of-equilibrium state is stable and is maintained

because there is an exchange, either of matter, which enables the system to build itself up, or of regulatory signals, enabling this physical system to acquire a certain form of homeostasis. We are back to Claude Bernard. In the discussions I had with Prigogine, he liked to emphasize that the exchange of regulatory signals provides the system with a considerable wealth of information. It wasn't just the chemical components of the organization that were out of equilibrium, but also the way it organized itself. I was very interested in these considerations at the time, particularly the idea that, in these dissipative structures, there could be all-or-nothing transitions in relations with the outside world. This is what Prigogine predicted in his calculations. Such a model could be useful for thermodynamic understanding of the central nervous system, its relations with the outside world and, above all, learning.

*An article for the magazine La Recherche gave you the opportunity to collect recent data on nature and nurture...*

Following these powerful encounters, I sought to conduct a reflection on learning, on the innate and the acquired, at the Institut Pasteur, in parallel with my work on the nicotinic receptor. It was at this time that I wrote an article for *La Recherche* magazine (July-August 1970), the year the receptor was discovered, under the title "The innate and the acquired in the structure of brain", I mentioned several aspects of the question, in particular the contributions of genetics. We knew from long the existence of mouse mutants with rather curious behavioral dispositions, such as the *dancing mouse*, mentioned by Robert Yerkes in 1907. The Japanese and Chinese had identified years ago lines of dancing mice out of sheer curiosity, and knew that this characteristic was hereditary. At the time I was writing my article, I was very impressed by



Richard Sidman's work in 19652, which had led to the identification of 90 lines of mutant mice with abnormalities of the nervous system, in particular the cerebellum, located in the posterior part of the brain. He named these mutants: *swaying*, *weaver*, *nervous*, *staggerer*. Among many other observations, he also demonstrated the genetic control of cerebellar networks. Then, I remembered Daniel Bovet's work - after he left the Pasteur Institute - on the genetics of learning behavior and its pharmacology in the mouse. He published a seminal article on this subject in 1969, co-authored with Oliviero and F. Bovet-Nitti, entitled: "Genetic aspects of learning and memory in mice"<sup>3</sup>. It gathered data on learning differences between mouse lines. The study focused on the diversity of mouse responses to learning to avoid an electric shock. Bovet showed that there were significant behavioral variations from one line to another. He concluded that there was a genetic basis for learning abilities. He went on to show that the flight response to electric shock had an emotional aspect, that there were emotional dispositions, themselves under genetic control, and that the care of newborn mice by foster families could vary from one situation to another, that there was in fact a genetic basis for learning abilities. In short, he highlighted a set of relationships between genetics, learning and the emotional system: what we call the *reward system*... We'll come back to this in the next chapter. Bovet had thus laid the foundations for the first genetic study of behavior and its pharmacology.

*You refer to the work of David. H. Hubel and Torsten Wiesel and to early visual experience...*

In my article in *La Recherche*, I mentioned other important works, such as those by Hubel and Wiesel, on the

development of the visual system. This is a founding moment in the theory of epigenesis. Sidman's and Bovet's work defined the genetic envelope, while Hubel's and Wiesel's showed the relationship with the environment, which is complementary. If we look at the development of the visual system in the cat, we see that a whole diversity of neurons spontaneously develops, which contribute to visual performance: analysis of shapes, colors, movements, etc. There is an apparent form of innateness: a "genetic envelope" in the cat. Jacques Monod took up this point again in *Chance and necessity*, in 1970. However, he didn't mention the work of Wiesel and Hubel<sup>4</sup>, which was fundamental for me. These established that, if an adult cat is blinded by suturing its eyelids for several months, no lasting damage to the visual cortex is observed. However, if the same experiment is carried out on a kitten at birth, the result is different. Light deprivation in one eye renders the animal irreversibly blind in that eye. This is because the eye is no longer in contact with the physical environment, and in particular with light stimuli. The environment is indispensable for validating innate dispositions. Without it, an irreversible lesion appears, accompanied by abnormal organization of cortical neurons and their dendritic spines.

### 3- MEETING EDGAR MORIN

*All this forms the basis on which your theoretical model will be developed. Meeting Edgar Morin was another important step...*

Edgar Morin was a prominent representative of the humanities. I also benefited greatly from my contacts with this field of knowledge. In 1960, together with Georges Friedmann

and Roland Barthes, Edgar Morin founded the "Center for studies and mass communication" (CECMAS). At the time, it was original to research the complexity of communications and information exchange in technical societies, then in full development. This was the moment when Althusser was publishing *Read the Capital*, and Marcuse, *One-Dimensional Man: Studies in the Ideology of Advanced Industrial Society*. Morin is an unclassifiable man, described in turn as anthropologist, sociologist, philosopher, epistemologist, etc., a sort of "jack-of-all-trades". But this jack-of-all-trades had one stroke of genius: he understood that there was a step to be taken. In 1961, he created the magazine *Communications*, dedicated to the emergence of a new planetary culture. His multidisciplinary approach appealed to me. He advocated openness to all disciplines, not only those of the human sciences, but also biology. In 1969, he was invited to the Salk Institute in San Diego. He had met Jacques Monod. Morin decided to integrate molecular biology into his intellectual enterprise. The various disciplines, while retaining their own focus and competencies, had to interact with each other.

*This is where we find the essence of the Morinian method: bringing together without standardizing, distinguishing without disjoining, linking while taking up the challenge of uncertainty. With the paradigm of "complexity": "complexus" means "to embrace", "to weave together" »...*

That's not what interested me most in Edgar Morin's approach. I was more interested in his desire to integrate biology into the human sciences. Morin was something of a brilliant pioneer. In 1972, together with Massimo Piattelli-Palmarini, he organized a meeting at Royaumont, entitled "The Unity of Man", with the subtitle "Biological invariants

and cultural universals”, attended by Jacques Monod, François Jacob, Salvador Luria, myself, as well as Maurice Godelier, Emmanuel Le Roy Ladurie, Serge Moscovici, Jacques Mehler, Dan Sperber... This colloquium was crucial for me. Morin was interested in what he called "the event", in the case of mass communications. At his request, I wrote an article for his journal *Communications*: "Le cerveau et l'événement<sup>5</sup>". This preparatory paper served as the basis for my talk at Royaumont, in which I evoked Prigogine's work, the pre-determination of the subject to the event, a certain genetic determinism I'd already mentioned in *La Recherche*. I introduced the idea of the event's imprint on the brain structure. I was referring to the famous experiments of the ethologist Konrad Lorenz, who had lived among greylag geese and their goslings. He demonstrated that goslings attach themselves to the first living being they meet at birth, without this necessarily being their biological mother. The event, the "encounter" is imprinted for life in the young bird's head. The essential idea here is that of an imprint in the structure of the brain. Lorenz was selectively recognized by the goslings as an individual who had become irreplaceable. I thought more deeply to the synaptic theory of imprinting. Building on Hubel's and Wiesel's observations to enable a possible validation of innate dispositions, I proposed in the article for Edgar Morin a new concept, that of selection in the evolution of developing synapses. During development, the genetic program offers the possibility of choosing between several nerve pathways. In short, imprinting involves the selection of synapses.

*The proceedings of the Royaumont colloquium were published in paperback very quickly. Curiously, they are no*

*longer available...*

It's a pity, because it's an excellent book, still relevant today.

#### 4- THE THEORY OF SYNAPTIC EPIGENESIS

*Any reflexions that will lead you to develop a theory of epigenesis?*

This work was followed up. I wanted to formalize the idea of "synapse selection" mathematically. A young biology researcher, Antoine Danchin, working at the Institut Pasteur in the laboratory of one of my colleagues, introduced me to the mathematician Philippe Courrège. His major contribution to the writing of a first paper, in 19736, explains the axiomatic style adopted, which is rather difficult to read. He proposes a formulation of the theory of epigenesis in the form of a mathematical theory based on biological premises. This theory is internally coherent and can be confronted with experience - what he called "interpretations". Our work, *via* Monod, was transmitted and published in the *Proceedings of the National Academy of Sciences*. The biological postulates of this theory, known as "Epigenesis of neuronal networks by selective stabilization of synapses", are as follows :

1. The physical basis of the information processing carried out by the nervous system lies in the ability of neurons and their extensions to produce, propagate, transmit and integrate influx of which only the discrete character is retained.

2. Contacts between neurons, or synapses, are solely responsible for the transfer of information in the nervous network. Inhibitory or activatory synapses can exist in at least

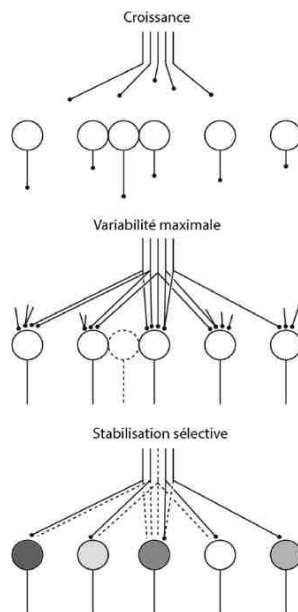
three states: labile (L), stable (S) and degenerate (D). Only the first two transmit nerve influx, and the transitions allowed are  $L \rightarrow D$ ,  $L \rightarrow S$  and  $S \rightarrow L$ .

3. The evolution of the conventional state of a given synapse is governed by the set of influx received by the postsynaptic neuron during a given time interval: this is the "evolutionary power" of the neuron soma, which retrogradely controls the stability of the nerve endings that come into contact with it during development.

4. The main stages of neuronal development, the maximum connectivity achievable, and the powers of evolution and integration of each soma are an expression of the genetic program and constitute the network's "genetic envelope".

5. Learning is defined as an acquired associative property resulting from the presence of variability in the connectional organization. Following interaction with the environment, or spontaneous endogenous activity, this property is established by the selective stabilization of certain connectional paths within a larger number of possibilities offered by the appearance of labile synapses during development.

The product of learning is a connectivity already present in the network and stabilized: a "selective stabilization" of synapses. This is where we introduce the word "epigenesis".



Model of epigenesis by selective stabilization of synapses  
(after Jean-Pierre Changeux, 1985)<sup>7</sup>.

*Was it you who introduced the notion of epigenesis?*

The term already existed, introduced by biologist Conrad Waddington in the early 40s of the last century<sup>7</sup>. His concept of epigenesis was very broad: the study of the mechanisms by which the genotype produces the phenotype. We owe him the metaphor of the "epigenetic landscape", which is supposed to represent the different paths possible during the development of an organism. His idea is that there can be diverse and varied landscapes, depending on the organism's relationships with itself and the environment. More recently, the word "epigenesis" has also been reutilized to describe chromatin modifications at chromosome level. It's a difficult term to use, given its multiple meanings. For my part, I prefer to speak of

"synaptic epigenesis theory".

The idea of variability is essential. Contrary to what we might think, the topology of the connectivity of the nervous network can vary from one individual to another even if genetically identical. The biologist Cyrus Levinthal worked on a species of fish (*Poecilia formosa*), which contained isogenic individuals (with identical genes), in other words, identical twins. He had characterized clearly identifiable neurons, the Müller cells, and observed the dendritic organization: between right and left, from one individual to another, there is variability in connectivity, although "identical twins" behave identically - hence the important "variability theorem". Between a pair of nerves with the same functions, there is variability between right and left in the same individual<sup>8</sup>

This "variability theorem" demonstrates that, in a developing neural network, the same incoming message, i.e. in other words, the same stimulus can stabilize the same input-output message yet with a different connectional organizations. In other words, the same type of learning can be achieved from connectional networks that vary from one individual to another. This is very interesting, because language areas in the brain can, depending on the individual, be located on the left or on the right, sometimes even in between, but you can never tell from listening to someone speak whether they are lateralized to the right, to the left, or to both sides! The lateralization of speech areas is a fine illustration of the variability theorem.

We should also point out that individuals producing the same action on the world, under identical conditions, can mobilize different networks. This obviously poses a problem for brain imaging. We can no longer see the brain as a rigid map where functions are distributed in a perfectly defined



way. We need a more flexible and variable view of the individual, even in the case of identical twins.

This is a fundamental consequence of the model. Another is that, following an interaction with the environment, there may be a learning process, an "imprint", which is not transmitted genetically, but epigenetically, from parents to children or between individuals in the same community. There will therefore be what is known as "cultural" diversity, and thus the appearance of a culture. The neural imprint cannot be dissociated from the cultural imprint, which is itself a neural imprint transmitted from one individual to another through language, music, dance and so on. So, not only is there the emergence of a culture, but also a diversification of cultures.

All these points were addressed during the Royaumont debate in 1972. Together with Antoine Danchin, we explained the consequences of epigenesis, and how Noam Chomsky's theses could be reinterpreted. At a subsequent meeting in 1975, again at Royaumont, organized around a confrontation between the latter and Jean Piaget<sup>9</sup>, I presented my theory of epigenesis, to which Piaget reacted positively; as for Chomsky, he did not openly oppose it. I had managed to find my place between the two.

*Between genetic psychology and deep structures...*

Later, we'll look at the consequences of epigenesis for the development of higher brain functions, such as language, consciousness, learning, culture...

## **5- THE MOLECULAR BIOLOGY OF SYNAPTIC EPIGENESIS**

With Antoine Danchin - this time without Philippe

Courrège, who only agreed to co-author mathematical papers - we wrote an article for the journal *Nature*<sup>10</sup>. It was widely read and quoted. In it, we set ourselves apart from Hubel and Wiesel's work, which we had called "functional verification" or "validation of a pre-existing innate structure", and from a purely empirical mechanism where everything comes from the outside; for our part, we proposed "selective stabilization", embellished with a diagram (illustration no.7) that met with great success. In this paper, we also tried, as closely as possible to my own interests, to propose biochemical stabilization mechanisms. As a result, we tackled the question of molecular biology and sought to demonstrate this proposition. We developed an initial theoretical hypothesis, according to which receptor molecules can diffuse onto the neuron body; when nerve endings arrive, receptors aggregate under some endings and stabilize, but not under others, which are then eliminated. A molecular mechanism at receptor level leads to the establishment of a stable synapse, both post-synaptically and pre-synaptically. This is one of the first models of selective stabilization on a molecular scale.

Other types of mechanism can be proposed. Our model is mathematical, with three states ("labile", "degenerate" and "stable"). The experimental question is to understand the regulation by excitatory and inhibitory systems, by growth factors and, why not, by the nicotinic receptor. The aim is to experimentally address the molecular basis of epigenesis.

In those years, I became interested in how to approach the evolution of nerve endings. In 1970, P. A. Redfern had observed that, at birth, there were 3-5 nerve endings per motor endplate<sup>11</sup>. This is an electrophysiological observation made either in culture, or on the developing rat or mouse. But when you get to the adult synapse, there's only one left. The question was whether this elimination was controlled by

activity, as the model intended. With one of my collaborators, Pierre Benoît<sup>12</sup>, we showed, either by cutting a tendon (tenotomy), or by introducing a general anesthetic, that if we modify the state of activity of the network, the elimination occurs differently or not at all. When activity is blocked, there is no elimination. That's the first point.

We have extended this work to include stimulation experiments in the chicken embryo. A method for stimulating the spinal cord in the developing embryo was then developed, which showed that, with stimulated synapses, the number of endings drops from 2-2 to 1-4, whereas with paralysis, the number increases from 2-2 to 3-7. The number of endings can therefore be controlled by activity. This experiment has been reproduced with other systems.

A spectacular experiment along these lines was carried out on the tadpole<sup>13</sup>. The authors track the projections of retinal ganglion cells onto the tectum individually and in great detail. If both eyes are stimulated at the same time, a coordinative function is acquired and synaptic elimination occurs; if stimulations are asymmetrical, multi-innervation is maintained, causing a serious handicap in the animal.

We have also verified this on the cerebellum. I've already mentioned Sidman's experiments. In certain cerebellum mutants, which he called "*weaver*", "*reeler*", "*nervous*" (anxious) and "*staggerer*" (hesitant), disorders of behavior appear, following a disturbance in connectivity. Jean Mariani<sup>14</sup>, from my laboratory, has shown that the mutations mentioned by Sidman can alter this evolution and maintain multiple innervation (several climbing fibers) in adults. Preservation of multiple innervation creates a handicap. Only synaptic elimination allows the developing network to acquire the "normal" physiological functions of the adult.

Studies are underway to elucidate the molecular

mechanisms responsible for the effect of cerebellar mutations. Together with my Japanese post-doctoral fellow Katsuhiko Mikoshiba<sup>15</sup>, we discovered that a high-molecular weight protein is missing in the "*nervous*" mutant. Once back in Japan, Mikoshiba showed that this protein is the receptor for inositol trisphosphate, an important receptor in the control of calcium signaling in the cell. A strong link can now be established between molecular level, synaptic epigenesis and behavior.

Other work has been carried out by various groups, such as Pasko Rakic, Jeff Lichtman, Carla Shatz... which validate the selective stabilization hypothesis. We should mention here a small problem of nomenclature, in that the Americans, instead of using the term "synaptic selection", have tended to use the term "*pruning*", which refers to the loss of synapses in the course of selection. But if there were only pruning, there would be no stabilization.

*This is all at the presynaptic level, but what about at the postsynaptic level?*

How can we decipher the molecular mechanisms of the postsynaptic model? One of the first experiments carried out using bungarotoxin showed that, under the nerve endings of the electroplaque (as of the neuromuscular junction), there is a very high concentration of receptors. Jean-Pierre Bourgeois at Pasteur has measured this density, which is of the order of 15,000 molecules per square micron<sup>16</sup>. These receptors could cooperate, but do not. They are held in place by a protein we later identified, 43K-Rapsyn<sup>17</sup>, which attaches itself to the receptor molecules, pinning them in place as it were. So there's a process of stabilization by a cytoplasmic protein that sticks to the receptor molecules<sup>18</sup>.

We have also been able to analyze the fact that, in the case of the neuromuscular junction, there are nuclei located under the nerve ending, under the postsynaptic density, which are specialized in receptor synthesis. During development, receptors are present everywhere, and are gradually eliminated from the synapse, concentrating only below it. By concentrating below the synapse, only the so-called “fundamental nuclei” will synthesize the receptor.

We have contributed to the analysis of genetic mechanisms specialized for expression below the synapse and repression by electrical activity outside the synapse. For nuclei outside the synapse, their receptor synthesis is repressed by activity. The effect of activity involves specialized regulatory proteins - or "transcription factors" - which control the transcription of receptor genes by activity. Maintenance of receptor synthesis below the nerve terminal mobilizes different transcription factors, insensitive to activity, but which respond to chemical signals released by the nerve terminal. A molecular biology of synaptic epigenesis is emerging...

## **6- CULTURE AND ITS EVOLUTION**

An important and unique feature of the evolution of the human brain is, as we have said, the extension of its postnatal development up to the age of fifteen. The process of postnatal synaptogenesis reveals a cascade of multiple interlocking stages in which the process of epigenetic selection, variation-selection/elimination, takes place. Epigenesis happens as soon as the first neural networks are established, and continues from embryo to adulthood. There is therefore a succession, an interlocking or nesting of epigenetic stages that constitute a considerable wealth. At certain critical stages of development,

specific to human beings, various cognitive aptitudes appear successively, including those involved in social life, such as the ability to speak and write language. These stages are superimposed on, or interwoven with, others that are enriched by the individual's history and his or her relations with his or her social and cultural environment. It has been established, for example, that the fetus recognizes not only its mother's voice, but also the language she speaks.

*Descartes already said he was « assured that the human soul, wherever it is, always thinks, even in our mothers' wombs<sup>19</sup> ».*

This essential mode of interaction is involved in the acquisition of individual experience, its storage in internal memories, but also in "external" memories, tools, sculptures, books... There is the genesis and transmission of distinctive human traits that we call culture, or rather cultures. Culture is constantly evolving, and is perpetuated by epigenetic relearning from generation to generation within the social group. The production of a culture encompasses many aspects of human behavior, including technologies, language, social practices (kinship and marriage), traditions and beliefs, value systems, institutions for a particular social group, and so on. It is the product of successive epigenetic stages that manifest themselves during development, and which, as we know, can present their characteristic variability from one social group to another.

*Writing was to play a decisive role in the transmission of culture. Yet its invention, in the history of mankind, came late...*

Among the many manifestations of cultural evolution,

writing and reading appear to be recent inventions. 40,000 years ago, *Homo sapiens* began engraving and painting abstract designs on cave walls. Clay counting tokens are known from Mesopotamia (9,000 BC), and the first pictograms from Ur date from around 4,000 BC. The acquisition of writing and reading places considerable demands on our cognitive system. The acquisition of reading and writing can be seen as a typical example of the epigenetic implementation of "cultural circuits".

Historically, the first evidence of specialized writing and reading circuits in the brain was the discovery by French neurologist Jules Dejerine (1914) of *pure alexia*, also known as *alexia without agraphia*<sup>20</sup>. People with pure alexia suffer severe reading problems, but continue to write. Other language-related skills generally remain intact, such as word naming, oral repetition and oral comprehension. Alexia results from brain lesions in circumscribed regions of the left brain, the medial occipital lobe, the medial temporal lobe and the splenium of the corpus callosum. Dejerine had already suggested a "disconnection" between the intact right visual cortex and the language areas of the left hemisphere. This interpretation is still accepted today.

More recently, the circuits involved in literacy have been examined using brain imaging. They confirm Dejerine's pioneering vision. These studies have taken advantage of behavioral evidence of different phonological processing in illiterate and literate subjects. When repeating real words, the literate and illiterate groups activated similar areas of the brain. In contrast, illiterate subjects had greater difficulty in correctly repeating pseudowords that did not activate the same neural structures as literate subjects.

Comparison of positron emission tomography (PET) scans of illiterate and literate groups showed a considerable change

in brain activation. For example, in a pseudoword contrast, activation in the literate group was more marked in the right frontal opercular-anterior insular region, left anterior cingulate, left lentiform nucleus and anterior thalamus/hypothalamus than in the illiterate group. These findings were consolidated and extended with functional magnetic resonance imaging (fMRI) of illiterate and alphabetized groups<sup>21</sup>.

The acquisition of reading and writing can be seen as an example of epigenetic "cultural circuits" established as a result of the epigenetic appropriation of rapidly developing connections, around the age of five or six. It operates at a time of still very rapid synaptogenesis and persists into adulthood.

*Does alphabetic writing use the same circuits as ideographic writing?*

Western alphabetic writing systems use circuits that differ in part from those used by Chinese ideographic systems. Japanese writing uses two sign systems, the phonetic and combinatory *Kana* and the ideographic *Kanji* - borrowed from Chinese writing. With *Kanji*, every sign has a meaning. Following in the tradition of Jules Dejerine, in 1943 the Japanese neurologist Tsuneo Imura<sup>22</sup> described an aphasic syndrome he called Gogi aphasia, the main feature of which is selective impairment of *Kanji* processing with preservation of *Kana* processing or phonetic signs with oral fluid repetition. Lesions in Broca's or Wernicke's area, in the left hemisphere, profoundly affect the use of *Kana* and less so those of *Kanji*. The brief presentation of *Kana* characters and *Kanji* signs to each of the two eyes, independently, suggests left-hemisphere superiority for *Kana* and right-hemisphere superiority for *Kanji*, particularly when nouns are involved. The results



suggest that *Kana* and *Kanji* are processed differently by the right and left cerebral hemispheres. Thus, the connectivity of the adult human brain can be seen as a complex tangle of cognitive, social and cultural circuits epigenetically defined during development, as part of a human-specific genetic envelope...

## 7- THE *HABITUS* OF THE HUMAN SUBJECT

Contrary to popular belief, there is no convincing evidence that culturally-acquired phenotypes can sooner or later be passed on genetically from one generation to the next. They have to be learned in every generation, from adults to children, and passed on epigenetically from generation to generation, from the mother's womb to the adult stage. The ability to share culturally-acquired knowledge from one generation to the next requires specialized teaching and elaborate pedagogical strategies specific to *Homo sapiens*, which are absent in non-human primates<sup>23</sup>.

*What are the consequences?*

The skills and practices associated with the symbolic experience and emotional labeling characteristic of rational thought (science), rules of conduct (ethics) and shared feelings (art) become stable, internalized epigenetically in the brain's connectivity, and become exclusive of the others. Their "forgetting" is considerably slower than their speed of acquisition through synaptic stabilization processes. They contribute to what Pierre Bourdieu<sup>24</sup> (1984) calls the subject's

*"habitus"*: internalized patterns of perception, action and routine evaluation, which often last a lifetime. For him, it's "an immanent law, deposited in every agent by early education". *Habitus* is not a "habit", but rather a "powerfully generative" system, discussed in the final chapters of this book.

Since the domestication of fire, perhaps, the grouping of human individuals into stable, autonomous and geographically dispersed groups has led to the differentiation and divergence of cultures between human groups, with different languages and knowledge, varied techniques and, above all, very diverse belief systems, thus raising cultural barriers to which we shall return.

Finally, social and cultural evolution is associated with the development of extracerebral memories in the form of spoken material, written and pictorial language, with a time span ranging from 100 milli-seconds to thousands of years. Spoken and written language, and perhaps even more so artistic activity, are seminal innovations that distinguish humans from other primates; they triggered the development of modern civilization and were, probably, central to the expansion of man's powers over himself and the world. Most importantly, language, writing and cognitive development in general (concerning objects, numbers, categorizations and reasoning or decisions) rely on epigenetic cultural transmission framed within a solid human-specific genetic envelope. The significant postnatal increase in human brain size, accompanied by the complex exuberance of epigenetically acquired cognitive, social and cultural circuits, offers the developing human brain the possibility of new, seemingly limitless social and cultural interactions, which contribute to the subject's *habitus*.

## VI.

### "I seek to understand"<sup>1</sup>

#### 1- THE COLLÈGE DE FRANCE AND NEURONAL MAN

*Your name is associated with the Collège de France, where you taught for thirty years...*

This is a very original institution, created in 1530 by François I on the advice of the humanist Guillaume Budé. At the outset, it was a college of "royal readers" charged with teaching disciplines ignored by the University of Paris. From the outset, the Collège was clearly directed against, or on the bangs of, the scholastic tradition that prevailed at the Sorbonne, and which was characterized by its extreme conservatism. The mission of the "royal readers" was to keep the king informed of new ideas, whether religious (the Reformation was in its infancy) or scientific (starting with mathematics), without having to go through the "Sorbonicoles", mocked by Rabelais. The institution did not disappear with its founder. Subsequent monarchs, and then modern heads of state, added to the number of "readers". From six at the time of its foundation today, there are just under fifty professors - a relatively small number to teach the full range of disciplines, from basic sciences to literature, philosophy and

social sciences. The distribution of professorships covers a very broad spectrum, as illustrated by the College's motto: "*Docet omnia*" ("It teaches all"). It is both a place of excellence for the transmission of all knowledge, and open to all. And this has been true from the very beginning.

*There is no registration or diploma required or issued...*

The Collège de France, dedicated to fundamental research, has a unique feature: it teaches, regardless of age, degree or nationality, "knowledge in the making in all fields of literature, science and the arts". Teachers are obliged to teach a certain number of hours per year (around ten), which may not seem like much from the outside. In fact, these courses represent a considerable amount of preparatory work. Every year, a *new* and original course has to be developed. The "public" is very heterogeneous: students, professors, engineers, even retired politicians who come to the Collège to learn. It's a milieu that's both cultivated and demanding, and above all loyal. You find the same audience year after year. They are always likely - an additional constraint for the teacher - to refer to what was said a few years earlier. Classes last a good hour, and I've personally always wanted to set aside time at the end for discussion with the audience. In the last few years of my teaching career, there were around three hundred people taking my course.

*How did your election to the Collège de France go?*

Unlike the Académie Française, for example, the Collège's system is such that you don't apply to be a candidate. It's a self-recruitment process. The Assembly of professors decides on the practicalities of electing a new member.

*So it's a question of co-optation...*

This co-optation occurs when a chair becomes vacant and a teaching position becomes available. The tradition is not to take over the title of a chair, but to create a new one, with a new discipline and a new title. The idea is to create a scientific dynamic. The first vote is on the title of the Chair, and the second on the person who will occupy it. The election therefore takes place in two formal, official stages. In practice, when we create a chair title, we have an idea of the right person to occupy it. The procedure begins with a recommendation at an informal meeting where names are circulated. This is the decisive moment. As far as I'm concerned, I was asked by François Jacob to be in the "second line" when he presented François Gros as the "first line". You can't put forward just one candidate; there always has to be a second, in case a problem arises. It's usually someone "promising" and younger, whose name we want to make known. As it happens, I was part of a committee ("Biological Membrane") within the DGRST (General Delegation to Scientific and Technological research), an organization created by General de Gaulle. It's a "parallel" organization, as France likes them, in charge of distributing subsidies to various research laboratories.

The "Biological Membrane" committee was chaired by François Morel, himself a professor at the Collège de France (chair of Cellular Physiology)...

*But you were already Assistant Director at the Collège, in the Chair of Molecular Biology...*

Yes, but in Jacques Monod's chair. Being *Assistant* -director was not an advantage, on the contrary, as the Collège is committed to a stringent renewal of teaching. François Morel,

having been made aware of my work, told me that, when the time came, it might be possible for me to join the Collège. One day, I heard through the grapevine that Étienne Wolf's chair (experimental embryology) was going to be vacant. This was in 1974. I mentioned it to Jacques Monod and François Jacob. They told me it was a good idea, but that I was still very young. I then went back to François Morel, who was in favor of my election and who initiated my candidacy. In the end, it was François Jacob who, at the informal meeting of professors, set in motion the process of creating a new chair in "Cellular Communications". On this occasion, he declared that I was "one of the rare researchers capable of posing the most varied problems of biology in biochemical terms". Jacob was not a biochemist.

*Is voting at the Collège by simple majority?*

I was elected in 1975, by a large and indeed simple majority, against a candidate who represented continuity, coming directly from Etienne Wolf's laboratory. I began my teaching in 1976. Thirty years later, in 2006, I stepped down...

*How did you design your course?*

My first course dealt with molecular aspects, the receptor, etc. The subsequent year I moved on to more integrated cellular aspects, then to neuron ensembles and circuits, right up to higher functions. After seven years of teaching, professors are given the opportunity to take a sabbatical. During these first years of teaching, I had accumulated a great deal of knowledge through the preparation of my courses. It was then, in 1981, that I met Odile Jacob, François' daughter, who had just been recruited by Éditions Fayard to develop a collection devoted to the latest advances in science. She came

to me with the idea of writing a book based on the basic data from my teaching at the Collège, adding a theoretical dimension that would include a new vision of the state of the sciences of the nervous system, of the emerging neuroscience, but, in my own way, going from the molecular to the cognitive. I hesitated a great deal, fearing that this would interfere with my current experimental work...

*Has your research work suffered as a result of your writing task ?*

In 1982-1983, as I mentioned, several teams were working on cloning the receptor, including our own. But even though I continued to be very assiduous in the laboratory, perhaps I didn't concentrate enough on this project. But in the end, I accepted Odile's proposal. That's how *L'Homme neuronal* (*Neuronal man*) came about. It took a lot of work and time. I'd get up early in the morning, around 5 or 6 o'clock, and work until midday. Then, after popping into the Hôtel Drouot to see if there was a painting to be discovered, I'd go to the Institut Pasteur to attend the daily seminar, before returning to my lab until 8pm. A steady rhythm that lasted for a year and a half.

*Did you choose the title?*

I've already explained this<sup>2</sup>. Jacques Lacan's son-in-law, the psychoanalyst Jacques-Alain Miller, invited me to a meeting at the *Ornicar*<sup>3</sup> magazine. The debate, with a dozen or so opponents, was lively and intense. At the end of the meeting, in which I found myself alone "in the lion's cage", Miller proposed that I call my position the "defense of *neuronal Man*". It took me three months to write the first chapter. In it, I give a retrospective historical overview of knowledge about

the brain, from ancient Egypt, with the Edwin Smith papyrus, to contemporary times, via Greek theories (which questioned the seat of the soul: the brain or the heart?), Descartes, La Mettrie, Gall and others. The chapter ends with pages devoted to brain chemistry and neurotransmitters. For me, chemistry is an essential part of this "opening". I don't stop at the electrical aspects alone, with Galvani and Volta.

In the remainder of the book, I describe the neuron, the organization of the cerebral cortex, action potentials and more. A chapter is devoted to the links between electricity and channels and the isolation of the receptor (the "molecular locks"). One chapter deals with "acting out", in which I try to describe a more integrated dimension, what we now call "circuits". I chose to use a phrase from Diderot as an exergue: "Disturb the origin of the bundle, you change the animal." In these pages, I describe: the cricket's song, which is a fairly automatic behavior; the circuits involved in fish swimming; the limbic system in humans; emotions; and brain localizations. This is a very interesting level of analysis, which is still favored by those who study the brain. The aim is to uncover the neural circuits involved in a particular behavioral act. The next chapter, devoted to "mental objects", is by far the most original, along with the one on "epigenesis". Based on a new synthesis, I try to understand how mental processes can be described in neural terms. Can we have a neural representation of the percepts, memory images and concepts that make up the forms that exist in our brains? I've grouped this theme under the general term "mental objects ».

The Canadian Donald Hebb, mentioned above, was a precursor in this respect. As early as 1949, he was already talking about Neuronal assemblies<sup>4</sup>. In *Neuronal Man*, I wrote: "The *mental object* is identified with the physical state



created by the *correlated* and *transient* entry into activity (electrical and chemical) of a large population or 'assembly' of neurons distributed at the level of several defined cortical areas. This assembly, mathematically described by a *graph*, is "discrete", closed and autonomous, but not homogeneous. It is made up of neurons with different singularities, which have been identified by selection during embryonic and postnatal development<sup>5</sup>. It's a kind of mosaic of neuronal activities that come together to form mental representations. This chapter of *Neuronal Man* also develops another idea: considering the acquisition of these representations, which may be exogenous or endogenous, I propose a "Darwinian" mechanism of spontaneous production of sketches, which I have called "pre-representations", followed by their selection during interaction with the outside world. This Darwinian metaphor will also be mentioned by Gerald Edelman. I suggest that learning by selection occurs by "resonance". When a pre-representation resembles what a percept evokes, stabilization occurs.

We're about to take the next step towards another mode of selection, which we'll be discussing shortly. It is interesting to have a model of these pre-representations that is based on the brain's spontaneous, endogenous activity, which is itself modulated by the external and internal worlds, giving the brain a projective "style": it projects pre-representations onto the external world and, depending on the relationship with it, selects some of these pre-representations. The brain's spontaneous activity has a "hypothesis-generating" function and a "predictive" or "projective" style. Alain Berthoz has taken this idea into account in his own work.

*This vision of how the brain works is the opposite of what most people think...*

And computer scientists in particular... They only see the brain as an input-output system. The brain is organized around the type of input it receives and the behavior of the input that results. Here, however, it's the other way around: we're dealing with a selective Darwinian model, not a Lamarckian one. The brain is autonomous: it produces its pre-representations, projects them onto the outside world as a hypothesis and selects them in the form of knowledge. This scheme changes the way we think about the brain. On this basis, and to bring this aspect of *Neuronal Man* to a close, I tried to formalize this model, as I had done for epigenesis, with Philippe Courrège and Antoine Danchin. In 1982, I asked Thierry Heidmann whether it was possible to construct a model of synaptic efficacy change based on allosteric equilibrium<sup>6</sup>. We formalized the idea - which will be the subject of a report to the French Academy of Sciences - that the equilibrium between desensitized and resting states of the postsynaptic receptor can vary and modulate synaptic efficiency. In addition, we hypothesized that the allosteric balance of a synapse can be controlled by an allosteric signal from another synapse (S1 modulated by S2). If the two coincide, the result is classic Pavlovian conditioning. We succeeded in devising a molecular model of the change in synaptic efficacy. For the rest of my work, this was a critical moment in linking allostery and learning in the brain. It is a kind of keystone in the construction of a "cognitive" edifice from the elementary building blocks that are allosteric proteins, enabling the link to be made between allostery and the higher functions of the brain.

This work was pursued with Thierry Heidmann's brother, a

physicist, and resulted in a second note in the *Comptes-rendus* of the French Academy of Sciences: on the basis of elementary learning (established with Thierry), we can create a selection of pre-representations by resonance, between internal transient pre-representations and external transient pre-representations, perceptions from the outside world<sup>7</sup>. For me, these two articles were one of the first consequences, or implementations, of *Neuronal Man*. While the book was initially conceived as a work for the general public, aimed at my audience at the Collège de France, in the end it served as the starting point for a scholarly work.

*L'Homme neuronal was a huge success, thanks in part to Bernard Pivot (Apostrophes) and the women's press. It sold over 200,000 copies. This popularity is without doubt unique in the annals of a scientific work of this stature.*

It's a very different book from those that existed at the time, by John Eccles or Eric Kandel, for example, electrophysiologists who deliberately omitted the molecular level, showed little interest in cognitive processes and made no attempt to link the molecular dimension to the understanding of higher brain functions, unlike *Neuronal Man*. To this must be added my determination to situate my work in the physicalist tradition. Perhaps that's what made it such a success...

## **2- COGNITIVE MODELS DEVELOPED WITH STANISLAS DEHAENE**

*Soon came the time of a fruitful collaboration with a young researcher, Stanislas Dehaene.*

Thierry Heidmann having left for other worlds, my laboratory

where he had done very well, I thought I'd find a way of interacting with colleagues, more competent than myself, who could help me in mathematical formalization. I therefore sought to enter into a new partnership. The opportunity came from Jacques Mehler, whom I'd met at Royaumont. He had developed a theory of learning by unlearning, which could be compared with my own theory of learning by synaptic selection and elimination. But he had published, with an English colleague, a book in which he asserted, firmly and even abruptly, that it is not necessary to know the neural organization of the human brain to understand language. A good computer program should suffice. This rejection of the link with neuroscience gripped me, irritated me even. I told Jacques Mehler that we needed to clarify all this and find common ground, if only in terms of modeling. He offered to introduce me to two of his students, both normaliens and mathematicians. One of them was Stanislas Dehaene, then in his early twenties. He had told me that he had read and appreciated *Neuronal man*...

*So this is the beginning of your « complicity »...*

We've worked together for almost thirty years! This collaboration has brought me a lot of happiness.

*He's become a bit like your pupil...*

Much more than that. Although I trained him in neuroscience, I didn't want to be associated with the direction of his thesis, which was in cognitive psychology. During our long collaboration, he went from being a student and post-doctoral fellow to a colleague. He was my collaborator. We would spend one afternoon a week, or every two weeks, sharing a number of ideas, with a view to building models.

*But what is a model?*

The purpose of a model is:

1. To represent a behavior or mental process on a minimal but realistic basis (neural architectures and activity distributions), if possible in mathematical terms.
2. To build a formal organism capable of establishing causal relationships between a specific behavior or even a *subjective* "mental" process and *objective* neural measurements.
3. That it can be experimentally tested from the molecular to the cognitive level.

However, every theorist is aware that, being a product of his brain, the best model will never give a complete and exhaustive description of reality. Democritus had already noted this point. Also, Newton's physics, for example, describes the movement of the planets in an extremely partial way.

Stanislas and I agreed that a theoretical model only makes sense if it relates to a behavioral task that is accessible to experimentation, and that any formal model must be based on plausible neural foundations. It must be as "neuro-realistic" as possible, from the molecular to the cognitive level. In the tradition of "enlightened materialism", this is a minimalist model, necessary...and sufficient?

Our joint publications all include a preliminary section on biological premises. They gather together a number of observations and set a goal: what are we trying to demonstrate? We have adhered to this formalism throughout our work together.

This research activity, which was somewhat marginal in relation to what Stanislas was doing with Jacques Mehler, was also marginal in relation to what, at the time, occupied me mainly in my lab. In short, we found ourselves working together on a project that turned out to be highly original. We were modeling together, but each of us was putting our ideas to the

test through appropriate experiments. He, in humans, taking advantage of the development of brain imaging; I, working on mouse genetics.

*Stanislas Dehaene will soon be joining you at the Collège de France...*

His ambitious and forward-looking research in cognitive psychology, and our work together, convinced me that he should belong to the Collège, where he still teaches.

Here are a few milestones in our research.

First, the validation of the selective learning model. In 1986, Gérard Toulouse, a solid-state physicist, and I proposed a model based on a representation of the brain derived from statistical mechanics - magnets - with random connections (or "spin glasses", already mentioned) and pruning of a complex tree of states generated with maximum parsimony of genetic information<sup>8</sup>. Our conclusion was that the formalism of statistical mechanics could be used to study the brain. This work is still quoted in time, but it didn't have the hoped-for follow-up, as it didn't open up any new concrete perspectives.

The first article we co-authored, with Stanislas, concerned a network that assembles neurons so that their activity is chained together in temporal sequences, like words in language<sup>9</sup>. Our aim was to string together meaningful representations. We did not succeed in formalizing the semantic aspect of language, but only the "chaining" aspect. As an example, we chose the acquisition of song in a passerine bird, the marsh sparrow (*Melospiza georgiana*) or the song sparrow (*Melospiza melodia*), based mainly on observations made by the American ethologist Peter Marler<sup>10</sup>. Learning to sing in adults involves several stages:

1. Imitation with production of unstructured vocalizations (a

“sub-song”).

2. Appearance of a “plastic song” with authentic syllables, but four to five times more numerous than in adults.

3. “Crystallization of song” with elimination of supernumerary syllables: syllabic attrition. The young bird learns a particular sequence based on what it has heard from adults.

We designed a model based on the synaptic interaction device - the fruit of my collaboration with Thierry Heidmann - including the molecular aspects. It's interesting to note that this configuration has been retained in all subsequent models, right up to that of consciousness. All our models are based on relationships between neurons, founded on the presence of allosteric receptors. The general idea is that, initially, the network is made up of "*clusters*" of autonomous, synergistic neurons with connections between them. The application of a "rule" (sequence to be learned) stabilizes, by resonance, the corresponding sequence of groups, with the elimination of other possible sequences. A comparison can be made with the acquisition of language in humans, by drawing a parallel between the babble of a child and the sub-song of a young bird. This also reflects the fact, already considered in *Neuronal Man*, that there are losses of language perception in the course of a child's development.

Patricia Kuhl and her Japanese colleagues have shown, for example, that the syllables "*ra*" and "*la*" are not distinguished by adult Japanese, or even by children from the age of twelve months... whereas younger Japanese babies are able to distinguish them. This perceptive ability has therefore been lost in adulthood, which is in line with the model...

The second stage concerns cognitive learning by *reward*, and no longer by *resonance*. Stanislas and I were interested in a different type of task, one that we wanted to be more

elaborate than simple birdsong, and one that we wanted to be more realistic. Call it a "delayed response task" <sup>11</sup>.

*What is a "delayed response" task?*

A monkey or dog is presented with two upside-down bowls. Under one of them, in the animal's presence, a treat is hidden (the hoped-for reward). The animal is then removed to another room for a few tens of minutes. When it returns, it is presented with the two bowls. In most cases, the animal chooses the one with the hidden treat. If, repeating the experiment, the position of the treat in the bowl presentation is changed in front of the monkey, the monkey chooses the correct bowl, whatever its position. The treat is therefore neither to the right nor to the left, but where it is. This is delayed response, because there's a time lag between the moment the animal sees the thing and the moment it makes its choice. We're talking about learning a basic rule.

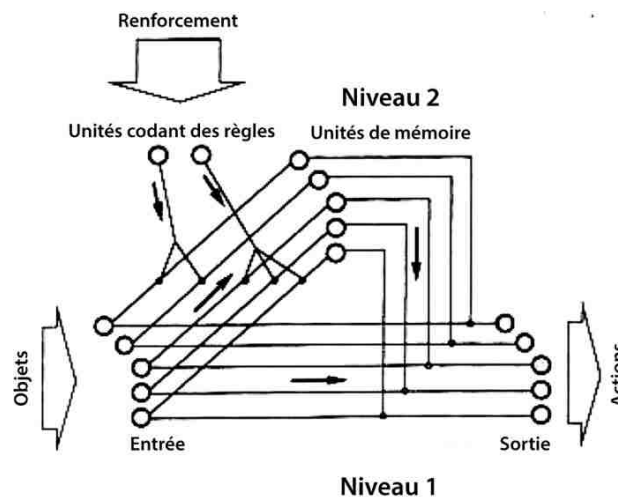
Here, the resonance model wasn't working. We came up with the hypothesis that there might be *validation by reward*. Among several objects to choose from, we select the one that is accompanied by maximum reward. We immediately thought of the dopaminergic system (which is activated by pleasurable stimuli such as food, sexual pleasure and social interaction, as well as by aversive and stressful experiences) and the role of the frontal cortex, the part of the human brain that undergoes the greatest development during hominization. Damage to this area impairs test-taking success.

We were led to distinguish two hierarchical levels of neuronal architecture:

- The first level is sensorimotor automatism. At this level alone, the organism does not learn the delayed response task. It is unable to access higher cognitive functions.



– A second level contains the elementary structures that enable it to perform the task. It controls the functions of the first level. It supervises it (*cf.* Tim Shallice); this is where the program changes as a result of reinforcement, enabling access to a "cognitive" level higher than the lower "automatic" level. This is an important conclusion in the current context of neural networks and Artificial Intelligence, where neural architectures of this type receive little or no consideration. It is in line with Daniel Kahneman's (2011) distinction between system 1 "*thinking fast*" - instinctive – and system 2 "*thinking slow*" - deliberative.



#### 8. Formal organization performing the delayed response task.

This highly schematic drawing illustrates the distinction between two hierarchical levels: an automatic lower level and a regulatory or "supervisory" (Tim Shallice) upper level sensitive to reinforcement by the reward system.

(Adapted from Stanislas Dehaene and Jean-Pierre Changeux, 1989).

*You've also used the "Wisconsin Card Sorting" task. What does it involve?*

In fact, the modeling was continued with a more sophisticated task requiring a certain amount of “creativity” on the part of the patient: *the Wisconsin Card Sorting task*. A patient is presented with four cards that differ in shape, color and number. The examiner asks the participant to extract from a pile of cards one card after the other and match them to one of the four uncovered cards, following a rule: according to color, shape or number. When he does so correctly, he receives a positive response from the examiner. Without telling the patient, the examiner changes the matching rules during the test and only tells him/her whether the match with the base card is good or bad. The patient will find the new rule by taking care of the answers. Stanislas and myself tried to design a “formal organism” that passes the Wisconsin task<sup>12</sup> and we succeeded. It borrows reward validation from the delayed-response task model, but adds a new architecture for rule-selection. The patient has several possible matching rules "in his head". The model, as it is constructed, opens the possibility for each rule to be independently activated, and thus to inhibits all the others, until the right rule is found -which is the case for the one that causes a positive reward and is stabilized. The others are eliminated. There's a *generator of diversity* and a self-evaluation loop which means that the patient won't reutilize the same “bad” rule a second time. He'll be looking for a new rule. This is an important step towards the higher functions of the brain... It's what we're all trying to do to give a good lecture at the Collège de France!

*You will also be led to consider the child's sense of numbers...*

Indeed, a major piece of work concerns number recognition

in children<sup>13</sup>. The theme was in line with the work of Jacques Mehler's laboratory, but of course without any neural basis. Some birds, such as crows, can distinguish numbers up to 7 or 8 without counting. So can rats. It's not just the ability to recognize a number, but also the ability to compare two numbers and decide which is bigger. Newborns can do this. We set out to build a neural model, including unordered number detectors, to which we added a short-term memory network. This device enables two sets of objects to be compared, and their subjective numerical distance to be evaluated: evaluation between 8 and 9 is more difficult than between 2 and 3, even if the distance is identical. Computer simulations of the network show that the number detection abilities of infants can be explained without assuming that they can count. The basic neurological underpinnings of number recognition are found experimentally in monkeys. The model, therefore, has some plausibility. We have access to relatively evolved cognitive functions.

*There's also the "Tower of London Task".*

This task assesses planning, organization and executive functions<sup>14</sup>. Three pegs of different lengths are placed on a wooden board. Three identically-sized but differently-colored balls are also provided, which can be placed on the three pegs. By sliding the balls, the patient must obtain a pre-designated configuration. Patients with frontal cortex damage show deficits in planning a goal-directed sequence of movements. This test is a kind of puzzle, requiring relatively anticipatory, top-down and bottom-up planning. We gain access to a major projective capacity of the human brain, that of anticipating its actions on the world...

This joint modeling effort convinced me of the very

concrete plausibility of crossing, step by step, the levels of organization that give access to the higher functions of the brain, and thus bridging the gulf separating cognitive psychology and neuroscience... The *res exensa* from the *res cogitans*... Still, we had to provide more experimental evidence!

### 3- EXPERIMENTAL WORK ON THE ROLE OF THE NICOTINIC RECEPTOR IN COGNITION

Our work with Stanislas Dehaene was fruitful, but rather limited. Intellectually, they bring plausibility to the hypotheses we had formulated. Some of these were already present in *L'Homme neuronal*, but had not been formally implemented with well-defined neural bases, making it possible to explain relatively complex tasks. This was a significant first step. At the same time, in my lab, I was continuing my experimental work on a very simple animal model, the mouse; its cognitive capacities remain limited, but they give access to molecular genetics. What's more, we had unrivalled experience of nicotinic receptors, whose properties in mice are very similar to those in humans. I was therefore interested in the role of nicotinic receptors in learning and cognition in mice. I had to choose a *neuronal nicotinic* receptor. Most of the work describing the allosteric properties of the receptor concerned the *muscle* receptor from fish electric organ. Following on from the work of Patrick and Heinemann<sup>15</sup>, who had identified and expressed the genes, we set out (with Michele Zoli) to find out the distribution of neuronal nicotinic receptor subunits genes in the brain during development and in adults. The gene encoding the  $\beta 2$  subunit was found to be highly expressed in virtually all regions of the central nervous system, and to be a

neuronal receptor absent from glial cells<sup>16</sup> (see Chapters 3 and 4). Next, we set out to find out to what extent the  $\beta 2$  subunit, integrated into its pentameric structure, could play a role in cognitive functions - one of the direct consequences of the model proposed with Thierry Heidmann and the work carried out with Stanislas Dehaene of integrating the molecular level into our cognitive architectures. The task was a difficult one. We had to call on a new technology known as "*in vivo* gene deletion", which consists in deleting the structural gene ("*knock out*") from the mouse strain's genome. At the time, this type of genetic engineering required exceptional skill. I asked a brilliant American post-doctoral student, Marina Picciotto, to undertake this delicate operation. We had to start from a stem cell; make the deletion within it; reintroduce the cell into the embryo; obtain chimeric adults; and finally have a homozygous mouse with a deletion on both strands of chromosomal DNA.

*To carry out this highly complex work, you were able to benefit from the Institut Pasteur's proximity to many groups specialized in molecular biology.*

The mutant mouse survived, but with altered properties. We discovered that high-affinity nicotine binding sites were absent in the brains of the mutant mice homozygous for the  $\beta 2$ -subunit deletion. In addition, electrophysiological recording of brain slices revealed that thalamic neurons were unresponsive to nicotine application.

The mutant mice survived and reproduced, but exhibited unusual behavioral traits. We subjected it to a passive avoidance learning task, a test of associative memory. The mouse is placed in a well-lit room where it is able to feed and drink; it is then moved to another room, this one dark, where it

receives an electric shock and an injection of nicotine. It learns not to enter this chamber. Nicotine appears to have an effect on this learning process. However, as a major result, the mutant mouse no longer responds to nicotine. This effect is lost. The nicotinic receptor containing  $\beta 2$  is necessary for the passive avoidance learning task. This was its first demonstration<sup>17</sup>.

We tried to observe whether this characteristic was preserved in aged mice. We let them age and found that the  $\beta 2$  mutant mice showed neocortical hypotrophy (thinning of the cerebral cortex): neurons are lost in the hippocampus and glial cells grow in place of neurons. There is thus an overall degeneration. These mice, aged between twenty-two and twenty-four months, are severely altered neuroanatomically and bio-chemically, and also show impaired learning ability<sup>18</sup>.

*We can therefore conclude that there is a positive cognitive effect of the presence of the  $\beta 2$  subunit...*

These results encouraged us to continue our work on more elaborate cognitive tasks, similar to those modelled with Stanislas. The next step was to examine, in detail, this type of behavior in mice. With Sylvie Granon and Philippe Faure<sup>19</sup>, we chose a very simple task. We placed a mouse in an empty, open, circular enclosure. What do we observe? It behaves somewhat erratically, wandering to the periphery, then passing through the center, staying there for a while, looking around, then returning to the periphery. Sophisticated quantitative analysis of these fast and slow movements enabled us to distinguish between an *exploratory* behavior and more automatic, less "réfléchi" *navigational* movements. When compared with a  $\beta 2$  mutant mouse, we observe that

exploratory behavior is less pronounced than navigational behavior. This mouse traverses the space directly without pausing in the center. Without "thinking", as it were.

It's an interesting discovery. We can observe that this exploratory behavior is fundamental in humans: the human brain has an exploratory capacity that has enabled it to approach the understanding of its environment and to seek to give it meaning - the birth of the first cultures...

*Isn't the scientific himself, in his own way, an explorer...*

There is, if you like, a certain analogy between the exploratory behavior of the mouse and scientific inquiry...

This experiment is cognitively interesting. The same device has been used to assess more sophisticated features of exploratory behavior, if not more so. Two objects have been placed in the circular enclosure. The "wild" mouse learns to move from one object to the other, rather than seeing them as independent. The mutant mouse does not. Another type of behavior, referred to as "social behavior" in mice, has been examined, even if it appears somewhat distant from human social behavior. An intruder of the same sex was introduced into a cage and its interaction with the host mouse was examined. The mutant strain tends to follow the resident mouse, showing a reduced ability to interrupt ongoing behavior. Social interaction is modified by the deletion. It will also be shown that certain lesions of the frontal lobe cause disturbances in cognitive and social behavior in both mice and humans. This enables us to make links with certain pathological attention disorders in humans, such as attention deficit hyperactivity disorder (ADHD).

Nicotine, acting on nicotinic receptors, acts as a cognitive stimulant. This "positive" role can be pharmacologically valuable in the case of highly cognitively disabling diseases

such as Alzheimer's or Parkinson's.

*There's also the problem of nicotine addiction....*

This is a major subject. Our work has had, I believe, quite a big impact in this field, especially in the case of smoking. Tobacco, it should be remembered, was first smoked by the Native Americans, before being introduced and cultivated in Europe in the mid-sixteenth century. Jean Nicot, a diplomat, popularized it in France. In the following century, Richelieu introduced a tax on the product, and Colbert, in 1674, turned the trade into a state monopoly.

The WHO has established that smoking is responsible for over 7 million deaths a year worldwide, 75,000 in France alone. 27% of the population uses tobacco regularly, a very high proportion, even if it is on the decline. Depending on the survey and the country, between 57% and 75% of smokers want to quit. Only a small percentage, 3-6%, manage to do without. There is no truly effective medication. It's an open pharmacological field, but unfortunately making rather slow progress.

There are several aspects to intoxication with this drug: physical dependence, which corresponds to a physical need to smoke. The brain functions normally only in the presence of the drug. I was able to verify this with Jacques Monod, who needed to smoke several packs of cigarettes in the morning before he could work normally. This addiction, due to the substances present in tobacco, notably nicotine, results in an unpleasant sensation of withdrawal when you don't smoke.

It's interesting to note that the smoker knows that inhaling tobacco smoke is dangerous, that he's taking risks, but he's



unable to control himself. There's a "loss of control" that goes hand in hand with compulsive drug-seeking. This applies to all drugs. When the drug is stopped abruptly, there is a withdrawal syndrome, which can be very serious, and even, with opiates, lead to death by overdose.

We have, of course, considered the case of nicotine self-administration in mice, and in particular in the mutant strain<sup>20</sup>. In this strain, the dopaminergic system - which we know to be involved *in reward validation* with our cognitive models - no longer releases dopamine in the presence of nicotine. In wild-type mice, nicotine stimulates dopamine release in the ventral striatum, which is not the case in mutant mice.

*So what about self-administration behavior?*

Mesencephalic dopamine neurons in mice lacking the  $\beta 2$  subunit no longer respond to nicotine. Nicotine self-administration, which accompanies compulsive behavior, is impaired in mutant mice. This is a mouse model of nicotine dependence. This was a very important "first", initially directed against tobacco merchants who claimed at the time that tobacco was not addictive. We showed that there was addiction in mice, and that the nicotinic receptor played a critical role.

One of my post-docs, Uwe Maskos, who was interested in genetic engineering, will be looking to locate the molecular elements essential for self-administration. It has been established that  $\beta 2$  is everywhere in the brain of wild mice. In *knockout mice*, however, it's nowhere to be found. The team created a vector that included the  $\beta 2$  gene and its promoter, before injecting and re-expressing it in the brain of the mutant mouse, where the dopaminergic cells are

located. The receptor is very selectively re-expressed in the ventral tegmental area, and it is measured that the receptor has indeed been re-expressed. It is then possible to observe the recovery of dopamine released by nicotine. This makes it possible to target, at the organism level, the neuronal bodies that are essential for the activation of the dopamine receptor of the nicotine-stimulated reward system, the effect of nicotine and self-administration<sup>21</sup>.

We have been able to establish that, when we re-express, at the level of the ventral tegmental area, we can recover both dopamine release and nicotine self-administration. This is an important step towards understanding certain cellular and molecular mechanisms. Under these conditions, we can see that the famous exploratory behavior is partly recovered.

This is a fine demonstration of the molecular and cellular mechanisms involved, not only in certain cognitive functions in mice, but above all in drug dependence. Other aspects will also be highlighted: sustainable self-administration requires not only the presence of dopaminergic neurons in the central tegmental area, but also of inhibitory GABAergic neurons. A combination of at least two types of excitatory and inhibitory neurons is required. It can also be shown that other subunits than  $\beta 2$  inter- come:  $\alpha 4$ ,  $\alpha 5$ ,  $\alpha 6$ , but not  $\alpha 7$ . Indeed,  $\alpha 7$  is not involved in nicotine self-administration. It has also been established that, in the signs of abstinence, there is a differential contribution of  $\alpha 7$ ,  $\beta 2$  and  $\alpha 5$ , as well as an intervention of the nicotinic receptor, but that the receptor oligomers are not the same.

The phenomenon of nicotine dependence is not fully understood. Other mechanisms are being studied. In adolescent smokers, brain imaging shows that the prefrontal

network is altered. In the case of cocaine dependence, Nora Volkow, who heads the National Institute on Drug Abuse in the United States, has established that there is, in drug users, not only an alteration of the dopaminergic system, but also of the prefrontal cortex.

Drug addiction is a disease of the brain that urgently requires appropriate treatment. Police and judicial repression are therefore not enough, as they do not act as a deterrent, due to the "loss of control" that is one of the fundamental characteristics of nicotine addiction.

In short, we must not lose sight of the brain's multi-layered organization, in order to understand its higher functions, from the molecular to the cognitive. We need to consider the "dual" nature of certain pharmacological agents, such as nicotine (or nicotinic agents) - which is both a cognitive stimulant and an addictive drug - in terms of their level of action in the brain's hierarchical organization. There is thus a bottom-up and top-down integration of the various levels.

A vast and fascinating field of research has opened up, focusing on the possible discovery of non-addictive cognitive stimulants...



## VII.

### Becoming conscious

#### 1- DEFINITIONS - BACKGROUND

*We must now turn to the question of consciousness, which has been dealt with at length by classical and contemporary philosophy, and which you are considering from your own point of view, that of neurobiology.*

An abundance of scientific literature is devoted to this question. In *L'Homme neuronal*, I had already tackled the problem of consciousness and the neural bases of "becoming conscious". I concluded the chapter devoted to this question with these words: "Operations on mental objects will be 'perceived' by a *monitoring system* composed of highly divergent neurons, like those in the brain stem, and their reentries. These sequences and interlockings [...] function as a whole. Should we say that consciousness emerges from all this<sup>1</sup>?" I was referring to the classic work of Moruzzi, Magoun and, above all, Michel Jouvet on waking, sleeping and dreaming, on what we might call "becoming conscious" with an emphasis on the "ascending reticular formation" of the brain stem and its extraordinary biochemical diversity. Throughout these pages, I highlighted the "awakening of the cortex" in the formation of conscious percepts, control by attention and, above all, the operations performed on mental

objects, their sequencing and their exchange with the environment. Mental objects in conscious space have properties that non-conscious representations do not. An important property of conscious mental objects is their concatenation. We've already mentioned this process in connection with language and its sequences, which, when linked together, enable us to construct a meaningful sentence. I was also referring to the frontal cortex and its relationship with the limbic system. In this context, I was mentioning the early work on brain imaging and "ideography" pioneered by David Ingvar<sup>2</sup> of Sweden. This type of imaging was still in its infancy. He observed hypo-frontality in schizophrenic patients: the frontal cortex is less active than in "healthy" subjects.

Early research into consciousness was closely linked to the development of new technologies. Brain imaging, as a complement to electro-encephalography, magneto-encephalography and electrophysiology, made it possible to explore the neural bases of consciousness in humans (using less invasive methods) and animals.

*Perhaps you could outline the history of work on consciousness...*

My 1992 lecture at the Collège de France was devoted to "Neural bases of states of consciousness and attention", theme on which I wanted to continue my research. On this occasion, I sketched out a historical overview of the work on consciousness. It wasn't a question of recounting past history, but of keeping in mind the progressive development of notions, concepts and observations on which subsequent research would be based. This is an essential point.

The word "consciousness" has been used in very different senses by philosophers, moralists and neurobiologists. "Consciousness" comes from the Latin *conscientia*, from *cum scire*, "accompanied by knowledge". For the neuropsychiatrist Henri Ey, it is "knowledge of the object by the subject" and, reciprocally, the "reference of the object to the subject itself". The individual is both subject of his knowledge and author of it.

For the neurobiologist, consciousness corresponds to a "function" at the highest level of organization in living beings. In historical terms, without going back as far as Antiquity, we can mention the contributions of a few scientists interested in the development of "consciousness" or "conscious processing", during evolution

"The first name that comes to mind is that of the French naturalist Jean-Baptiste de Lamarck, the founder of transformism or evolutionism. He recognized that the nervous system develops *progressively*, from the simplest to the highest organisms, "by gradual and insensitive (inner feeling" compositions and developments". In his 1809 work, *Philosophie zoologique*, he spoke of a "singular faculty with which some animals and even man are endowed", which he called "sentiment intérieur" (inner feeling) - an interesting qualifier. Later, Herbert Spencer, in his *Principles of Psychology* (1855), extending Lamarck's ideas on this point, proposed a *compositional* genesis of nervous systems. He describes them as *simple* to *compound*, then with *double* composition, by convergence and divergence of fibers achieving higher ratios of integration, until a consciousness independent of the immediate surrounding environment becomes possible. There would be an evolutionary process of grouping nerve cells, neurons, up to a certain level where Lamarck's "inner feeling" becomes autonomous.

*Does it make sense to talk about emergence here?*

I don't really like this word, which Monod uses, as it has too idealistic a connotation. I prefer to speak of origin, apparition, development or production. In this case, we're not talking about an emergence, but a progressive appearance. There are interlockings that reach a level where this particular physiology of the "inner feeling" can develop, with the intervention of an environment where sequences find the opportunity to link up.

*It would therefore be more accurate to speak of an evolutionary process...*

We can, in fact, speak of an evolutionary process. In the course of evolution, certain neural organizations are selected, which fit into one another. As a result, the nervous system increases its capacity and performance. Later, at the end of the 19th century, neurologist John Hughlings Jackson introduced evolutionism into mental pathology. For him, "the diseases of the nervous system must be regarded as reversions of evolution, that is, as *dissolutions*". The highest centers form the physical basis of consciousness. They are the least organized, most complex and the most willing. At their level, the "most vivid" states of consciousness are "allowed to wrestle with each other". This is where "internal evolution" can take place. The degradation linked to pathology (he speaks of "dissolution") proceeds in the direction of the higher centers towards the more resistant, less complex, more automatic ones. This is what happens with Alzheimer's disease. We're dealing with a kind of "mental Darwinism", in reverse, so to speak.

Evolutionary theories, shared by contemporary neurobiologists, agree that consciousness appears at the highest and most complex level of organization of the central nervous



system, and creates a relatively independent or autonomous "milieu", a space of "simulations", of potential actions, where "internal evolution" can develop, thereby achieving a considerable saving of time, experience and energy in planning actions on the outside world. This is a very important aspect: a species devoid of consciousness would be obliged to proceed exclusively by trial and error, and would therefore spend a great deal of time and energy trying to obtain an adequate response, whereas with the conscious system, an internal simulation takes place which represents a considerable saving of time. When it comes to ethics, for example, it's clear that this creates a distance between acting on the world and deciding to plan a particular type of action. This is not a utilitarian thesis, but a fact: conscious beings can achieve in a fraction of a second what an organism without consciousness would take a considerable time to effectuate, just assuming it could.

William James's (1842-1910) *The Principles of Psychology* (1890) remains a founding text in the field of psychology and more specifically psychology of consciousness. For him, psychology is "the description and explanation of states of consciousness" and must be treated by the *analytical method*, as a *natural science*. He went so far as to suggest a possible "reduction" of psychology to cerebral experience. He wrote that "the immediate condition of a state of consciousness is a *determined* activity of the cerebral hemispheres". This essential idea was already clearly stated at the end of the 19th century. James made several important contributions: the notion of "stream of consciousness", meaning that no two ideas are ever identical; the intrinsic *variability* of states of consciousness (the fact that there is an evolutionary dimension to the dynamics of conscious mental objects); and the brain as an "organ of unstable equilibrium". The "intrinsic variability" and "unstable equilibrium" are not unlike what Prigogine would later call a

"dissipative structure", subject to stable, fluctuating, out-of-equilibrium states.

James goes on to say something important, which I and others, such as Gerald Edelman, will take up again, namely that personal consciousness is interested in certain elements of its content and disinterested in others; it is constantly making *selections*. James takes a resolutely evolutionary view, not only of the origins of the conscious state, but also of the way in which it operates. The question of "free will", for example, which has so occupied philosophy, is for him extremely simple: "it only concerns the amount of attentional effort we can exert at a given moment". The foundations laid down over a century ago by William James have no reason to be called into question.

*We can imagine that electrophysiology must have sought to provide answers to all these questions...*

Indeed, more recent theories, such as that of Llinas and Paré (1991)<sup>3</sup>, base their analysis on electrophysiological observations that agree with those of James. Their recordings of the cerebral cortex reveal remarkable similarities between wakefulness and REM sleep. They argue that wakefulness is an intrinsic state fundamentally similar to REM sleep, but specified by sensory inputs. Wakefulness is "plugged in" to the outside world, while REM sleep is autonomous and "locked in" to the inner world. In the view of these two researchers, the rich connectivity between thalamus and cortex contributes to the genesis of different oscillations in wakefulness, slow wave sleep and REM sleep. These electrophysiological recordings show that there is desynchronization during wakefulness - the subject passes through multiple internal states - whereas, during slow wave sleep, synchronized slow waves are observed. Cholinergic

neurons in the brainstem are thought to be involved in the transition from one mode to the other. They are part of this ascending bundle of the reticular formation. At this stage of research, we can see a first attempt to link physiology and the state of consciousness, emphasizing a vertical thalamo-cortical aspect. Consciousness is therefore not exclusively cortical, but thalamo-cortical, which ensures oscillatory activity. The cholinergic system is involved in "setting the clock" - already seen by Jouvet - for the *state of* the brain, whether awake, asleep or in a coma. These extremely precise neural bases remain true.

In the same years, Francis Crick and Christof Koch suggested that 40 Hz synchronous cortical oscillations were causally involved in conscious visual perception. This simplistic, controversial hypothesis did, however, have the merit, *via* the media, of convincing the scientific community of the value of objective measurements of conscious processing by the human brain. Until then, electrophysiologists had not been interested in consciousness, with the exception of those I have mentioned. Cellular physiologists, who still dominate the field of neuroscience, didn't want to hear about it either. Crick's idea acted as an incentive, helping to ease the minds of scientists who might be involved in this field of research. In 1994, he published a book entitled *The Astonishing Hypothesis*, which reiterated - "without astonishment" - the central thesis of *Neuronal Man...*

*Won't other teams be looking to develop biological theories of consciousness?*

Such is the case of American biologist Gerald Edelman, who, in *The Remembered Present* (1989), proposes a biological theory of consciousness, based on the concept of "reentrant signaling" (or "distributive feedback"), formulated by the author as early as 1978, as an essential component of

the neuronal selection mechanism involved in the establishment of a "global state" of consciousness.

I've already mentioned the word "reentrant" in relation to the cortico-thalamic relationships, but here we're dealing with a generalization of the phenotype that results in a global state of consciousness. Together with Italian neuropsychiatrist Giulio Tononi, Edelman proposes an Integrated Information Theory (ITT), in 1998<sup>4</sup>, which attempts to address two properties of consciousness: integration (the unity of conscious experience) and differentiation (the large number of states available). This is basically the idea of William James, but expressed in neurobiological terms. This analysis is not without its problems: Edelman and Tononi underestimate the role of the prefrontal cortex. According to the latter, it is the confluence of posterior sensory areas and association cortexes that allows us to understand access to consciousness. We shall see that this is probably not the case, even if the subject remains - to this day- debated...

From these various theories, we can retain two things: firstly, the established fact that there are neural bases for mental phenomena such as consciousness, wakefulness, sleep and dreaming; and secondly, the role of the thalamo-cortical system, which can be described in great detail at cellular and molecular level. Then there's the role played by the prefrontal cortex, already glimpsed in the 19th and 20th centuries by the Neapolitan physiologist Leonardo Bianchi, the prefrontal cortex corresponding to the most evolved part of the human cerebral cortex.

## **2- THE GLOBAL NEURONAL WORKSPACE**

My 1992 course at the Collège clarified my thinking: there was a solid scientific context from which to progress and develop

innovative theories. At the end of the course, I presented Bernard Baars' "*Global Workspace Theory*" (GWT), which I felt was the most psychologically relevant, along with Llinas' neural theory. I also suggested that the formal neural network proposed by Stanislas Dehaene and myself to simulate the Wisconsin's task could "serve as a starting point for the development of a more general model that would include a 'conscious compartment'". My course, nourished by all these readings, was for me the occasion to lay the foundations for a more elaborate scientific reflexion of consciousness or the "conscious compartment". I then wondered whether it wouldn't be a good idea to continue the modeling work undertaken on cognitive aspects, discussed in the previous chapter. Two events prompted me to take this step directly. Both involved Stanislas Dehaene, firstly, because he had set up an independent research group devoted to brain imaging at the CEA in Saclay; and secondly, because on his return from a post-doctoral stay at the University of Oregon in 1994, which had interrupted our collaboration for two years, I had shared with him the content of my 1992 course, its conclusions, and Baars' work. To my great satisfaction, Stanislas decided to continue our joint work, to take an interest in modeling the "conscious compartment" and to apply imaging methods to the study of conscious space. To this end, he recruited Lionel Naccache, a physician and neurologist.

### **Global Neuronal Workspace**

We began by working on Baars' definition of the "global workspace", which we incorporated into our model, calling it the "*global neuronal workspace*<sup>5</sup>", a kind of credit to Baars. The word added, "neuronal", clarified and specified the orientation of our research. In his book on cognitive psychology, Baars

distinguishes between the "global workspace", which he contrasts with non-conscious autonomous processors. There is, as it were, a global - i.e., conscious - space that embraces these non-conscious processors and which in turn disseminates information from one system of processors to all the other processors, but in a certain way, which he compares to a "theater", with only one thing being processed at a time, in accordance with the second rule of the Cartesian method. It's a bit like William James's theory: at every moment, the processors compete or cooperate to get their messages into the conscious workspace. The latter appears to be a kind of " Stock exchange of processors ", where these specialized processors interact, coordinate and control each other in *competition* or *cooperation*. It should be pointed out that there are various kinds of processors: sensory, motor, reward, memory....

We can call this ability to make a "free" decision based on a certain number of mental objects, both evoked and internal, "freedom of choice" or "free-will", as we like.

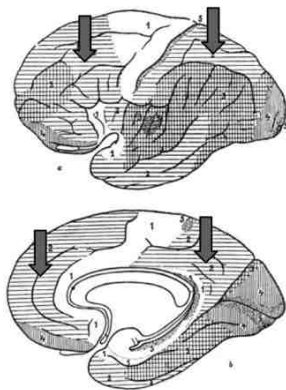
There are, however, two major shortcomings in Baars' work: on the one hand, he does not envisage a reward system, and the process of selection by "value" is not specified. Secondly, and more importantly, like Edelman, he does not propose any neuronal globalization mechanism, and hence any conscious "content". He confines himself to ascending reticular formation. He conceives of no horizontal network perpendicular to it, no original implementation in terms of neural networks.

*From here, you and Stanislas Dehaene will be looking to fill a gap in the neural basis of the conscious workspace.*

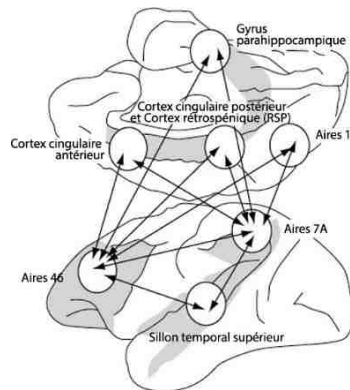
This was a major focus of our joint work. We proposed the hypothesis that the global neuronal workspace would mobilize a

vast set of interconnected cortical neurons with long axons, already observed by Cajal, up to several tens of centimeters long. These long axons would ensure the "horizontal" grouping of relatively distant and distinct areas of the cerebral cortex, including the corpus callosum (*see* Fig. 9). There was no need for some mysterious element. At the time, I had also read in the text (from my personal library) the Austrian neurologist Constantin von Economo, a follower of Korbinian Brodmann who, as early as 1925<sup>6</sup>, had shown that neurons, whose long axons interconnect several cortical territories horizontally, are pyramidal cells found mainly in layers I, II and III of the cerebral cortex and which always maintain their connections with the thalamus. The long-distance connection mapping data obtained by Patricia Goldman-Rakic<sup>7</sup> in monkeys are in line with those established by von Economo by the aforementioned French neurologist Jules Dejerine, who noted in the 1901 the importance of white matter bundles, long myelinated axons, in the human brain.

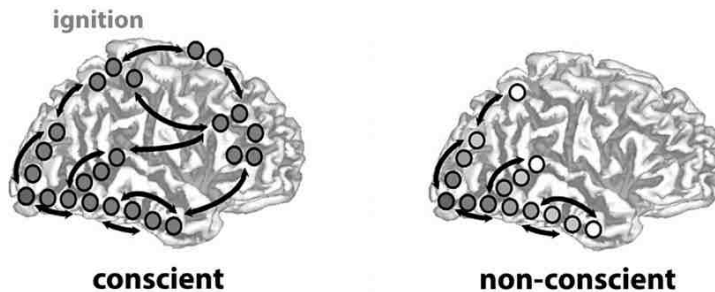
Hence the idea that we could create a diagram that would highlight what Baars called "conscious global workspace", but on the level of a particular type of large-scale neural network within the central nervous system. This would involve the long-axon, pyramidal neurons of layers II and III, which, as von Economo noted, are mainly found in the pre-frontal, dorsolateral, infero-parietal and cingulate cortices; in line with Llinas, still with rich connections to the thalamus. In a way, we're dealing with a set of connections that globalize information at the level of a common conscious space.



Constantin von Economo, 1929.



Patricia Goldman-Rakic, 1988.



Stanislas Dehaene and Jean-Pierre Changeux, 2011.

9. The Global Neuronal Workspace. Von Economo proposes that, in humans, the type 2 cortex (horizontal hatch) contains the soma of neurons with long axons and includes the prefrontal-parieto-temporal-cingulate cortices, which are found in monkeys (Goldman-Rakic) and contribute, according to Dehaene and Changeux, to the network of the Global Neuronal Workspace that flare up during ignition.

In this first work with Stanislas, following our usual practice, we chose a cognitive task to develop our model. This task, known as Stroop's task, would enable us not only to attempt to describe a conscious process, but also to specify



what the content of consciousness might be. It's not a conscious "state", but a conscious "content". In Stroop's task, a subject is asked to name the color of the ink with which a color name is written. Words are presented: "blue", "yellow", "red", but the color of the ink does not correspond to the meaning of the word. The word yellow is written in blue ink, and so on. This is known as an "incongruent" word. It appears that it is more difficult to name the color in which the word is written than to read it. The subject usually makes the mistake of naming the word, by automatism, and has to react by seeking to regain control, consciously, through a higher-level circuit. This is where the inter-reward system comes in. In this test, unlike the Wisconsin task, we involve the conscious neural space, including the reward system; we therefore have both a description of conscious content, conscious processing and what William James called *selections*. What we have described is – if we may - a computational implementation of James.

Michel Kerszberg, a Belgian theorist who worked in my laboratory at Pasteur, took part in the discussions. A model was thus proposed, enabling us to make predictions about the relationship between the processing of conscious objects and the cerebral territories likely to be activated when the conscious workspace intervenes. The computer simulation of the task proposes predictions for imaging the cerebral cortex, in time and space, at the various stages of the Stroop task: observation, error, correction and repetition of the solution once the error has been corrected. It can therefore predict a number of cortical states, in particular the key role of the prefrontal cortex, when the conscious neuronal workspace is activated.

*What was your contribution here?*

My contribution was essentially to set up this theoretical framework and to foresee the possibility of subjecting it to experimental demonstration. As this could not be carried out in humans at Pasteur, due to a lack of adequate technical resources, Stanislas took over while we kept working on simpler animal systems at Pasteur. This was part of the division of responsibilities established between us while keeping a strong intellectual collaboration.

Significant experimental data have been obtained over the last twenty years, by various groups including Dehaene, Naccache *et al.* and many others. Much of it is in agreement with the original conscious neural workspace model of 1998<sup>8</sup>, although controversy still surrounds it. The distinction with the model of Tononi and his colleagues, as we have said, is not without its problems. The latter believe that it is the confluence of posterior sensory areas and association cortices that allows access to consciousness, whereas we privilege the anterior cortex and, within it, the prefrontal cortex. In my opinion, the difference lies in the fact that the groups concerned are not pursuing the same objective. We are interested in access to consciousness, in "conscious content", which involves the frontal cortex in a privileged way<sup>9</sup>, while our partners are more concerned with "states of consciousness" - wakefulness, sleep, general anesthesia<sup>10</sup> - which, from the outset of this study, we have clearly distinguished from conscious content.

To advance this analysis, following intense discussion, Stanislas developed a task, experimentally simpler than Stroop's, which concerns a perceptual phenomenon known as "attentional blink". It involves studying the perception of images presented successively at a rapid pace, in the form of

an incessant flux. The advantage of this simplified test is that it separates the parameters and makes it easier to understand the problem. The subject is asked to respond to two temporally successive visual targets (images, letters, etc.), T1 and T2. When their presentation is separated in time by at least one second, the subject consciously perceives two independent stimuli. On the other hand, if T2 is separated from T1 by only 100 to 500 ms, the subject loses the ability to respond to T2. All he sees is T1, and the duration of this conscious episode prevents him from becoming aware of T2. The probability of perceiving T2 decreases, as if the subject's attention had "flickered". The visual information has been processed, but not consciously. Hence the idea of comparing conscious and non-conscious processing (*cf.* image 9).

With Claire Sergent, we examined the experimental conditions and developed a computational model at cellular level<sup>11</sup>. This enabled us to go quite far in describing T1 and T2 and their relationships, and to highlight the propagation of visual information from bottom to top, progressively, from the primary visual to the temporal and frontal cortex. In this way, we can describe, step by step, the access to consciousness and, in agreement with Edelman, show that re-entries (from the upper compartments to the lower compartments) are necessary for access to conscious space to occur - the "becoming conscious" - in an unambiguous way, giving rise, under these conditions, to a new type of representation within the conscious workspace. We suddenly move from non-conscious representations to conscious ones. In short, the model allows us to describe entry into conscious space at the cellular - and even molecular - level, and to demonstrate that access to this space is an "all-or-nothing" process. To qualify this phenomenon, Stanislas and I proposed the term "*ignition*", which would be the electrophysiological signature of the entry

into conscious space of a visual percept<sup>12</sup>. This work had the merit of modeling the distinction between conscious and non-conscious processing, as well as the ignition phenomenon. We return to the Cartesian distinction between *res extensa* and *res cogitans* ("extended thing" and "thinking thing"), between the non-conscious and the conscious. When we access the higher level of brain function, we enter the conscious neuronal works-pace. Ignition occurs...

*A kind of blaze...*

A "spontaneous collective firing" of neurons, an ignition! Various experiments were subsequently carried out by different groups, using electrophysiology to clearly distinguish these successive stages, right up to the prefrontal flashover (*cf.* image 9)<sup>13</sup>. The first model, which involved distinct cortical territories, was rather global; here, we're at the cellular and even molecular level. There's a change in the level of analysis that allows us to go further. There's another point I'd like to come back to in connection with the nicotinic receptor: in human beings, in the state of conscious wakefulness at rest, there's a spontaneous activity, a kind of electrical wandering that's accompanied, from time to time, by peaks of ignition. During wakefulness, the subject does not interact with the outside world, but there are in his brain of ultra-slow *fluctuations*, which have long been observed. These activities are possibly assignable to some kind of inner decision-making. Even in a state of rest, we're always thinking about something...

*Paul Valéry said that to speak of a fixe idea is contradictory in terms...*

Ideas always follow one another... When conscious space is occupied by spontaneous activity, on the occasion of "ignition", external sensory activity is blocked. This is what I described with Stanislas in the 2005 model.

*It's reminiscent of the experiment Stanislas Dehaene likes to call the "invisible gorilla" test. Participants are shown a video of two basketball teams exchanging passes with a ball. They are asked to count the passes. During the game, a gorilla crosses the stage from right to left, beating its chest. Stanislas Dehaene calls it "attentional blindness".*

When attention is drawn by intense internal activity, sensory signals that enter the system fail to penetrate to the Global Neuronal Workspace. This is one of the important predictions of this model.

### **Self-awareness and loss of control**

*But what about self-awareness ?*

There are, as we said, various processors: sensory, motor, reward, memory. There is also the self-reference that makes part of the processors of the conscious neural workspace. During a trip to Sweden in 2010, at the invitation of pediatrician Hugo Lagercrantz, I had the opportunity to meet a Danish neurologist Hans Lou, who told me about his work on meditation, specifically yoga *nidra*. A little cautious at first, I eventually agreed, after discussing his methods and practice with him at length, that his work was serious and interesting. Measurements (by imaging or EEG/MEG) were carried out in conditions where a human subject, listening to an oral

recording, experiences a state of total relaxation with minimal attention and anticipation of action. The experiments carried out, using different methodologies, provided convergent evidence for the activation of a particular circuit during intense introspective reference to the self, which Hans Lou would call the "medial paralimbic"<sup>14</sup> area. It comprises the prefrontal/anterior cingulate, parietal/posterior medial cingulate and subcortical regions in common with the Global Neuronal Workspace. Interestingly, there's the frontal and the cingulate, the cingulate being the part of the brain specialized in emotions. It has been experimentally established that there is a causal relationship between this activation of the medial paralimbic system and introspective reference to the self.

Following this work, I wondered whether this experience could be related to the loss of self-control that accompanies drug dependence, and more particularly nicotine addiction. We had planned to carry out an experiment with smokers and non-smokers, with nicotine and without nicotine. However, the Danish ethics committee rejected this form of experimentation, so we settled on another addiction, that of gambling. We were able to demonstrate characteristic neurological signs: activation of the medial paralimbic system. Magnetoencephalography showed that "pathological" gamblers were more impulsive than "healthy" controls in a stop-signal task, and that they also showed reduced synchronization in the gamma band at rest. There is clearly an alteration in paralimbic network activity<sup>15</sup>. Here, we have perhaps specified one of the points that had hitherto remained in the shadows: the relationships existing between a processor and self-memory, self-reference and Global Neuronal Workspace. And this work has a concrete application.

## **The progressive development of consciousness**

*What's essential, if I'm following you correctly, is not so much consciousness itself as "becoming conscious"...*

Idealist philosophies of consciousness tend to conceive of it as an immaterial, "mysterious" reality, irreducible and inaccessible to scientific knowledge. Yet it's impossible to deny that altered states of consciousness exist, such as sleep, dreaming, waking, and those induced by anaesthetics or drugs. To this we must add that consciousness did not appear all at once, but gradually, both during the biological evolution of the species (phylogenesis) and during the embryonic and postnatal development of the individual (ontogenesis). Ernst Haeckel, an illustrious supporter of Darwin's ideas, had suggested that ontogeny could recapitulate phylogeny. With Hugo Lagercrantz, in one of his visits to Pasteur, we began a new dialogue on the evolution of consciousness during human development<sup>16</sup>. We adopted the distinction, proposed by various ethological and educational researchers, between four levels of consciousness.

1.- Minimal consciousness in simple organisms, such as mice or rats, is characterized by the ability to create representations, store them in long-term memory and use them "declaratively" in the absence of imitation. It is therefore a kind of minimal conscious perception of a sensory stimulus. It is observed in premature babies from 25 to 30 weeks of age.

2.- Recursive consciousness, observed in certain monkeys, which manifests itself in the use of objects and the search for hidden objects, imitation and divided attention. It is characterized by sequences of representations and a recursive aspect that will be found in language. The human newborn would be at this stage.

3. - Explicit self-awareness develops in infants at the end of their second year. Explicit self-awareness is also characterized by recognition in the mirror and the use of arbitrary rules of conduct when relating to others. Chimpanzees reach this level of awareness.

4. - And finally, reflective consciousness and theory of mind, with the capacity for conscious *reporting of* a subjective experience lived by oneself or another, which develops exclusively in children between the ages of 3 and 5. Empathic dispositions (recognition of others' mental states: intention, emotion, etc.), which are to be distinguished from sympathy the ability to share others' feeling, the willingness to oppose violence done to or by others, and to eliminate the resulting suffering. We'll come back to this notion later in the chapter on ethics.

*Kant, in a famous text, points out that a child who can already speak does not achieve self-consciousness as a Subject until rather late. He begins by talking about himself in the third person (Hans wants to eat, etc.), before using the first person, "I", and accessing thought: "before, he only felt himself; now he thinks himself».*

Consciousness is not an irreducible, single entity, given all at once: it develops gradually. Together with Hugo Lagercrantz, we reflected on the first three stages of development, reserving the last level for further research. In particular, we asked ourselves whether premature babies aged 25 to 30 weeks are "conscious". *Ex utero*, the premature baby can open his eyes and make minimal eye contact with his mother, but it is very difficult to conclude that he is already consciously processing external information. *In utero*, the



fetus is in an almost constant state of somnolence, under the effect of endogenous substances produced by the placenta that "inhibit" wakefulness. At birth, as shown by Lagercrantz, the fetus undergoes a stress that provides an awakening, linked to the abrupt transition between the warm, aqueous environment of the mother's womb and the cold, dry, external world, with which it undergoes intense sensory interaction.

*In utero, the fetus can react to external stimuli, such as its mother's voice or a particular piece of music. So it's not completely asleep...*

It can recognize its mother's voice - as Jacques Mehler demonstrated as early as 1978<sup>17</sup> – and record the prosody of its mother tongue. It is sensitive to a musical melody that it will remember once it is born. Yet the late fetus is in a rather peculiar state, neither awake nor totally asleep.

It's important to note that a baby's brain is not a miniature adult brain. As it develops into adulthood, its mass will increase fivefold, with a considerable increase not only in the number of synaptic connections, but also in their organization. As I said, man spends half his life building his brain.

### 3- NICOTINIC RECEPTORS AND CONSCIOUSNESS

Also with Hugo Lagercrantz, we looked at certain newborn pathologies, such as "cot death", the causes of which are still not precisely known... We hypothesized that tobacco smoke might have an effect on the baby's environment. Using the mouse as an experimental model, we sought to take advantage of mutants lacking the  $\beta 2$  subunit of the nicotinic receptor. Mouse respiration can be measured using a device called a

plethysmograph, which records every breath the animal takes. If a sleeping mouse is subjected to a shock of oxygen deprivation - like a baby prevented from breathing by a pillow or blanket - it wakes up and reacts very strongly. A sort of self-defense reaction. Mutant mice lacking the  $\beta 2$  subunit can be shown to have a diminished arousal response<sup>18</sup>.

The nicotinic receptor is therefore involved in the arousal response necessary for the animal's survival. However, the idea that there may be a link between cot death and nicotine exposure remains an unconfirmed hypothesis. Another implication of this work on mice is that ultra-slow fluctuations are found in the mouse, assignable, as in humans, to internal ignitions of the conscious space. However, this phenomenon cannot be observed in the mutant mouse. Pharmacological application of a receptor antagonist or mild general anesthesia to a wild-type mouse disrupts the generation of ultra-slow fluctuations. Hence the idea that the nicotinic receptor is involved not only in arousal, but also in access to consciousness<sup>9</sup> in ignition...

With Uwe Maskos, my former collaborator, now head of unit at the Institut Pasteur, and his collaborator Fani Koukouli, who had worked on ultra-slow fluctuations, we became interested in schizophrenia and the alterations in consciousness that accompany it. This is not, of course, to claim to "explain" the disease, which mobilizes many genes, but to highlight a few observations. David Ingvar had already observed hypo-frontality in schizophrenics. Precise tests - recognition tasks, conflict or error monitoring - reveal functional deficits in the Global Neuronal Workspace, in short cognitive deficits recognized by brain imaging and physiological work. A genome-wide study identified point polymorphisms in the human CHRNA5 gene, which codes for the  $\alpha 5$  nAChR subunit - a little-studied subunit of the nicotinic

receptor. Two-photon calcium imaging makes it possible to monitor changes in the activity of the prefrontal cortex. If we introduce the human gene, or make a deletion of the gene in mice, we see the appearance of an hypo-frontality. We then have a mouse model which also shows social deficits accompanied by a reduction in the level of activity of the prefrontal cortex.

The question then arose: where are these nicotinic receptors located in the cerebral cortex? Are they located on the pyramidal cells of the Global Neuronal Workspace, or are they absent? In layer III of the cortex, nicotinic receptors are absent from pyramidal cells. On the other hand, they are present on inhibitory cells whose neurotransmitter is GABA. There are even hierarchies of inhibitory cells, so that when mutations occur at their level, there is increased inhibition of pyramidal cells contributing to the Global Neuronal Workspace<sup>20</sup>. The model shows that genetic alterations in the  $\alpha 5$  subunit create a disruption in the inhibitory system - itself composed of several types of inhibitory cells - leading to a decrease in pyramidal cell activity. If the mice are treated with nicotine, they recover. This establishes that not only there is a disturbance of the Global Neuronal Workspace, a hypo-frontality, but also that it also mediated by inhibitory systems. The nicotinic receptors not only act directly on the state of the Global Neuronal Workspace via the reticular formation but also indirectly via intrinsic cortical inhibitory systems. Alain Berthoz, my colleague at the Collège de France, and Oliver Houdé, a pioneer in the development of cognition in children, have strongly emphasized the importance of inhibition in cognitive functions.

#### 4- ALTERED STATES OF CONSCIOUSNESS

*But there are also altered states of consciousness...*

I'll mention two: general anaesthesia and coma.

The wounded of Napoleon's wars were amputated or operated on without the slightest anesthetic. Sometimes a little alcohol or morphine...

*Paracelsus had discovered laudanum, a mixture of alcohol and opium, for this purpose...*

The discovery of general anesthesia brought considerable relief to surgical procedures. The first general anesthetic to be used was nitrous oxide, N<sub>2</sub>O, or nitrous protoxide, synthesized in the 18th century by the English clergyman Joseph Priesley. He was accused of witchcraft. The product was used recreationally in travelling circuses... and to produce whipped cream! Later, in the first half of the 19th century, Michel Faraday discovered the narcotic power of ether vapors and also used them for recreational purposes. But it was Henry Hickmann, at the same time, who described the state of "suspended animation" provoked by the product, enabling pain-free surgery on animals. Dentists were the first to use general anesthetics systematically. The pioneer was Horace Wells (1815-1848), who experimented with N<sub>2</sub>O on himself during a tooth extraction. Then came chloroform, which the clergy denounced as "Satan's trap" that "apparently blesses women", but "robs" God of the cries for help. This did not prevent Queen Victoria from using anesthesia to give birth to her seventh child.

*Analgesia should not be confused with anesthesia....*

General anesthesia causes unconsciousness, but is not analgesic. A subject can lose consciousness and continue to suffer, even if he or she doesn't realize it. To treat pain, a complementary analgesic must be added. Other gases will be used for this purpose, such as halothane or methoxyflurane. There is also a whole range of injectable agents, such as diazepam, for example, which is an anxiolytic and sedative, a positive allosteric modulator of the GABAA receptor (*see* chapter 4), propofol, ketamine and, of course, opiates.

Functional imaging reveals that general anesthetics inhibit activation of the Global Neuronal Workspace. When the concentration of general anesthetic is increased, there is a decrease in the regional activity of the thalamus, parieto-occipital cortex, cuneus, precuneus, orbitofrontal cortex and posterior cingulate cortex, which belong to the connective network of the Global Neuronal Workspace<sup>21</sup>. It seems plausible that, in humans, general anesthetics are - in part - potent allosteric modulators of the inhibitory GABAA receptors<sup>22</sup>. If the same GABAA receptors were stimulated very strongly by an allosteric modulator, such as a general anesthetic, this would create an increased inhibition leading to a drop in cortical activation and the subject falling asleep.

It's important to remember that general anesthesia is a modified state of consciousness.

*A coma is also a state of consciousness...*

Coma is an altered state of consciousness, a state of minimal awareness<sup>23</sup>, as Steven Laureys puts it, with intermittent signs of awareness of self or the environment, whatever the cause, accidental or pathological. It's obviously a major challenge to try and find ways of freeing a patient from

coma, of "waking them up", as it were. The coma state has been extensively studied. I'd like to focus on two examples of success in restoring consciousness to a comatose patient.

The first, by Nicholas D. Schiff,<sup>24</sup> involves deep brain stimulation of the central thalamus. This intracerebral electrical stimulation awakens the patient. It's a somewhat cumbersome and invasive treatment, but "a certain number of cases", as is always the case in medicine, it enables the patient to regain consciousness, at least temporarily. It is not a treatment, however, because when stimulation is suspended, the patient "slips back" into coma. Stimulation takes the patient from a state of very reduced activity in the cerebral cortex and thalamus to a functional state with reactivation of the frontal lobe. This work has recently been taken up by a team in Stanislas Dehaene's laboratory. They apply Schiff's method to primates under general anaesthetic, stimulating the thalamus in its central region. As the territories of the conscious neuronal workspace are reactivated, the monkey wakes up from its general anaesthetic<sup>25</sup> the time the stimulation takes effect... This method proves the reproducibility of Schiff's experiments.

The second success story is based on a rather astonishing observation, again thanks to Schiff: some patients in the coma were in a state of agitation and sleep disturbance. To calm them, he administered zolpidem, a powerful sleeping pill known in France as Stilnox. This product is related to the benzodiazepines. When patients are treated with zolpidem, some wake up<sup>26</sup>. He described a comatose lady treated for insomnia who began to communicate, eat and move for twenty minutes. Another used a comb and a spoon. This means that the product does have an effect on the state of activity of the cerebral cortex of comatose subjects. We find the same allosteric action on inhibitory neurons, but acting in the

opposite direction. When you inhibit an inhibitor, the result is an activation. There is a balancing effect in a network of inhibitory neurons, as in the case of schizophrenia, with, on this occasion, a positive waking effect, like that provoked by nicotine in schizophrenics. Whether this occurs via the nicotinic receptor or, more likely, *via* the inhibitory GABAergic receptor is unclear.

*There is therefore a whole chemistry of consciousness.*

This chemistry is undergoing major developments, with considerable practical applications.

### **Hallucinations and the origins of religion**

As part of the new discipline of the pharmacology of consciousness, which links the molecular level to the Global Neuronal Workspace, I was led to take an interest in hallucination phenomena. This transient disturbance of consciousness is one of the characteristic clinical signs of schizophrenia. The conscious space of the awake patient is intruded by sounds, images, language, etc., in the absence of any sensory experience with the outside world. This can also affect the "healthy" subject - think of Pascal and his visual hallucinations. The patient perceives information beyond his or her control. It's a "loss of control" - a very interesting notion. British researchers Chris Frith and Richard Frackowiack have found brain territories activated during auditory verbal hallucinations in schizophrenic patients<sup>27</sup>. These are essentially the subcortical nuclei, as well as limbic and paralimbic structures. The cortex is indeed activated, but under unexpected and aberrant conditions. We observe a kind of invasion of conscious space by unpredictable spontaneous

representations.

*Does this sign also accompany the use of so-called hallucinogenic drugs?*

A considerable number of drugs cause hallucinations. Since ancient times, they have accompanied religious rituals. The use of cannabis, for example, has been documented in shamanic rituals dating back to the Vedic period in the Indian subcontinent in the 15th century BC. I became interested in this subject following an encounter a few years ago with a thesis student at the Institut Jean Nicod, attached to the departments of philosophy, social sciences and cognitive studies at ENS-Ulm. His name was Martin Fortier. His thesis - on "the comparative anthropology of hallucinogenic rituals" and what he called "the neuropharmacological shaping of culture" - immediately fascinated me. He asked me to assist him prepare his thesis and possibly sit on the jury. Unfortunately, in the meantime, he was struck down by Ewing's sarcoma.

Knowing that I was interested in nicotine, he had pointed out to me the eminent place occupied by tobacco in the shamanic rites of Amazonian Amerindians. The species of tobacco used is *Nicotiana rustica*, not *Nicotiana tabacum* - which is consumed by smokers in the West - and it is ten times more concentrated in nicotine. Often consumed in juice form, *Nicotiana rustica* has psychotropic properties, even causing hallucinations in those who drink or smoke it. Amazonian shamanism uses tobacco as a means of shaping dreams, producing "more vivid and intense" ones. This finding is hardly surprising, given the role played by elevated acetylcholine levels in REM sleep.



Martin Fortier, in order to better define his project, had limited his work not to nicotinic, but to two other main categories of hallucinogens: serotonergics (HS), which include all psilocybin mushrooms and others, all substances used in the Amazon basin, whose effects are similar to those of LSD. Also included is the substance extracted from peyote, a small cactus found in Mexico and the southern United States. The other category of hallucinogens includes anticholinergics (HA), which are not antagonists of the nicotinic receptors but block cholinergic *muscarinic* receptors. It includes above all solanaceous plants. These include various species of *Datura*, *Brugmansia* and *Duboisia*. Martin had highlighted the striking phenomenal differences between the two types of pharmacological agents, HS and HA. Serotonergics generate a hallucinatory world parallel to the real one; the "psychonaut", continues to distinguish between the two worlds, does not confuse the puma he hunts, with its bow and arrows, and the symbolic totemic animal that appears to him in his hallucinations. HAs, on the other hand, become entangled in the real world; they obliterate all lucidity. Unlike HS, muscarinic hallucinations (HA) place the psychonaut in a state of delirium.

In short, there are lucid and non-lucid hallucination states. In the latter case - and this is only a hypothesis - there may be a decoupling of the prefrontal cortex from the conscious neuronal workspace.

The idea that a hallucinatory world and a real world can coexist in conscious space caught my attention. From this we can deduce that there are brain processes that enable us to make the distinction. In only one case, self-awareness and awareness of the outside world are maintained while thalamo-cortical intrusions disrupt the conscious space under the

influence of drugs. Hallucinations are conscious, but outside the subject's will.

*It's reminiscent of Maupassant's short story Le Horla, with the hero struggling with hallucinations... But Martin Fortier brings in the religious dimension.*

The religious question was often at the center of our debates. He didn't take the strict determinism view that religion needs hallucinogens to exist; he even maintained that it can exist without any altered state of consciousness. For him, hallucinogens don't generate or *manufacture* religion (strong determinism), as some propose, but *shape* it (weak determinism). According to whether it uses a particular drug, HS or HA on a massive scale, a culture will select specific religious traits. Religious ritualization is linked to the chemistry of hallucinogenic drugs, which act as *cultural attractors* (Dan Sperber). As for the question of the origins of religions, the answers are highly varied and fall outside my field of research. They may come from anthropology (and sociology), according to Durkheim or Lévy-Bruhl, or from psychology. On the one hand, the neuro-psychologist will look for signatures of religious belief in the functioning of the human brain; on the other, the anthropologist (and sociologist) will make it a product of society, or vice versa. These two explanations are not incompatible. In both cases the brain is involved.

## VIII.

### The Rule of the Good

#### 1- NATURALISTIC PHILOSOPHIES OF ETHICS

*Faithful to the "physicalist oath", your comments on ethical issues must be in keeping with a certain tradition that can be qualified as "naturalist"...*

Naturalistic philosophies of ethics are as old as philosophy itself. They developed in parallel with the revealed religions. Among these philosophies, we can distinguish between those that precede the idea of evolution and those that incorporate it. I'm obviously more interested in evolutionary naturalist philosophies. But a number of naturalist philosophers who predate evolutionary theories may have had some very pertinent ideas, including Descartes, Spinoza and Kant.

The first Greek thinkers of the 7th century B.C., from the Archaic period to the end of the Bronze Age, drew up the first classifications of the world and were already distinguishing the "natural" from the "supernatural". For Thales of Miletus, "everything is full of gods", but he "leaves the gods at the door". These "sage" sought to discover the material cause of things and what the world was made of. In this way, detached from the sacred texts, they developed the first naturalistic

explanation of the world...

*Jean-Pierre Vernant, your former colleague at the Collège de France, has written some essential pages on this subject... With the Mimesians, Reason suddenly became incarnate. Descending from heaven to earth, it would have burst onto the scene of history for the first time...*

Indeed, Vernant's analyses are invaluable, showing how argumentative and contradictory debate gradually took hold in Greece, first in Athens, to become the prerequisite for any philosophical and scientific advance. Then came the Atomists, Leucippus of Miletus and his pupil Democritus, who maintained that only atoms and the void are real, and that differences between physical objects are merely a matter of the form, arrangement and position of *atoms*. For them, the soul is corporeal in nature, "igneous", composed of the same fire as celestial bodies...

*These ideas were later taken up by Epicurus, with the addition of the primary element of chance, what his Latin disciple Lucretius called clinamen...*

An interesting idea, which as we shall see leads us to Darwin. But let's go back to Democritus, who in addition put forward the first cephalocentric thesis: "The brain, guardian of thought or intelligence, conceals the principal links of the soul [...], it watches like a sentinel over the upper extremity, the citadel of the body entrusted to its protective guard." In particular, it produces moral judgment.

*Democritus would be a kind of precursor to studies on the brain...*

Plato, for his part, believes in an intentional element and purpose in nature. Spinoza, Diderot, Darwin and Freud all criticized this aspect of Plato's thinking. The existence of a "World of Ideas", separate from the sensible world, makes learning unnecessary. Ideas are innate. There is a conjunction of the highest Ideas: the Good, the True and the Beautiful. Hence the title, in the form of a wink, that we give to our book of entretiens: *The Beauty and the Splendor of Truth* (with and rather than is). For Plato, man can only attain morality by "looking" at the Idea of the Good, "that which has no other end than itself". An eternal, sovereign essence, he is to the intelligible world what the sun is to the visible. This essentialist schema is found in all three religions of the Book, and persists more or less explicitly in contemporary ethical debates.

Among his major contributions, Aristotle considers the social dimension of ethics. Man, according to his famous definition, is by nature a "political animal" (*zôon politikon*). This aspect is overlooked by the atomists. Man lives naturally with his fellow creatures. He is the only animal to live in a city (*polis*). He lives in a community (family, village, city), because it's in his nature to do so. They do not seek survival for its own sake. Man is also the only animal endowed with *logos* (reason/speech), which makes him more political than other animals. Man, by nature, tends towards the "good life", which is inseparable from the "political" life. Aristotle makes friendship (*philia*) a virtue, in that it binds individuals together in all its forms (within the family, the village or the city). Love (*eros*), on the other hand, creates dependency between

individuals.

*But Aristotle is fixist!*

Indeed, the various animal species are classified according to a *scala naturae*, with man at the top. The fixist point of view dominated philosophy and the natural sciences until Lamarck, at the beginning of the 19th century, defended a transformist conception of the living universe (1809): according to him, there is a slow, gradual passage from one species to another, accompanied by increasing complexity of the nervous system and cognitive functions.

A little later, in his *Origin of Species* (1859), Darwin further developed Lamarck's work by proposing a plausible mechanism, natural selection, for the phylogenetic origin of living species. This was a considerable intellectual revolution, the consequences of which, one hundred and fifty years on, are not completely assimilated by our societies: the replacement of the static world of natural theology by a world in evolution, without cosmic teleology or finality, and with the abolition of any justification for anthropocentrism. The essentialist vision referring to a divine "design" is replaced by populationist thinking based on the process of natural selection, consisting of the interaction with the environment of undirected variation and opportunistic reproductive success. In Chapter IV of *The Descent of Man* (1871), Darwin addresses the question of the "moral sense", which, in his view, marks the most important difference between man and animal, even though the moral sense has its origins in the animal, under the following conditions:

– "if he possesses social instincts that lead him to find pleasure in the society of his fellow human beings, to feel a

certain sympathy for them that leads him to help them in a general way:

- "If he retains in his brain the image of all his past actions and the motives that led him to act as he did" and "if he feels a sense of *regret* when he realizes that the social instinct has given way to some other instinct";

- if it uses language to "express desires, the common opinion, on the mode according to which each member must contribute to the public good";

- if it involves "sympathy and social instinct, which are considerably strengthened by habit".

In an almost "Lamarckist" way, if you like, Darwin believes that the broadening of sympathy is integrated into biological evolution through acquired experience. Admittedly, he does not sufficiently distinguish between "cultural evolution" and "biological evolution".

He does, however, use the terms "sympathy" and "social instinct". On the subject of the evolutionary origin of moral rules and the extension of sympathy, he proposes the following idea: "As man enters civilization and small tribes come together in larger communities [...], simple reason indicates to each individual that he must extend his social instincts and sympathy to all the members of the same nation, even though they are not personally known to him." Man has "developed his sympathies to the point where he has extended them to men of all races, to cripples, idiots, and other useless members of society and, finally, to the animals themselves; the level of morality has developed more and more." There is an extension of sympathy to the "neighbor", to use Paul Ricœur's words. In short, there is a kind of progress in the moral evolution of mankind.

Thus, humanity was naturally led to the "Golden Rule", which is a form of universal morality: "Treat others with respect as

you would like to be treated" or other formulations of the same ethical requirement.

The Russian prince, geographer and anarchist thinker Piotr Kropotkin (1842-1921) formulated ideas that can complement Darwinian analysis, while at the same time opposing head-on the theses of Spencer's "social Darwinism" (which attempts to apply the Darwinian mechanism of natural selection to the social sphere). According to Kropotkin, there is an objective moral law, immanent to nature or deducible from it. In *L'Entraide, un facteur de l'évolution* (1902) (*Mutual Aid: A Factor of Evolution*), he states that "mutual aid is the dominant fact in nature". He notes that, under very difficult climatic conditions, in this case in Siberia, species survive to the extent that individuals group together and help each other: "The more individuals unite, the more they support each other, and the greater are the chances of *survival* and *progress* in intellectual development for the species". In the course of evolution, the instinctive practices of "Mutual sympathy" is the starting point for "all the higher feelings of justice, equity, equality and abnegation", and leads to the "moral trial". In short, the "feeling of moral obligation", of which man is aware, is to be found in nature. Kropotkin, in the unfinished *Ethics*, extends his reflection to the evolution of mankind: in the course of it, there would have been competition between social groups of man's ancestors, with the most cooperative being selected.

*Mutual aid would therefore be an adaptive advantage...*

It's a great idea. The strengthening of social ties would lead to an evolutionary, and therefore genetic, selection that would not otherwise occur. This theory is still of great interest to specialists in population genetics, even if it remains highly controversial, since it's necessary to move from the group to



the individual, and genetics is all about the individual.

To Darwin and Kropotkin we can add a third figure, Léon Bourgeois (1851-1925). President of the Council and several times a radical minister, he opposed both the Spencerian individualist “laissez faire” (and to capitalist contemporary societies) and Marxist authoritarian “socialist collectivism”.

" He is considered the inspiration and theorist of *solidarism*, which he defines, in his work *Solidarité* (1896), as "the fraternal bond that obliges all human beings to one another, making it our duty to assist those of our fellow human beings who are in misfortune". This obligation is not only compatible with freedom, it is its very condition. Bourgeois's reflexion, based on the biological model, hinges on the concept of "social evil", which is not due "solely to the personal faults of the individual". The model of "social evil" is the *contagious disease* that, with the work of Pasteur, "proved the profound interdependence that exists between all living beings. [...] In formulating the microbial doctrine, [Pasteur] showed how much each of us depends on the intelligence and morality of all the others". "It is a moral duty, he adds, to destroy these deadly germs, both to ensure our own life and to guarantee the life of all others. »

He refers, by way of illustration, to the work of zoologist Edmond Perrier (1844-1921), who, in *Animal colonies*, attempts to articulate science and morality, with the constitution of a "artificial order" that has the force of the sociobiological law of union for life. For Bourgeois, human societies form “solidary groups” "of which the equilibrium, conservation and progress obeys the general law of evolution. His analysis enriches Kropotkin's on an essential point, since, for him, in human societies, we encounter "a new element, a

special force: thought, conscience, will". Society itself is not "just", even "unjust", and so a duty of *solidarity* and mutual responsibility is created: "Society is a contractual organism. It requires the *consent* of the beings that make it up." This will be the *contract of solidarity*. The state intervenes only as an authority that sanctions these agreements and ensures compliance. The "moral good," he says, "is to want and conceive of ourselves as members of humanity", united against risk so that "natural inequalities are not compounded by inequalities of social origin".

As an aside, we might mention the Italian neurobiologist Rita Levi-Montalcini, who a few years ago came up with the idea of supplementing the "Declaration of Human Rights" with a "Declaration of Human *Duties*". This is an old notion, first put forward by Abbé Henri Grégoire, who in 1789 had the idea of drafting a "Declaration of Rights and Duties". But, as he was a priest, the revolutionaries saw this as a religious bias, he was unable to make himself heard, and the idea remained a dead letter. From the outset, the Pastorian tradition has been attentive to the implications of scientific progress for social life. Pasteur insisted that the ultimate aim of his work was the "bien de l'humanité", the "good of mankind". Numerous Pastorians have illustrated this orientation: from Émile Duclaux - Pasteur's disciple and successor at the head of the Institute, an early Dreyfus supporter and vice-president of the "Ligue française pour la défense des droits de l'homme et du citoyen" (French League for the Defense of Human and Citizen Rights) to Jacques Monod, through to Élie Metchnikov and Charles Nicolle. In light of recent developments in biology research, Monod called for "a total revision of the foundations of ethics"<sup>1</sup>. "Science," he said at the end of his inaugural lecture at the Collège de France (1967), "ignores values; the conception of the universe that it imposes on us

today is devoid of all ethics. But research is in itself an asceticism; it necessarily implies a system of values, an "ethics of knowledge" whose validity it cannot, however, objectively demonstrate. »

I don't think it's plausible to base ethics exclusively on scientific knowledge. It's imperative to take into account the social dimension, which Monod doesn't mention.

### **Morality and ethics**

*How do you distinguish between "moral" and "ethical"?*

The word "morality", in its current sense, did not appear until the 17th century, when it became increasingly secularized. In 1637, the term meant (for example, in Descartes' *Discourse on Method*) the "science or doctrine determining rules of conduct". Pascal, twenty years later, spoke of a "set of rules of conduct unconditionally admitted and considered applicable". It is a set of obligations to act and interdicts to respect. It is a rational, systematized discourse specific to a particular culture on what is and isn't permissible. We speak of "Stoic", "Christian", "Kantian" morality and so on. There is thus a "descriptive" relativism of morals, which must be seen in relation to the diversity of cultures on the planet's surface, even though there seem to be moral rules that apply universally (Anne Fagot-Largeault). The word "ethics", a late distinction from the word "moral" is defined in relation to it.

*It should be noted that the two words, one of Latin origin (mores), the other Greek (ethos), have roughly the same meaning: mores, ways of living and acting...*

Ethics is an "open" reflection, as Spinoza calls it in his

eponymous treatise. It's a philosophical way of thinking that takes into account all morals and seeks to uncover universal invariants. For me, clearly, ethics lies beyond morality, as a kind of additional reflection.

Paul Ricoeur, in *Soi-même comme un autre* (1990) (Oneself as Another), gives a definition of ethics, which he wants to be free of any ideological or religious bias, and therefore secular, which suits me perfectly: "The aim of the good life with and for others in just institutions". The "good life" - a concept of Aristotelian origin - is both the happy life and a morally fulfilled life for each individual in the city. "With and for others": Ricoeur introduces the "social" dimension so dear to Aristotle. "With others", the relationship with others is essential. "For others", each of us must care for the other...

*"With others" is the relationship with the "like"; "for others" is the relationship with the "neighbor", with "my" neighbor.*

"For others" is the "Golden Rule": "Don't do to others what you don't want them to do to you" as Auguste Comte altruism, where Christians would speak of compassion or charity. It's not enough to do no harm to others; we must also help and support them. Ricoeur's phrase "in just institutions" adds a political framework - difficult to define, in any case - a social organization that frames practices; institutions deemed "just", and therefore non-discriminatory, can be nation-wide or extended to the whole world, leading us, if we broaden our viewpoint, to consider survival and quality of life in a universal way. The ethics of knowledge, as developed by Jacques Monod, is not enough, as I said, because it omits the social dimension. My approach as a neurobiologist leads me to consider ethics in a more encompassing way, by attempting to

define a common "core" of neural predispositions to moral judgment common to all representatives of the human species *Homo sapiens*, in the same way as cerebral predispositions to language, whereas particular morals are a matter of cultures and their variability in time and space. During our discussion<sup>2</sup>, Ricoeur rightly compared the diversity of religions to that of languages...

The philosopher Hume insisted on the difference between scientific activity, which establishes what *is* or what *is not*, and the propositions of a moral system, which define what *must be* or what *must not be*. In my opinion, the approach of seeking the neural bases of ethics remains faithful to Hume's critical thought, which is "to confine research [...] within the limits of experience". The Scottish philosopher is not, therefore, setting us up against an objective. We can bring the two approaches together, and try to deduce what *should* and *shouldn't be done* as a scientific activity in general.

### **Moral variability and ethical universalism**

When I spoke to you about epigenesis (Chapter 5), I ended with a brief presentation of the social consequences of the theory: the representations produced by an individual's brain can not only be stored in his or her brain, but can also be propagated at the level of the social group and passed on epi-genetically from one generation to the next, without any necessary modification of the genome. This is an essential point. Intrinsic variability in man-made cultures has been in place since the origins of *Homo sapiens*, and perhaps even before. This position is in line with that of twentieth-century anthropologists such as Malinowski and Mauss, who use the word *culture* to designate all the acquired forms of behavior in human societies.

Claude Lévi-Strauss, in *Race and Culture* (chapter 9), makes an interesting point: "cultural mutations" can occur "at certain times and in certain places", bringing innovation. He speaks of possible "coalitions of cultures": their grouping, their evolution, their fusion even, at given times, can lead to forms of ethical innovation.

Various historical and anthropological observations reveal the presence of cultural invariants within the spatio-temporal diversity of moral rules. The "Golden Rule" is common to most philosophical and religious traditions.

*Karl Jaspers, to designate the period (6th-5th century B.C.) when the great values to be enunciated by the great prophets of the Middle Ages, who had a universal impact in cultures that were geographically far apart, spoke of the "Axial Age" of mankind. Buddha in India, Confucius and Lao Tzu in China, Zoroaster in Persia, Parmenides, Democritus and Socrates in Greece, the great Hebrew prophets in Judea and Palestine...*

The "Golden Rule" expresses a norm of reciprocity within the social group, based on an understanding of oneself in relation to others. There is thus a "hard core" of predispositions to moral purpose specific to the human species - and therefore directly or indirectly inscribed in its genome - as well as an epigenetic variability in their application in the form of particular moral rules.

## **5- THE NATIONAL CONSULTATIVE ETHICS COMMITTEE**

*You will be asked to chair the French National Ethics Committee...*

The Comité consultatif national d'éthique (CCNE) (*Consultative National Ethics Committee*) was created by François Mitterrand on February 23, 1983. The INSERM Medical Ethics Committee had already existed since 1974, with the task of studying the acceptability of clinical research projects. Now "national", the Committee's remit has been extended to cover "moral problems raised by research in the fields of biology, medicine and health, whether these problems concern individuals, social groups or society as a whole".

One day in 1992, Hubert Curien, then Minister for Research, asked me to succeed Jean Bernard at the head of the CCNE. My initial reaction was negative. In the past, I'd been in contact with this organization, shortly after the publication of *L'Homme neuronal*, in 1983. France Quéré, a Protestant theologian of strict observance, had almost "summoned" me to explain to her how "neuronal" man could develop morality if he no longer had a soul to accept the divine will? My explanations didn't convince her. I then set out to deepen my reflection, which a few years later led to a lively debate with Alain Connes, my mathematician colleague at the Collège de France. In the last chapter of *Matière à pensée* (1989) (*Conversation on Mind, Matter, and Mathematics*), I endeavored to update the old idea that moral rules, like mathematics, are the products of man's brain in society, while Alain Connes, as a Platonist, maintained the thesis of a mathematical world separate from the physical objects that surround us. Mathematical objects, which would exist independently of the human brain, would constitute a more stable reality than material reality. Of course, according to him, the human brain can provide access to this "mathematical" world, but only a limited number of privileged individuals can access it... namely, mathematicians!

In Chapter V of *Matière à pensée*, I distinguished between

"deductive or authoritarian theories, based on *a priori* axioms of Good and Evil; and inductive theories, whose imperative is to reject any metaphysical or ideological *a priori*". I proposed a "critique of beliefs, ideologies and moral standards in the light of the development of science, in order to derive new, more objectively justified rules of conduct ».

The rather elaborate reflections developed in this book may have inspired President Mitterrand and his advisors. In the end, I accepted the offer that was made to me, but with trepidation, as I knew it would take up a lot of my time and might interfere with my scientific life. I remembered the long hours spent writing *L'Homme neuronal*.

It's difficult for me to take stock of the twenty-nine opinions issued by the Committee during my three successive two years terms as Chairman. I tried to promote a type of debate within the CCNE that was new to me, although it was inspired by the meetings I used to organize every week in my laboratory at the Pasteur Institute, where we freely debated the scientific issues raised by each other's preliminary discoveries.

*A kind of critical community...*

... yet progressive. It was a question of being critical and, at the same time, moving things forward. I tried to set up a scientific, medical, economic and legal debate at the CCNE that would, of course, lead to a joint recommendation. During the discussions, I sometimes found myself in rather difficult situations, insofar as there are always, in this kind of meeting, tenors who take the floor and claim to know the problem better than the others. They could be scientists, philosophers or theologians. My concern was to ensure total freedom and fairness of debate, with the aim of unmasking ideological bias, refuting fallacious argumentation, letting the controversy



develop through "trial and error", as in a scientific debate, while giving priority to original suggestions that provided positive answers. I intervened to stabilize, so to speak, certain positions, whatever their origin, with a view to building a common edifice, brick by brick. It was necessary to seek to invent new forms of humanity and solidarity, what I have called "ethical innovation", and thus "deconstruct" the immoralism of certain traditional standards when they are automatically and inconsistently applied to scientific problems whose novelty and singularity could not have been anticipated by their initiators. It was desirable for the members of the Committee, in their interventions, to disregard their ideological or denominational identity, while at the same time drawing on their personal experience. I tried to ensure that everyone's *humanitas* was expressed with sincerity. At the same time, we had to ensure that the debate was not exclusively rational. This is the risk of argumentation that is too detached from the reality of the world. Paul Ricoeur rightly insisted on what he called the "applicability" of moral recommendations: they must be adapted if they are to be assimilated. It was in this spirit that I introduced the notion of "reasonable": it's not enough for a recommendation to be rational, it must also be "reasonable". Kant had already expressed a similar concern.

It was also important to ensure that the Committee did not simply state contradictory positions without taking sides. I've always opposed this. The CCNE's mission is to deliver an opinion, which presupposes an agreement between its members that is both innovative and applicable. The twenty-nine opinions issued have been almost unanimous on such controversial subjects as drug addiction, autism and embryonic stem cells. I tried to ensure that the Committee's benevolent, but always critical, community could agree on a project capable of reconciling openness to research progress, respect for the individual, solidarity, justice and the common good.

This conciliation had to be concrete. For me, it was both a highly enriching and, in many ways, exemplary experience. The lesson is that we can agree on ethical questions between people of different cultures, backgrounds and convictions.

*Could you give some examples of the opinions issued?*

Let's look at the three examples I've just mentioned. We spent almost a year on the issue of drug addiction. We agreed that this is first and foremost a medical problem: drug addiction is an illness. It is not an exaggerated hedonism to be condemned, but a pathology from which the addict cannot rid himself. Police or judicial repression is inappropriate. It's absurd to imprison a sick person! We need to find ways of helping drug addicts to overcome their addiction, and thus develop care. To this end, there needs to be at least a minimal legal framework to define and apply this care. A 1970 law in France classified substances into two categories, "licit" and "illicit". The licit substances were tobacco and alcohol, all the others being illicit! We immediately realized that such a classification was meaningless. In fact, legal "drugs" could be among the most toxic. A proposal was made to scrap the 1970 law, replacing it with a new one that would assess the "dangerousness" of toxic substances, their mode of consumption, uses and abuses. Traditional societies that use drugs - such as shamanic societies, for example - still strictly regulate their use, which is limited to specific occasions and specific drugs. We have tried to draw up a new classification based on the pathological effects of each of these drugs, and consequently on the need to find appropriate therapies. If a certain amount of repressive regulation is acceptable, for the sake of society, it must be based on the objective dangerousness of the drug in question. We are not talking here about the repression of drug traffickers.

All common sense. Yet this “opinion” was never implemented! It never even passed through the National Assembly, the French parliament...

Another interesting opinion concerned autistic children. Here, our Committee met with a little more success. At an annual public meeting, as the Committee presented its new recommendations, a group of people at the back of the room protested noisily, asking that their children be saved. They were families of autistic children who were complaining about the abuse their children were being subjected to in the hospital environment of the time. Psychoanalysis reigned at the time. The organic dimension of this mental pathology was largely ignored.

*We can only recall the harmful impact of Bruno Bettelheim's theses, which placed the responsibility for triggering the illness on the mother. Many of them will feel guilty, without any efficient help being given to their children...*

Even though we know that there are multiple hereditary predispositions. It's a pathology with very complex origins. I tried to find one or two French psychiatrists who could speak to our assembly. At the time, there were none, or at least none who accepted our invitation. I ended up calling on a Frenchman who had emigrated to England, who accepted the project to develop biological psychiatry. The autism symposium took place, and we issued an opinion to the effect that this pathology had to be taken into account, and that ways had to be found to ensure that the behaviors associated with this mental illness were expressed in such a way that the child could live in harmony with his or her environment, and that parents would find a response to their request for care. Our recommendation also called for the development of cognitive exercises that could help avoid, or epigenetically attenuate, the expression of the autistic phenotype.

This opinion has at least had the merit of freeing a field of research in France from the psychoanalytical stranglehold.

We also issued an opinion on stem cells. The CCNE had been approached by a group of researchers working on animals who had developed embryonic stem cells, which they correctly imagined could be used therapeutically. This point has since been widely confirmed. The Committee took up the issue on its own initiative, even before human stem cells had been obtained. Various ethical questions arose: is it acceptable, for example, to modify a human being's genome with or without his or her consent? We made a whole series of recommendations. This was at the end of my last term. Although I had done everything in my power to transfer our opinion into law, I had to face the facts: the ethical debate had become a political affair. The Prime Minister at the time, Lionel Jospin, who had the matter referred to him by our Committee, took no action on our recommendation.

We were in an election period. It took seven years for it to become law! That's a very long time for such an important subject, which is constantly and rapidly evolving. The English, on the other hand, were quick to adopt legal provisions on a case-by-case basis that are equivalent to our bioethics laws. When Jacques Chirac asked me to accept a fourth mandate, I refused, knowing that I would be spending most of my time not reflecting to ethical questions, but confronting a political debate. But I'm not cut out for that...

*Did you get any scientific profit out of it?*

"Scientific profit" is a big word. It was an opportunity to discover work in progress, such as that on stem cells, for example, or on recent genetic research into autism. Above all, it was an opportunity for a personal reflection that my scientific work didn't offer me, namely an opening onto society, onto the

social dimension of the issues dealt with.

## 6- NEURAL BASES OF ETHICAL AIM

In the final chapter of *Matière à pensée*, concluding our "dialogue" with mathematician Alain Connes, I addressed ethical issues. I wondered about the possible neural origin of moral rules, which would be "of the same nature", but different from mathematical representations. Ten years later, I took up and developed these questions in my exchanges with Paul Ricœur - one of the rare French philosophers of the time to place ethics at the heart of his thinking. In our joint book *La Nature et la Règle* (1998) (What make us think?) we had a lively debate about the ethical goal and its neural foundations. Unexpectedly, we agreed on this theme, even though we had totally different views on how to understand the brain. In any case, it was an opportunity for me to clarify my idea of the neural basis of ethics.

### Mental objects and ethics

In a 1776 supplement to Diderot and d'Alembert's *Encyclopédie*, Johann Sulzer declared that the moral, the esthetical and the intellectual are distinct modes of human understanding. For the neurobiologist, they are communities of mental objects, physical states created by the *correlated* and *transitory* (electrical and chemical) activation of a large population or "assembly" of neurons distributed across several defined cortical areas. There is a great diversity of mental objects. The neurons mobilized by the moral, the aesthetic and the intellectual are certainly partly common, but mobilize different brain territories. What's more, mental objects access

conscious space. This is an essential point. These mental objects - and moral representations are obviously among them - can be subjected to judgment.

If we take into account the number of neurons (billions) and synaptic connections (a million billion), we arrive at astronomical combinatorial possibilities. The human brain is then faced with such a quantity of possible combinations that it could not manage them all.

What's needed is an intermediate situation that brings together and constrains the number and content of representations accessible to the conscious space. I have argued, particularly in *L'Homme de vérité* (2002), and in an article co-authored with the philosopher Kathinka Evers<sup>3</sup>, that the human brain possesses the general capacity to elaborate "rules" - the "filters of the norm" referred to by Ricoeur - most often embedded from bottom to top, which constrain and limit, from top to bottom, the number and nature of accessible brain representations. They act as a kind of "acquired epigenetic neuronal framework ».

Étienne Koechlin and his colleagues<sup>4</sup> at the École Normale Supérieure have shown that, in the conscious subject, the frontal cortex is involved in the discovery of abstract action rules of this type, in the search for relationships between context and action. This work does not directly concern ethical and aesthetic rules. In my opinion, analogue epigenetic rules generally define the "rules" of human conduct.

The idea of "rule", conceived as an active epigenetic organization contributing to the selection of relevant representations, is essential.

## **Survival and the good life**

The *survival of the individual* and the *perpetuation of the species* remain the primary causes from which no human being can escape. For Spinoza, every being *tends* to persevere in its own being: this is *conatus* (*Ethics*, III, prop. 6). "The effort of a being to preserve itself is the first and only foundation of virtue" (*Ethics*, IV, 22). Hans Jonas, for his part, in *The Principle of Responsibility* (1979), based on its philosophy of biology, establishes the moral imperative that man *must* exist, and concludes that it is man's duty to preserve mankind from premature extinction. A long tradition of moral philosophy refers to pleasure, suffering and emotions. These are mental states, but of a particular qualitative type that - subjective and passive, with pleasant or unpleasant tones, constantly renewed - are communicated socially, in particular through facial expression, as Darwin had already noted. It's an "inner" state, but one that can be communicated. Various neurobiological models have been proposed, including that of Estonian scientist Jaak Panksepp (1943-2017), who associates fundamental emotions (desire, anger, fear, distress) with specific brain circuits and neurotransmitters in both humans and animals. He clearly distinguishes a set of neurons involved in desire, or "motivation", the *conatus*, while underlining the importance of other emotions that can disrupt what I personally call "affective harmony". There is a neuronal situation of competing circuits that creates a fundamental instability, putting the *affective harmony* of everyday life to the test. The aim is to prevent one or other of these emotions from invading the conscious space, thereby running the risk of falling into mental pathology. What is a mental pathology, such as paranoia, if not an exacerbation of the sense of self, of pride? The "good life" consists in achieving this "emotional harmony", not only through the

satisfaction of "natural" needs, but also through a kind of emotional balance.

Hence the application of ethical standards...

*We find a similar idea in Rousseau: in contrast to classical morality, which imagines reason dominating or taming the passions, he sees virtue as resulting from a kind of balance between the passions. A kind of emotional harmony...*

### **Ourselves and others**

*And then, as you alluded to in relation to Darwin, there's the relationship to the face, through which others appear to me.*

The relationship with the face is essential to human social life. For the blind, it may be speech... In any case, the "face" enables us to identify others, assess age, sex, ethnicity, emotions, and help us understand spoken language (lip-reading) and intentions. There are well-defined neural bases for these various functions, as evidenced by certain cortical lesions (bilateral temporo-occipital) leading to a deficit in face recognition (prosopagnosia), while other cognitive performances are preserved. It is even possible that an epigenetic trace, of social or cultural origin, may leave a deeper mark on the brain than an alteration, which is often compensated for during development.

The distinction between oneself and the other is made not only by the face, but also by cultural differences, belief systems... We return to Ricoeur's distinction between the "close" and the "neighbor". It's easy to imagine the close relative as part of the same city, the same cultural community, the same nation, but what is the neighbor? Ricoeur refers to the parable of the Good Samaritan in Luke's Gospel. Ivan



Illich imagines the Samaritan as a



10. The Parable of the Good Samaritan, marble relief,  
Antwerp, Church of St. Charles Borromeo  
© Photo12/Alamy/jozef sedmak

Palestinian caring for a wounded Jew. The neighbor, unlike the relative, is defined neither by social proximity nor by community affinity; he or she is not a relative, but a human being accidentally bumped into, who needs to be helped...

*My neighbor is my closest neighbor (proximus), even though I have no ties of proximity with him or her, either by blood or marriage. The "nearest" is at the same time the « farthest »...*

What "self", "loved one" and "prochain" (neighbor) have in common is that we all belong to the same *Homo sapiens* species, with the same desires, the same sensitivity and the same will to survive and live well. A genetic and neurobiological community unites us on the scale of humanity as a whole, even if our national or cultural affiliations seem to divide us.

### **Attributing mental states to others**

*Man also has the ability to attribute mental states to others...*

The human brain possesses a unique predisposition in the animal kingdom to recognize intentions, desires, knowledge, beliefs, emotions, etc. in others. This ability to attribute mental states, to "put oneself in another's shoes", enables us to identify possible differences/identities with our own mental states, and to plan our actions towards others in a way that accords (or not) with internalized moral standards. Such a device contributes to the evaluation of "oneself as another" (Ricoeur).

An important feature of this "*theory of mind*" is the ability to attribute false beliefs to others, to comprise that other people may believe things that are not true. Various cognitive psychology tests have established this, such as the "Sally-Anne" test, which aims to assess a person's aptitudes to understanding that others possess mental states different from their own. However, this remains speculative. - Hence the word "*theory*" - insofar as I can't know everything the other person is thinking. As the mental states of others are not directly observable, the subject represents them in theoretical or hypothetical form, in order to predict his or her behavior. But the concept is now widely accepted and its usefulness recognized.

In the early years, the "theory of mind" develops in stages.

The understanding of interindividual interaction is gradually enriched in the child's brain: *via* the relationship with the mother, with play partners, the social relationship is fleshed out and, during the fourth year, the child has the "theory of mind ».

Brain imaging in schizophrenia, as well as in autistic children, shows deficits in attribution. These deficits are located in the pre-frontal cortex.

Various attempts have been made to identify the brain territories involved in "theory of mind". Among these is the electrophysiological work of Giacomo Rizzolatti's Italian group<sup>5</sup>. In monkeys, they recorded sensorimotor neurons in the premotor area of the frontal lobe, which are activated when the animal grasps a peanut. However, the same neurons become active in the same monkey, not only when it performs the act itself, but also when it observes the experimenter taking a peanut. These neurons have been dubbed "mirror neurons". These data suggest that mirror neurons could form the basis of a "theory of mind". This is a possibility. But they do not offer the means to access hidden mental states; they only reveal a situation of imitation.

Other imaging studies confirm, as might be expected, that the prefrontal cortex is involved in the "theory of mind". More specifically, there is increased activity in the *right* orbito- medial prefrontal cortex, or in the *left* medial and lateral prefrontal cortex.

### **Sympathy and « violence inhibitor »**

*As you have already mentioned, this raises the question of empathy, which must be distinguished from sympathy...*

*Empathy*, as studied by Darwin and, more recently, by Alain Berthoz, has a dark side. It can be used to discover a person's weakest point, and thus make them suffer. Empathy is not

opposed to intentional cruelty; on the contrary, it enables it. *Sympathy*, another prosocial component, involves us in the emotions (positive or negative) or pain of others, and leads to compassion, the feeling that leads us to be sensitive and touched by what affects others, prompting us to offer our help and affection. Think of the Good Samaritan.

Various experiments have been carried out on this subject. Let's take a look at the *violence inhibitor*. Konrad Lorenz (1996) and Eibl-Eibesfeldt (1970) discovered a cognitive mechanism of non-verbal communication in animals: the victim produces signals - for example, of submission in dogs - which stop the aggressor's attacking behavior. This is a common posture observed in fights between males. One of them refuses to fight and leaves. The violence inhibitor has worked.

English psychologist Roger Blair has extended the concept to include "psychopathic" children, who are said to have a selective deficit of the violence inhibitor<sup>6</sup>. These children show no emotional response to the distress of others; they are violent and aggressive, showing neither remorse nor guilt, although they are aware that they cause suffering (theory of mind intact). According to Blair, these children, although antisocial, have a normal ability to attribute.

The cognitive device of sympathy, combined with the attribution faculty *specific to humans* and the "social bond", could be at the origin of the fundamental and universal *moral emotions of empathy and sympathy*.

### **Moral judgment**

*What place do you reserve for moral judgment?*

For Ricoeur, consciousness is "a deliberative space for thought experiments in which moral judgment is exercised in the

hypothetical mode". This view accords with the neurobiologist's Global Neuronal Workspace: a space for simulating virtual actions, where an internal evolution of mental objects, as well as a dynamic of activities, can develop with considerable economy of time, experience and behavior. Present in this conscious space are intentions, action programs, modes of intervention on the external world, the self, moral rules and internalized social conventions. The conscious neural workspace, which mediates between the external world and the nervous system world, allows "freedom" of choice to the extent that reward systems will spontaneously access these various possibilities - and ethical reflections. The existence of such a space for deliberation makes the great difference between man and ape<sup>7</sup>.

There are "thought experiments", to use Ricoeur's formula, which anticipate the consequences of each of the open possibilities and which can be described in neural terms.

## 7- FOR UNIVERSAL PEACE

*The question of violence, omnipresent between men, cannot be ignored...*

In the third part of his *Elements of Physiology*, devoted to brain phenomena, Diderot humorously suggests that "the wise man is but a compound of mad molecules". For the neurobiologist, wisdom is the result of the atomic, cellular and molecular activity of the more global elementary circuits we have described in neuronal terms.

Several colleagues have criticized my vision of man as overly optimistic. For my philosopher colleague Anne Fagot-Largeault, it evokes the "communion of saints". In short, there's hardly any sign of "evil" emerging. Marcel Henaff,

whom I had the pleasure of meeting while he was teaching philosophy and anthropology at the University of San Diego in California, shared with me his book *Violence dans la raison*<sup>8</sup>, in which he takes up the paradox raised by Konrad Lorenz. Man is a particular being that the vagaries of evolution have created a state of major imbalance: physical weakness, exceptional intelligence and super-powerful means of destruction. The evolution of *Homo sapiens* came to a halt, as it were, when the brain gained access to cognitive devices that enabled it both to establish social links and to question nature, to understand the world. While the cognitive component developed strongly, the social component remained in the background. Perhaps the reason for this, if we follow Kropotkin, is that human social groups very quickly came into competition with each other, bringing a component of violence into play.

Moral rules, in my opinion, were instituted in an attempt to harmonize, not man's relationship with his environment, but man's relationship with his fellow men. They were necessary to ensure man's survival as a social group.

Although the "Golden Rule" appeared two and a half millennia ago, and the 1789 Declaration of Human Rights more than two centuries ago, the same unbearable cruelty, the same barbarism that Europe experienced yesterday and the day before, from the Wars of Religion to the Nazi death camps, is being repeated today in many parts of the globe. There's no doubt that empathy and sympathy have remained at a lower stage of development.

*George Steiner's work on the extermination camps clearly illustrates the proximity between the most abysmal barbarism and the highest culture. A camp leader who went about his planified tasks of mass murder during the day, would return*

*home to supervise his children's education, read Goethe to his family or play a Bach sonata on the piano...*

The American neurosurgeon and psychiatrist Itzhak Fried, a professor at UCLA, has given a name to this paradox, in an article published in *The Lancet*: "The transformation of groups of previously non-violent individuals into repetitive killers of defenseless members of society has been a recurrent phenomenon throughout history. This transformation is characterized by a set of symptoms and signs evoking a common syndrome, the "E syndrome"<sup>9</sup>. My colleague at the Collège de France, Alain Berthoz, has worked extensively on this issue. There is no cure for this pathology, which is found in all men, at all times in history. There are only *means*, those available to free institutions (Ricoeur)...

*One thinks of Hobbes: "Man is a wolf to man." To get out of the state of nature, which is "the war of all against all", we need to imagine a free pact...*

In such a fragile world, with an uncertain future, it's up to us to constantly encourage people's brains to invent a future, and why not a pact, that will enable humanity to achieve a life of greater solidarity and peace.

*And what kind of future do we need to invent?*

I had three dreams before I formed a project inspired by Martin Luther King "I have a dream". The first is that all human beings should be able to develop in conditions that not only ensure them a good life, but also protect their environment. The second is that every child on the planet

should have access to a decent standard of living and free and compulsory secular schooling. The third is to ask the question: "Who benefits from science? In our capitalist societies, as Thomas Piketty has clearly shown, scientific and technological development not only does not reduce inequalities between men, it actually increases them. If we can't eliminate inequalities, let's dream of science helping to reduce them.

How can we make these wishes come true? In 1795, Kant wrote a *Project for Perpetual Peace* which, in many respects, has not aged a day, but most of its articles have never been put into practice.

*We may recall the conclusion of Kant's text : « If it is a duty, to which is added a well-founded hope, to realize the reign of public law, but by a progress extending to the infinite, perpetual peace, which must succeed what have hitherto been falsely named peace treaties (it would be more correct to call them truces), is not an empty idea, but a problem which, receiving its solution little by little, will come ever closer to its goal (for it is to be hoped that the same progress will be made in shorter and shorter times). »*

Today, members of the United Nations Security Council seem powerless to impose "global harmony". In 1998, in response to a request from Federico Mayor, then Director of UNESCO, "to take action for human rights in the 21st century", I proposed the creation of a "World Ethics Committee" which would not only address the issues raised by the life sciences and health, but would also encourage the world's inhabitants - and first and foremost their leaders - to recognize each other's values as responsible individuals who,



whatever their origins, all belong to the same species. We all share a common *humanitas*. This proposal, supported by President Jacques Chirac, has gone unheeded.

Should the idea be revived? One of the necessary conditions for such a Committee to be set up and to be able to enforce its recommendations is that, in a situation involving power relations, it must have the means to enforce peace, even with regard to the most powerful. We therefore need to imagine an institution capable of exercising this authority.

*Such a committee must have the means of coercion at its disposal... A distinction must be made between pacifism, which is always ambiguous and above all inefficient, and a pacific and pacifant project that requires the use of force...*

Any ethical decision - as current conflicts clearly show - must indeed use means of constraint superior to those of the parties concerned. Of course, everything also depends on the Chairman of such a Committee... If it could be an "ayatollah", it's a disaster!

*Who will have the authority to appoint the Chairman?*

It is conceivable that the members of a Security Council could democratically agree on the appointment of such a President, as long as they are deprived of individual veto.

## **IX.**

### **The rule of Beauty**

#### **1- INITIAL AESTHETIC MOTIVATIONS**

*As you mentioned at the start of our interview, you're a collector...*

In fact, I've been collecting insects since I was a child, and in addition to my "scientific" interest, I've always had an aesthetic preoccupation. I also showed an early interest in music, particularly the organ. I spent a lot of time tearing up scores of contemporary music, which enabled me to enter into this music and understand it. I also had a pictorial activity, notably during vacations in Banyuls where I painted landscapes; I also did ceramics. These activities kept me busy between the ages of fifteen and twenty. I gave all that up in favor of science. As soon as I joined Jacques Monod's laboratory, my research work became my full-time occupation. I may have detached myself from artistic practice, but art has always been present in my life.

*Did your parents have a taste for the arts?*

Not at all. As with science, nothing predestined me to take

an interest in art. It was my reserved domain, where I could assert my originality and detach myself a little from my family. My parents weren't hostile to art, but they had no knowledge of it.

*It's worth noting how important it will be for you to discover Italian painting in Florence.*

As I said, it was on a trip organized by my elder sister Christiane - a fascinating discovery. To speak of the "Stendhal effect" would be a little excessive, but it was a very memorable experience. At the École normale, in my "turne" (room) I had hung on the wall various reproductions of Italian Renaissance paintings and icons that I was beginning to collect. I also loved contemporary painting and had bought, at an affordable price, exhibition posters by Miro, Dubuffet, Klee... Klee interested me, in relation to Messiaen's music. I'd also acquired a large printed canvas by Lurçat. That was my student environment. Later, I met an artist, Louis Cordesse, with whom I had many discussions. He had been a pupil of Ernest Pignon. This was before I left for America. Once there, in Berkeley and then in New York, it was difficult for me to play the organ and find icons. So I became interested in Japanese prints, Hiroshige...

*You must have profited the great American museums and their prestigious collections...*

I visited a lot of museums during my American stays. It was an opportunity to enrich my artistic culture. In New York, I particularly remember my first visit to the Frick Collection and the Metropolitan Museum. On my return from the U.S. in

1967, I resumed my work on the receptor at the Pasteur Institute. I became interested in art and collecting again. I regularly went to the Hôtel Drouot in search of icons. While there, I noticed that there were also sales of ancient paintings at equivalent prices, in particular canvases by 17th-century French painters. In 1972, I made my first purchases: a Sébastien Bourdon and a Louis de Boulogne, which turned out to be poor copies. It was then that I met an expert, Alain Latreille, who worked for an antique gallery. We struck up a friendship. He made me understand that you always have to look for the original, make sure of its “attribution” if possible, know what you're buying, have an idea of the price, master the auction system and so on. This was an important step. A second meeting, in 1975, also played a major role: I had met Raymond Aron during my visits to the Collège de France, in preparation for my candidacy. We talked about painting, my interest in the classical period and my taste for collecting. He invited me to get in touch with his son-in-law, Antoine Schnapper, an art historian specializing in 17th-century French painting. I was able to admire his impressive personal collection at his home in Paris. It was through him that I met Pierre Rosenberg, curator at the Musée du Louvre and a leading specialist in the paintings of Nicolas Poussin, among others.

*Did you have the opportunity to discuss painting with Claude Lévi-Strauss, your colleague at the Collège de France and a great art lover?*

I often met him at the Hôtel Drouot, we had similar agendas, but was never able to establish a constructive conversation with him, at least on the subject of art. He was always extremely friendly, interested in my work, but not very

talkative. I had tried to interest him in a possible reflection crossing anthropology and neuroscience. Nothing came of it. Yet he successfully nominated me to a prize of the Académie Française... I had more success with his follower Maurice Godelier...

After collecting a number of paintings that seemed important to me, and being very sensitive to the idea of artistic heritage in 1983, my wife and I made an initial donation of a dozen paintings to the Museum of Meaux, as part of our "national artistic heritage". We later expanded this collection to around forty works. It's a bit like my artistic « testament ».

*What unites these dozens of paintings, apart from their period?*

They all come under the heading of history painting, the so-called "grand genre".

## **2- WHAT IS A WORK OF ART?**

Science has a social dimension: the validation of a scientific discovery by the research community is indispensable. There is no intrinsic truth. The truth corresponds to a moment in the history of scientific knowledge when a kind of conceptual crystallization can take place, on theoretical and experimental grounds. If the new concept that emerges is not validated by the scientific community, its existence is widely questioned, perhaps wrongly at times, but more often than not with good reason.

The work of art, like ethics, is above all an object of social communication. This is what the "Rule of Good" and the

"Rule of Beauty" have in common.

But what is a work of art? The French psychologist Ignace Meyerson (1888-1983)<sup>1</sup> identified man's ability to produce *works that stand out* from what he finds in the external environment as one of his characteristic traits. The work of art differs from other works produced by man. Like all works of art, it is an artifice, but it also possesses the exemplarity and remarkable stability that make it endure over time.

*Hannah Arendt distinguishes between the animal laborans, who works to satisfy his needs, a cyclical activity - what he produces is consumed and therefore destroyed - and the homo faber, who creates works destined to last, making him part of culture and history...*

Works of art are artifices that participate in communication within the social group: there is a creator and an observer; and the observer can become a creator. There is a form of reciprocity. According to Lévi-Strauss, art lies halfway between scientific knowledge and mythical or magical thought. Art thus occupies a singular place. Of course, we could ask whether this "tripartition" (science - myth - art) is worth revisiting. Catherine Millet, for her part, says that works of art are specific objects that "The essential function of the latter is now to bring to light, to displace, that core of humanity that religion no longer supports and that science cannot contemplate." I like this definition.

From all this, it's clear that a work of art has no "apparent utility": it's something to be contemplated, but not simply an object of pleasure.

During a recent dialogue with Pierre Rosenberg, we asked ourselves the question: "What makes a work a work of art?" His first reaction was to say that the problem had no solution!

I replied that no, it was certainly difficult to solve, but not without a solution. He retorted that, in his opinion, there was something in the question that escaped logical understanding. His answer testifies to the persistence of a certain metaphysical dualism that *precludes a priori the possibility of* understanding a work of art in the same terms as those used to describe nature. So be it," I said, "but that doesn't prevent us from trying to understand. Diderot, in his *Recherches philosophiques sur l'origine et la nature du beau*, was already wondering how it is "that almost all men agree that there is a beauty, that there are so many among them who feel it keenly where it is, and that so few know what it is". Does the eye (or the ear) have its reasons that reason does not know?

The state of rapture, or ecstasy, before a work of art, this state of happiness or extreme pleasure is illustrated by what is known as the "Stendhal syndrome", in reference to the aesthetic emotion experienced by the author of *La Chartreuse de Parme*, in Florence, in 1817, at the sight of the frescoes by the painter Volterrano.

When Stendhal saw the Tuscan Sibyls on the ceiling of a chapel in the corner of the Basilica of Santa Croce, he was dazzled, as he wrote (*Rome, Naples and Forence*, 1817): "Absorbed in the contemplation of sublime beauty, I saw it up close, I touched it, so to speak. I had reached that point of emotion where celestial sensations given by the Fine Arts and passionate feelings meet." On leaving the church, he was seized by a physiological disturbance: "I had a heartbeat, what they call nerves, in Berlin; life was exhausted in me, I walked with the fear of falling." This "Stendhal effect" testifies to the "aesthetic effectiveness" of an original, unique composition, provided that particular circumstances are brought together.

*Madame Verdurin, a Proustian figure, claimed that the intensity of emotion provoked by a work of art was an indisputable criterion of its aesthetic value.*

We often think of a work of art as something that gives pleasure, a word that bothers me a little because it's too polysemous. I prefer to speak of "evocative power", which is of course accompanied by a complex, variable and varied emotional dimension. In saying this, I'm thinking in particular of Goya's *Disasters of War*, a series of engravings produced between 1810 and 1815, very hard to look at, bringing to life a tragedy which, alas, is still being perpetuated today. These are undoubtedly works of art that arouse intense emotions in us, all the more so as they mobilize a whole ethical content of individual responsibility in the face of adversity.

In defining a work of art, we can't just think of pleasure as something that's always "happy". On the contrary, it can be unhappy and moving: just think of Goya's *El Tres de Mayo*.

In his book *The Psychology of Art* (1925-1932), the great Soviet psychologist Lev Vygotsky - renowned for his work on learning and the child's internalization of the social world - describes the cognitive process that leads to the production and contemplation of a work of art as an "emotional thought" that associates the products of the imagination, and/or fantasy, with the affects and feelings that accompany these images. Renewing the definition given by Aristotle in the *Poetics*, he describes *catharsis* as the discharge of emotions, accumulated by the spectator or reader, when "affected" by a work of art. It seems to me a very good definition. There's a kind of short-circuit in the brain that links the cognitive and the emotional, going beyond logical reasoning alone. So, if I may say so, I agree with Pierre Rosenberg: we need to go beyond simple cognitive reasoning.



We can also think of the illumination that Henri Poincaré spoke of in connection with the process of discovery in mathematics: "the character of beauty and elegance", the "aesthetic emotion", playing "the role of a delicate sieve", which precedes the conscious work of rigorous demonstration.

In short, the work of art is a human cerebral production, an "artifice" specialized in inter-subjective communication that calls upon meaningful "symbolic forms" and engages emotional states, knowledge and experience with "aesthetic efficacy". It is a *catharsis* that performs a singular synthesis of emotions and reason (Schiller), while mobilizing conscious and non-conscious processes.

### 3- COLLECTING

*Let's get back to the idea of collecting...*

I'm a collector, I told you. Collecting is a particular form of behavior that occupies such an important place in human behavior that we might wonder, with Jacques Thuillier, if it doesn't give us access to "one of the highest forms of culture". Ignace Meyerson, again, considers the creation and conservation of works, but also their *classification*, to be a human specificity. Collecting would then be at the source of scientific knowledge, of the doctrine of science that "breaks with nature", "to construct a new reality", where the perceptual categorization of sensory signals from a world that I would personally describe as "unlabeled" would take place. This vision is radically opposed to the Platonic-type dualism found among many mathematicians, which defends the idea of a reality in which things are always already assigned.

Collecting also enables the sharing of meanings specific to

the social group, thus helping to strengthen the intersubjective bond and "immortalize" the work through the succession of generations. Enduring works of art are essential testimonies to humanity's past, and form part of its shared cultural heritage.

This classificatory activity is not recent: the prehistorian André Leroi-Gourhan (1964) discovered, at Arcy-sur-Cure, the first intentional grouping of objects (fossils, in particular) by Neanderthal man, which he considers to be the first traces of a collection. It therefore predates the appearance of *Homo sapiens*.

The ancient Greeks built botanical and zoological collections, anatomy rooms and astronomical observation centers around sanctuaries dedicated to the Muses. It's hard not to mention the Museum of Alexandria (-290), the work of Ptolemy I Soter, and its famous Library, which sought to bring together "the books of all the peoples of the Earth ».

The Renaissance saw the emergence of cabinets of curiosities in aristocratic circles, more reminiscent of early prehistoric collections than of the Library of Alexandria. The role played by Bernard de Montfaucon in the early 18th century is important for our purposes. Abbot of Saint-Germain-des-Prés, in his book *Antiquité expliquée et représentée en figures* (1719-1724), he extended the method of systematic classification to Greco-Roman and medieval antiquities. Now it applies to the fine arts.

So there's a long tradition of collecting in the civilizations that preceded us, which continues today. The collector, by definition, is trying to put together a collection. At the outset, he has little experience, and his choice is hardly enlightened. Roger de Piles (second half of the 17th century), in his *Abrégé de la vie des peintres*, distinguishes between the "curious" who forms "an idea of a master from three or four paintings he has seen" and manifests himself in naive and irrational

infatuations, and the "*connoisseur*", skilled "by his talents, by his reflections and by his long experience". In time, I became a modest collector-connoisseur.

The connoisseur does not necessarily have the knowledge and skills of the expert.

*Perhaps we could follow the collector's itinerary...*

You have to start with the exploratory quest that precedes the acquisition. For me, it consists of going from room to room at the Hôtel Drouot, where there is a jumble of ancient and modern daubs, copies, masterpieces and all sorts of objects, a wandering and distracted gaze, suddenly arrested: attention is drawn to a singular work - a *mini-catharsis* - inaugurating a little personal adventure. Our reward system is strongly activated. The discerning collector will not remain at this stage - corresponding to the illumination Poincaré spoke of - but will enter a second stage, examining the work in its entirety and in detail, trying to grasp the artist's touch, the underlying design, the "repentirs", the relationships of colors, the precision of gesture to enlighten the eye. Art historian Ernst Gombrich rightly wrote that the "connoisseur reiterates in thought the artist's imaginative prowess". He brings the work to life by trying to find in it - the original and not the copy - what animates it, its liveliness. The work of art is a kind of living being. Following Vygotsky, we can define perception as "a process of re-creation", as a kind of "reprise" of creation itself. "Re-creation": there is both a construction from observation and the birth of a joy...

*Re-creation becomes recreation We must also stress the importance of "detail" in artistic contemplation (the Proust's*

*"little yellow patch of wall" in Vermeer's painting) and for the authenticity of the works...*

The collector internally simulates the conditions of the work's execution, examining the "details" that eventually lead to the distinction between the original, lively and dynamic, and the copy, dull and clumsy.

The next step is to try to match the work, thus recognized, with images of works already identified in museums and art books. It's a matter of comparing the perceived work with those stored in long-term memory, with the artistic culture acquired. The connoisseur is recognized by two qualities: his "eye", which enables him to assess the quality of the work of art, and his culture, born of direct or indirect frequentation of the works. Initially, I had no knowledge of art history, but my knowledge of the subject has gradually grown, thanks to the encounters I've just mentioned, and to various readings. Which doesn't make me an expert, but an "enlightened" amateur of 17th-century French painting.

*Can collecting become an addiction? It's sometimes called "collector's neurosis".*

Indeed, collecting can become a form of addiction and therefore a "loss of control". We know that reward neurons are involved in this behavior. Some collectors can lose all sense of the elementary rules of social life, as in the case of Queen Christine of Sweden, who in 1648 wrongfully confiscated the Holy Roman Emperor's extraordinary collection, Rudolf II, in Vienna, a few days before the signing of the Peace of Westphalia. She was one of those addictive collectors... When I started collecting, Pierre Rosenberg warned me: "If you start, you'll forget your scientific work. »

*And you forgot?*

No, not at all. I've managed not only to reconcile the two, but above all to let my addiction to science take precedence. Nevertheless, there's an addictive tendency in the accumulation of objets d'art.

*Could you give us some examples of your attempts to attribute a work to an artist or an artistic movement?*

Two of them stand out. Walking through the Hôtel Drouot in 1980, when it was based at the Gare d'Orsay, I was struck by the quality of a heavily soiled canvas depicting *Moses Saved from the Waters*. Its style was close to that of Poussin or Sébastien Bourdon. I bought it. Pierre Rosenberg came to see the work in my home and encouraged me to send a photograph to a British art historian. She was quick to reply, telling me that there was a preparatory drawing of the work in the Louvre, signed "Thomas Blanchet *inv. et facit Lugduni*". The painting established a link between Blanchet's stay in Rome and his return to Lyon. We have donated it to the Musée du Louvre.

On another occasion, still at Drouot, I spotted and acquired an extraordinarily well-crafted sketch, a curious allegorical subject combining Olympian divinities and Christian symbols. Its attribution remained problematic, until Jacques Thuillier, on his return from a trip to Lisbon, recognized it as the original *modello* of a large painting - *Allegory of the Foundation of the Casa Pia* - by the Portuguese painter Domingos Antonio de Sequeira (late 18th-early 19th century), exhibited at the National Museum of Ancient Art in Lisbon.

The work has also been donated to the Louvre.

### **History painting in the 17th and 18th centuries: the "grand genre"**

*Why did you specialize in religious and mythological painting of the 17th and 18th centuries?*

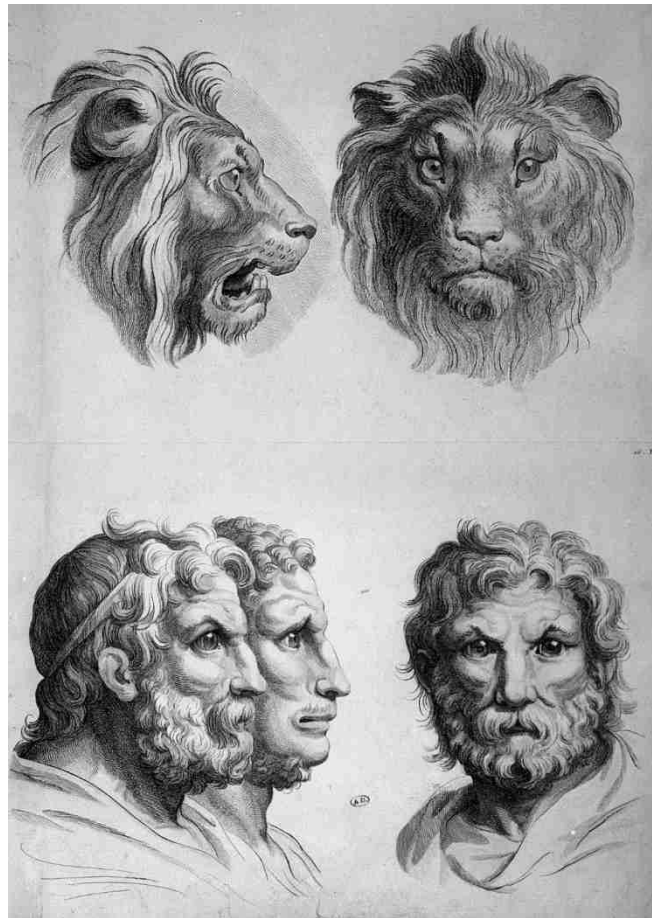
There are various answers to this question. One is the collector's childhood: having lived this period of my life in the shadow of the towers of Saint-Sulpice, the repertoire of Counter-Reformation forms and images may have become part of the corpus of my childhood and adolescent synapses, as did, as we have seen, my first visit to the Uffizi in Florence and the discovery of Cimabue, Giotto, Simone Martini, Masaccio... These "founding" experiences are perhaps at the origin of my first quests for icons during my student trips to Greece and Turkey. It is also possible that my taste for collecting works of art came to compensate for a professional activity that had become too abstract, oriented towards molecular mechanisms increasingly detached from the spectacle of "the forms of nature". All this is possible.

We must also bear in mind that, in the 1970s and 1980s, it was still possible to acquire quality works from this period at very good prices. Not "small masters", but forgotten artists, rediscovered by a generation of art historians: André Chastel, Pierre Rosenberg, Antoine Schnapper, Jacques Thuillier... My brain was nourished by their analyses.

My interest has always been in history painting, more specifically in the so-called "grand genre". Here we find complex compositions, scenes inspired by Greco-Roman mythology, the Old and New Testaments, all rich in meaning.

For me, this is essential: these are not simply painted forms that arouse pleasure, but *significant* forms. They convey "beautiful ideas", in Poussin's words, and offer a lesson in humanism far more general than a simple landscape or portrait.

Charles Le Brun's paintings at Versailles confirmed my interest in the "grand genre". Commenting on a speech by the painter to the Royal Academy of Painting (1668), entitled "L'expression générale et particulière des passions de l'âme", Julien Philippe<sup>2</sup> points out that Le Brun's theoretical project was not to paint the world from nature, but to reconstruct it, as a *rationalist*, in the form of a "formal system" that governs all beings and their relationships. I love this formula. It's as much about the universality of human beings themselves as it is about the universality of their history or beliefs. In Le Brun's work, the artistic approach is almost scientific in nature. Indeed, in his lecture, he takes up the mechanistic vision of Descartes' *Traité de l'Homme*, without explicitly referring to it, with the "little pipes", the nerves, the animal spirits, and so on. Going further, he argues that painting can transcribe the way in which the "inner movements" of a "soul joined to all parts of the body" perform their functions on the face.



11. Two lions' heads and three men's heads in relation to the lion. Plate from *Livre de portraiture pour ceux qui commencent à dessiner* by Charles Le Brun, 18th century, Paris, Bibliothèque des Arts Décoratifs © Bridgeman Images

So, according to him, we could objectively describe the expression of emotions on the face. In the past, there was a method known as physiognomy, which sought to determine a person's character from the features drawn on his or her face. In another lecture (1680), Le Brun, for the sake of universality, applied himself to comparing the "resemblance and relationship



of the parts of the human face with those of animals". This resulted in some very remarkable drawings (*cf.* image 11). Darwin, who was no particular Francophile, mentioned Le Brun's lectures, "which contain some good observations", in his book *The Expression of emotions in man and animals* (1887). I'm very attached to the humanism and ethical dimension present in 17th-century painting, which aim to reinforce social bonds.

#### 4- NEURAL BASES OF PAINTING CONTEMPLATION

*Your approach to painting includes, of course, the neurobiological dimension of aesthetic experience.*

I've already referred to the exploration of the painting as a first step. The global vision of the work is followed by the search for details through eye movement. The Soviet neurologist Alexander Romanovich Luria and his colleague Alfred Yarbus<sup>3</sup> have shown, through the analysis of eye movement tracking, that the observing subject does not randomly explore the image of an unknown face in front of him, but lingers on specific details of the painting. It's a sort of systematic journey, from the left eye to the right eye to the mouth.

The Ilya Repine's painting *The Unexpected Visitor* (~1884) shows a family gathered in a room, surprised by the return of an unexpected captive. Examination of the movements of the viewer's eye reveals several "centers of meaning", where the gaze stops, including first and foremost the faces of the main characters in the composition. This is a history painting. When the neurobiologist questions the viewer about details of the family's material situation, age, clothes worn by the figures, length of absence, etc., the eye movements are always

characteristic. Luria used this test to establish a neurological diagnosis: in a war-wounded patient with a right frontal lobe lesion, the tracing is disorganized, haphazard, and no longer varies with the instructions, even if the patient understands them. There's a kind of "arbitrary perseverance" that's the consequence of the frontal lobe lesion. We can deduce from this that the frontal lobe is involved in perceiving the organization of the picture as a whole, and in understanding its various levels of meaning.

### **Physiology of visual perception**

Another objective approach to picture exploration is based on brain physiology. This applies to music, of course. It should be noted that, far from being limited to works of art, the stages of perception are common to all kinds of objects.

When examining a picture, *bottom-up* processing takes place. The retina and ganglion cells are stimulated, and allosteric proteins, mainly opsins (specific to red, green and blue light) and rhodopsins (more general) come into play. The retina constructs an initial physical representation of the artwork on the retina. This representation then manifests itself in electrical activity, which is transmitted to the optic nerve and progresses to the thalamus, the primary visual cortex. At this stage, a kind of functional mapping of the visual area can be used to identify the shape of the object being viewed. There's a kind of isomorphism that corresponds, as it were, to the work of art entering the brain, which is then analyzed at the level of the visual system's multiple cortical areas. These cortical maps specialize in the processing of visual information, with two paths, one, the first is involved in the perception of movement, shape, figure/ground separation and

the organization of the visual scene in space. The second is involved in the recognition of objects, faces and color perception.

All this leads, progressively, to a distribution of the neural representation of the work in the various cortical areas up to the temporal cortex. Already, at this level, some neurons respond to faces, others to hands. Beyond the temporal and parietal cortexes, the representation of the painting reaches - or fails to reach - consciousness.

### **Access to consciousness: aesthetic ignition**

We're dealing with a dynamic of access to consciousness with an "*ignition*" - a notion already mentioned (*cf.* chapter 7) - that mobilizes the prefrontal, parieto-temporal and cingulate regions. The Global Neuronal Workspace is then activated. By way of hypothesis, "aesthetic ignition" can be said to possess a number of characteristic features that distinguish it from of a simple ignition. What sets it apart is that it mobilizes, in a multimodal way, a vast diversity of territories in relation to perceived images and memory images, but also the social and cultural context, elements of personal life, and many elements of the subject's *habitus* with rich emotional content - all within the framework of the "rules of art", of course. Its sudden, comprehensive and coherent invasion of the entire conscious space would be the objective signature of the work of art's *efficacy*.

Danish neuroscientist Morten Kringelbach has studied a baby's reaction to a so-called "normal" child's face and that of a child with a craniofacial anomaly (a harelip): the ignition in both cases is different<sup>4</sup>.

As far as painting is concerned, a number of preliminary

studies have been carried out, including one by Sémir Zéki, a Franco-British neurobiologist, who, using brain imaging, is said to have succeeded in highlighting the contribution to "aesthetic emotion" of a very specific area of the brain: the medial and lateral orbitofrontal cortex of the frontal lobes<sup>5</sup>.

Experimental data on music<sup>6</sup> are more abundant. For some people, listening to a piece of music can trigger intense emotions, tears or shivers - all "Stendhal effects" - that testify to an intense *catharsis*. Canadian researchers<sup>7</sup>, trying to pinpoint what was happening in the brain, found that these emotional manifestations were accompanied by increased activity in the reward systems and decreased activity in the ventromedial prefrontal cortex. There is clearly a contribution from the limbic system, which plays a decisive role in emotion regulation. The response is inhibited by an opiate receptor blocker, naloxone.

This inhibition explains why the exhilaration of contemplating a work of art can be similar to the effect of a drug. It's like the addiction we've just been talking about.

### **Neural basis of picture creation**

#### **And from the point of view of the "creator"?**

The painter, usually starting from sketches - Caravaggio, it seems, did not make any - tries to take up a good idea, a theme, which he will gradually build up through trial and error. Even Leonardo da Vinci proceeded in this way: he worked for several years on *La Sainte-Anne* in the Louvre, multiplying sketches - which have been preserved - until, through internal reward mechanisms, he selected the sketch that satisfied him the best. This selection leads to the

stabilization of particular assemblies of neurons in the brain. Even if the neurobiological mechanisms involved remain poorly understood<sup>8</sup>, we can think of the model proposed for the *Wisconsin Card Sorting* task (chapter 6), opening it up, of course, to the multiple worlds invested by the artist.

But the work of art is never truly finished, it has no end... Leonardo himself would return to paintings he had done several years earlier...

## 5- THE RULES OF THE ART

*We might recall Baudelaire's remark about Corot: "There is a big difference between a piece done and a piece achieved, a fini piece - that in general what is done is not fini, and that a very finie thing may not be done at all."<sup>9</sup> »*

That's exactly right. During the creative process, a combinatorial explosion could occur in our brains, with disastrous consequences. As we've noted, our brains are made up of billions of neurons and even more synaptic connections, so the combinatorial possibilities are extremely numerous. But the brain has the means to limit the number of possibilities. In the previous chapter, I referred to these as "rules". The brain limits the number and nature of representations accessible at a given moment, by constructing "epigenetic" rules stored in our memory, which constrain and organize the underlying representations from top to *bottom*.

These rules are essential, firstly because they enable the artist to paint, to create a framework within which the number of possible representations is limited, but also because these rules are often specific to an artist, to his or her

experience, and to his or her social and cultural environment. All artists develop their art through contact with other artists.

*Malraux said that artists learn to paint in museums...*

All this helps define a painter's style. "I like the rule that corrects the emotion", said Braque. Boulez maintains the opposite: "I like the emotion that corrects the rule". The rule is both specific to the artist and common to a school and a milieu. We need only compare European painting of the Renaissance with Chinese painting of the same period.

Several rules can be taken into consideration:

– First rule: art is not an imitation of nature (as opposed to Platonic *mimesis*), but a re-presentation of it, with its own codes. It "completes what nature was unable to do"<sup>10</sup>, extending it by "idealizing" it. A mere imitation would be, in Hegel's words, a "caricature of life". The first rule involves a sense of *novelty* and surprise. There is a very powerful cerebral device that detects the new, the unexpected, essential to the organism's survival. Pavlov and then Sokolov have shown how an animal subjected to a repetitive stimulus - sound, for example - eventually stops responding to it; they have called it called "desensitization". As soon as the stimulus changes, the organism reacts by orienting itself towards the new source, whether through gaze or posture. There's a neural basis for overtaking, for detecting novelty, involving territories of the frontal cortex and the limbic system. This intrinsic brain property helps us to understand both the renewal of an artist's production and the existence of an art history.

– The second rule is *parsimony*: the economist Herbert Simon (1916-2001) said that "being able to explain a lot from a little" is an essential quality for a scientific proposition<sup>11</sup>. In

my opinion, this rule of parsimony is common to both science and the humanities. A work of art retains the essentials that will move us. A single stroke is enough for Matisse or Picasso to create a recognizable and identifiable face. The same applies to poetry, which is capable of communicating a great deal of meaning with only few chosen words.

–The third rule, and perhaps the most important, is the *consensus partium* (Leon Battista Alberti, 15th century), the fact that the work of art is defined by a formal relationship of *convenience*: "The relationship between the parts and a whole by which the unity of the latter imposes itself on the multiplicity of the parts. » It's the *harmonia* of the Stoics...

*Which for them means the whole world; the cosmos is harmonious...*

For Diderot, in the article "Beau" in the *Encyclopédie*, 1752, The "perception of relationships is the foundation of beauty" and the difference of opinions concerning beauty results from the "divergence of relationships perceived or introduced [by men]". Matisse, echoing Alberti, would say: "I take from nature what I need, I meticulously combine all the effects, I *balance* them in description and color, and this condensation to which everything contributes, I don't achieve from the start." This universal quest for harmony has a Darwinian character, with its trial and error, as the story of Matisse's *La Blouse romaine* shows. For the painting of the Musée d'Art Moderne he produced fifteen successive versions...

There are neural bases to this quest for harmony, in other words, the recognition of certain forms of regularity in composition. A series of experiments on "illusory contours" is illuminating in this respect. These are formed when a subject

perceives a continuous bar of light from discontinuous luminous elements. If we record the activity of the cerebral cortex, we see that the brain compensates and creates an "illusory contour". The coherence of the world is reconstructed, albeit virtually. Marta Kutas and Steven A. Hillyard<sup>12</sup> demonstrated, in the 1980s, electroencephalographic responses different when reading sentences that make sense and others that don't. There's a kind of physiology of incongruity and, by extension, a physiology of harmony and coherence between the parts.

– Fourth and last rule: art implies the recognition of the other as oneself in the inter-subjective communication that the artist establishes with the viewer. As we have seen (Chapter 8), recent work has made progress in identifying the neural bases of empathy and sympathy. In their works, artists can express a protest against violence or war (Picasso's *Guernica*) and deliver an ethical message. These are Poussin's "beautiful ideas", the *exemplum*.

Current hypotheses on the neural bases of aesthetic affect and contemplation agree on the importance of a link between the prefrontal cortex and the emotional functions of the limbic system. There is an overall relationship and cooperation between the various parts of the brain. This can be described as "*resonance*".

Understanding the neurobiological mechanisms involved in the aesthetic experience is not a matter of "disenchaining the world", as some would have us believe. Seeking to understand how our brains work when we perceive a work of art (or when we taste a dish) is not in opposition to the pleasure we derive from it, but rather illuminates it.



## 6- DATIONS

*How did you become Chairman of the Commission in charge of dations?*

To tell the truth, I don't really know. Perhaps it has something to do with our first donation to the Musée Bossuet in Meaux, or perhaps it's because, from 1985 to 1989, I was a member of the Board of Directors of the École Nationale Supérieure des Beaux-Arts. In this capacity, I had strongly defended the entry of a collection of drawings (the Polakovitz donation) into the École's reserves. In any case, Jack Lang, then Minister of Culture, asked me to accept the presidency of the "Commission des dations".

### **National heritage conservation**

The idea of "dation" is linked to the notion of "national heritage". It can be traced back to Abbé Henri Grégoire, who, in a famous report on "vandalism" (14 fructidor de l'an 2 [1794]) - he was then a member of the Convention's Committee of Public Instruction - spoke out against the destruction of libraries and works of art perpetrated by revolutionaries. He called for respect for these "monuments" which "contribute to the splendor of a nation and add to its political preponderance". "Barbarians and slaves", he added, "hate the sciences and destroy the monuments of the arts; free men love and preserve them". Abbé Grégoire was instrumental in shaping the concept of "national cultural heritage ».

### **Dation**

On December 31, 1968, General de Gaulle and his Minister of Culture, André Malraux, promulgated an innovative law stipulating that "any heir, donee or legatee may pay inheritance

tax by handing over works of art, books, collectors' items or documents of high artistic or historical value". This law was explicitly designed to encourage the preservation of the aforementioned works of art in France. The law's scope was subsequently extended, by governments of both the right and the left, to include transfer right free of charge inter vivos (donations), the right to share and the wealth solidarity tax.

This legislative provision met with great success, for at least two reasons: the taxpayer's approach is voluntary (he or she remains the owner of the property and can renounce the dation at any time of its processing by paying the duties owed in cash) and a concern for fairness prevails, so that neither the State nor the taxpayer is prejudiced.

The Ministry of Finance forwards the file to an independent body for its opinion: the "Commission interministérielle d'agrément pour la conservation du patrimoine artistique national"(Interministerial approval commission for the conservation of national artistic heritage) also known as the "Commission des datations". The Commission is made up of five members: two representatives of the Minister of Economy and Finance, two of the Minister of Culture and Communication, and the Chairman appointed by the Prime Minister. The committee's role is consultative. The final decision rests with the Minister of Finance. In general, the opinions of the commission are followed, provided they are well argued and balanced, and the two representatives of the Ministry of Finance are in agreement.

I presided over this Committee - from 1989 to 2012 - just as I had done at the scientific meetings of my lab at Pasteur, or as head of the French National Ethics Committee, encouraging great freedom of opinion and speech. We were meeting about three times a year. Each time, a curator would come and present

the work (or works) in question. We had to take into account various criteria, all of them delicate, concerning both the work's "high artistic value" (how to determine this objectively?) and its price on the national and international market. It was a whole lot of investigative work. We were once shown a work stolen from Bordeaux Cathedral, which had been replaced on the spot by a fine copy.

We've had some lively debates about the "high artistic value" of works of modern or contemporary art. First, we had a rule against accepting works by living artists. There were a few exceptions, most notably Soulages. Tough discussions focused on certain artists, such as Bernard Lorjou. Well-known in the 1950s, along with Bernard Buffet, Jean Carzou and Alfred Manessier, he had built up a body of work marked by current events. I knew him for his huge canvas *L'Âge atomique*. A resolutely figurative painter, he was an opponent of abstract art and everything Beaubourg stood for. Some of his works were submitted for our consideration. The dation, after strong opposition from a member of the Committee - who had put his resignation on the line - was rejected before even being considered. Against this rejection, I was able to obtain a letter of support from Valéry Giscard d'Estaing. In the end, a few works were accepted. One of them - is this "punishment"? - was sent to the museum in Blois, a town whose mayor was Jack Lang.

Another example is William Bouguereau (1825-1905), a very academic, conservative painter who was hostile to Impressionism, which had very bad press with the curators of the major national museums. A dation proposal had provoked controversy within our Commission, between representatives of the Ministry of Culture and myself. Three magnificent works by the artist were finally accepted and now adorn the walls of the Musée d'Orsay.

The Committee has proved its worth over the years. The

Picasso estate (1979), which enabled us to keep an essential part of his work in France, and the acquisition of Vermeer's *L'Astronome* (1982) come to mind (this was before my term of office). Under my presidency, to name but a few remarkable works, we were able to bring Fragonard's *Renaud into the gardens of Armide*, Courbet's *L'Origine du monde* (Jacques Lacan estate), one of Monet's *Peupliers*, the extraordinary marble bas-reliefs created by Pierre Julien for Queen Marie-Antoinette's dairy at Rambouillet, exceptional furniture (the 18th-century *Salon Crozat*), the Edmond de Rothschild estate etc.

We have also added a number of 20th-century French works to our national heritage, from Henri Matisse's *Danse* to Marcel Duchamp's *Neuf Moules Mâlic*, and a major group of paintings by Joan Mitchell, the American "pop" painter who lived in France.

I also insisted on including photographic heritage, African art, puppetry and, as you'd expect, scientific and industrial heritage, with a 19th-century collection of insects from the Camargue, many of them extinct, the 1938 "electric egg", the first electric car by designer Paul Arzens, the first Bull transportable computers...

In 2012, Frédéric Mitterrand then minister of culture of François Fillion asked me to give up my apron.

## 7- EXHIBITIONS

*You have also curated a number of landmark exhibitions... which adds another color to your palette.*

Indeed, I've had the privilege of curating three major exhibitions.

The first was in Meaux, in 1988, following my first donation, entitled "From Nicolò dell'Abate to Nicolas Poussin: at the sources of classicism, 1550-1650", at the initiative of the town's Bossuet Museum curator, Blanche Grinbaum, Pierre Rosenberg and the town council.

–The second in Paris, in 1993-1994: "L'Âme au corps, arts et sciences, 1793-1993" (with Gérard Régner), at the Galeries nationales du Grand Palais, on the initiative of Jacques Sallois, then Director of the Musées de France.

–The third in Nancy, in 2005: "Light in the age of enlightenment and to day. Art and science: from the biology of vision to a new conception of the world", at the initiative of the municipality of Nancy and Pierre Rosenberg.

The "From Nicolò dell'Abate to Nicolas Poussin" exhibition was an opportunity for me to compare biological evolution (genetic) and the evolution of art (epigenetic). Could there be common rules in both cases? For this purpose, I've chosen a century - 1550-1650 - that straddles the "1600" cut-off point. Art historians generally classify works and artists by school: before 1600, the Fontainebleau School and "Manierism"; after 1600, Classicism. However, I felt that the 1600 cut-off point was arbitrary. It seemed more appropriate to establish a continuity between the two schools, with a persistent Bellifontain influence in classicism. This original point of view earned me a double-page spread in *Le Monde* by André Chastel. In support of my thesis, I wanted to provide some evidence.

Francis Ist, wishing to create a new pictorial tradition in France, in the spirit of the revival of Renaissance humanism, invited Italian painters to his court, starting with Francesco Primaticcio, known as *il Primaticcio*. Others would join him, such as Nicolò dell'Abate. Later, French artists such as Toussaint Dubreuil, Martin Fréminet and Ambroise Dubois took over. I've

tried to show the continuity between these painters and those of the classical period, with Poussin, Simon Vouet and Philippe de Champaigne.

The exhibition was divided into three chapters: "The Fontainebleau School", "The Masters of the Classics" and "The Classics".

– The mannerism of the Fontainebleau School is characterized, according to André Chastel, by the "sensual caress of forms, the tender acuity of silhouettes, the adherence of drapery". As a counterpoint, I had highlighted eloquent novelistic sequels, such as Le Tasse's *Jerusalem Delivered*, or poetic ones, such as Ronsard's *Franciade*.

– The "Masters of the Classics" formed the "hard core" of the exhibition. I had selected artists such as François Pourbus, who was admired by Poussin and of interest to Champaigne; Georges Lallemant, who settled in Paris and ran a renowned workshop frequented by Vignon, Champaigne, La Hyre and Poussin; and Quentin Varin, who created important church paintings. In this way, I've managed to "dislodge", so to speak, a number of high-quality transitional artists.

– "The Classics": as the great 17th-century generation has already been the subject of numerous exhibitions, my aim was not to present the main painters of the period, but to illustrate through a selection of works the persistence of the "Fontainebleau imprint", its sinuous elegance. The memory of drawings by Primaticcio and Nicolò dell'Abate, with their measured tension and generous voluptuousness, often guides the hand of Blanchard, Vouet or Le Sueur, and "warms the genius" of Poussin, despite their "classicism".

The preface to the catalog accompanying the exhibition is one of the first texts I devoted, under the title "Reason and Pleasure", to the relationship between "art" and "neuroscience".

In 1993-1994, the "L'Âme au corps" exhibition took up an old idea of Quatremère de Quincy's, namely to "translate" the *Encyclopédie* into a museum, to put it on show, so to speak. The Convention had proposed the construction of a single National Museum of Arts, Sciences and Technics, for educational purposes: "The sight of a collection is above all precepts." The museum was never built. Instead, three independent institutions were created: the Muséum d'Histoire naturelle, the Musée du Louvre and the Conservatoire national des arts et métiers. This museum divide deprived us of an encyclopedic vision of the world. When Jacques Sallois, then Director of the Musées de France, wanted to celebrate the bicentenary of the founding of the three great Parisian museums by the Convention in 1990, he asked me as a scientist and art lover to help organize an event that would recall "the great founding ideas of these museums, which were dedicated to popular education, progress in the arts and the promotion of cultural diversity, of the sciences, and to the encyclopedic dialogue of the various disciplines..." and which would contribute "to the Reunion of the arts and sciences, according to the expression of the Age of Enlightenment".

I wished to be accompanied by a curator from the Musées de France, and suggested Gérard Régnier, whom I had met on the occasion of the "Jacqueline Picasso" donation. Together, we tried to sketch out what such an exhibition might look like. Taking up the Convention's idea in its entirety was too utopian, and we had to make choices. A first sketch, entitled "Art, mirror of science", was too broad and was quickly abandoned in favor of another, more circumscribed theme, which focused on the representation of the human body, and more specifically the brain and its most elevated functions. The exhibition was entitled "L'Âme au corps", in reference to Diderot's *Elements of Physiology*, which aim to link the

"faculties of the soul" to a "bodily quality", "d'énraciner l'Âme au corps" (to root the "Soul in the body"). It was deliberately multidisciplinary, combining scientific knowledge, artistic models and aesthetic theories, as well as beliefs and ideologies. Despite all my scientific reservations about them, it was decided to include specifically mentioned "parasciences" such as mesmerism, spiritualism and psychoanalysis.

The exhibition began with the macroscopic anatomy of the brain, with the *anatomy theater* and everything to do with "l'Homme machine" (the Man-machine) (Vaucanson, La Mettrie), Mesmer and magnetism, and phrenology (Gall). The latter was illustrated by sculptures by David d'Angers, such as the *Portrait of Paganini*, with its frontal humps, and portraits of mental patients by Géricault.

A second section, covering the 19th century and organized around the idea of *evolution*, illustrated the decline of essentialist theories of natural theology to the benefit of Darwinian mechanisms of the evolution of species and the molecular biology of development. I had managed to find original drawings by Cuvier and documents by Lamarck, bearing witness to the birth of the idea of evolution. Also on display was a series of paintings, proposed by Gérard Régnier, in particular lithographs and canvases by Odilon Redon, such as his *Fantasmagories*, clearly inspired by Darwin's work.

To illustrate the next section, entitled "L'Homme prothétique" (The Prosthetic Man), I had managed to bring over some of Cajal's original pen-and-ink drawings from Madrid, enhanced with gouache. They showed Cajal's concern for accuracy in observing each individual neuron and neuronal circuit. There were also documents concerning the chronophotography of the physiologist Jules Marey (1830-1904), which consists in taking a series of snapshots of a rapid



movement such as a horse galloping on a single glass plate.

The final section was devoted to the contemporary neurosciences. "Les Drogues, les Émotions, le Rêve" (Drugs, Emotions, Dreams) celebrated Claude Bernard, who laid the foundation stone for the chemistry of cerebral communications, culminating in the identification of the chemical substances (neurotransmitters) used for signaling between neurons. Several singular paintings were on show, including Léon Spilliaert's *La Buveuse d'absinthe* and Edvard Munch's *Le Cri*, while the final rooms featured works illustrating the theme: "From Madness to Freud", culminating in Fernand Khnopff's *Le Sphinx* and Freud's divan.

The most recent exhibition, "Light in the Age of Enlightenment and today", in 2005, was designed to open a window on an important moment in the history of the Enlightenment of the history of ideas, and in particular the role played by the city of Nancy and the court of Stanislas. I chose to play on the meaning of the word "light", both as a physical phenomenon and in its philosophical sense, "the Enlightenment of an enlightened century", as Voltaire put it. The exhibition took the viewer on a journey from Newton's theories of universal gravitation and the nature of light, through the work of Voltaire's friend and great scientific mind Émilie du Châtelet, the anatomy and physiology of the eye and vision, Diderot's *Elements of Physiology*, Condillac's metaphor of the inner statue... All this was enhanced by magnificent paintings, including Falconet's *Pygmalion et Galatée* (commented on by Diderot in the *Salon of 1763*) and Joseph-Benoît Suvée's *L'Origine de la peinture*.

Three references were highlighted :

- Diderot's *Lettre sur les aveugles*, (Letter on the blind) which takes up the problem posed by Molyneux in the previous century: will a blind man who suddenly regains his

sight be able to recognize two objects - a sphere and a cube - that he previously identified only by touch? One of the exhibition's sections focused on the importance of learning in our knowledge of the world, based on the visual disability that attracted so much attention during the Enlightenment. This included paintings and drawings of famous blind people, such as Pierre Peyron's *Bélsaire recevant l'Hospitalité d'un paysan ayant servi sous ses ordres* (1779), or a terracotta by Clodion depicting Homer bitten by dogs (early 19th century) as well as plates from the *Encyclopédie* depicting cataract surgery. There were also documents illustrating the education of the blind, from Valentin Haüy (1745-1822) to Louis Braille (1809-1852).

- - "A voyage round the world" by Bougainville and its "Supplément" by Diderot": this part of the exhibition addressed the transition from the perceptive process to moral judgment.

Enlightenment philosophers paid close attention to the accounts of travelers and explorers. In his tale, Diderot reminds us that populations with so-called "exotic" mores follow ethical rules that, while different from our own, are in many ways more thorough-going and universalist. To illustrate these texts, I brought in a painting by William Hodge, *War Boats*, depicting an elegant warrior skiff from Tahiti, as well as engravings and gouaches from Cook's voyage, depicting the natives of Tahiti and their customs, and a model of an 18th-century frigate, navigational instruments, herbariums and drawings brought back by naturalist Philibert Commerson (who accompanied Bougainville), and even waxmodelled fruits - the work of Captain Robillard d'Argentelle - preserved under the general name of "Carporama" at the Muséum national d'Histoire naturelle in Paris.

– "L'abbé Grégoire et les Lumières de la connaissance". Born in Lunéville, the already mentioned, Abbé Henri Grégoire was a sworn priest, a member of the Convention and founder of the Conservatoire national des arts et métiers. He supported the abolition of slavery, the emancipation of the Jews and the Declaration of the Rights of Man, and defended the need for education for all, particularly in the sciences, and, as already mentioned, the preservation of the artistic heritage. These "Enlightenments of Knowledge" were illustrated in the exhibition by numerous works, including a portrait of Abbé Grégoire by Célestin François, the *Jeu de Paume Oath* engraved by David, the *Negro Trade* by Géricault and Jewish objets d'art from the Musée Lorrain. Machine washes, taken from Vaucanson's "Portefeuille", showed the importance of technological progress in the evolution of professions and social life.

The aim of the exhibition was to show that, starting from science, we could achieve a humanism that was more open to society, more generous, and perhaps the development of a new Humanist ethics. In short, it invited us to make the transition from science to ethics... A point of view not shared by everyone, but one that deserved to be showcased.

## **8- A NEW VALUE SYSTEM**

*Can we say that art creates new values?*

What we can say is that the epigenetic and social transmission of art generates a complex network of intersubjective interactions (mediated by the brain), which contribute to the social bond through the creation and

contemplation of works of art. This network evolves and builds up gradually. This idea can be illustrated not only by following the succession of artists throughout history, but also by looking at the work of a single artist. How can an artist integrate art history into his or her own creation?

*A sort of recapitulation...*

This relationship between creation and history is illustrated by Picasso's *Les Femmes d'Alger (O. J. R. M.)* (1907). As Hélène Seckel has shown, this painting is reminiscent of *La Vision de saint Jean* by El Greco (1608-1614), *Le Bain turc* by Ingres (1862) and *Les Baigneurs* by Cézanne (1890), as well as Picasso's own drawing, *Le Harem* (1906), all of which set the context and attest the influence of African art, primarily masks, in the birth of Cubism. There is a formal relationship between these various sources of inspiration. There's a kind of composition of forms, as if "bricolées" (tinkered), to use a term coined by François Jacob, that communicates to the viewer's brain a global, original, harmonious (the *consensus partium*) and provocative message. Both aesthetic and ethical, the canvas is an attempt to reconcile cultures. We might well ask whether this paradoxical synthesis of past history with present-day creation is not one of the founding elements of the history of art, and indeed of our cultures in general.

Art history would thus be a way of integrating the past with the present and anticipating the future, both in the artist's mind and in the evolution of relations between artists, as I showed with the exhibition "From Nicolò dell'Abate to Nicolas Poussin ».

Art plays an essential role in society through the production of *relevant* forms, which respond to the virtual (yet real)

landscape of the "subjective expectations" of human societies, thereby helping to connect (*reliere*) individuals within the group. These forms correspond to Poussin's "beautiful ideas" – the *exemplum*. Thanks to its ability to awaken, a work of art can deliver an ethical message that may be universal in scope.

The aesthetic component is present very early in the history of hominization, from the discovery of bifaces, and therefore symmetry, by *Homo erectus*. With *Homo sapiens*, the brain reaches the size and connective complexity of modern man. Art then took off in leaps and bounds. Think of the cave paintings in the Chauvet cave, dating back over 30,000 years. The art of painting had already been achieved....

*Georges Bataille has written some admirable pages on the Lascaux cave paintings, which arouse an aesthetic as well as an anthropological emotion: we are witnessing the emergence of the human. He speaks of these paintings as a "dance of the spirit »...*

The history of human civilization begins with a close proximity, at least in appearance, between the rationality of the first lithic industries and intense artistic activity.

We might think that there's something in man's brain that prevents him, despite the extra-ordinary advances of science, from having peaceful relations with his fellow human beings. There's a kind of evolutionary imbalance - I've already mentioned this, but I'll insist on it - a kind of "incompleteness" in the biological evolution of the *Homo sapiens* brain. In support of this thesis, it can be argued that the limbic and subcortical territories involved in emotional and social life did not particularly develop during hominization. On the contrary, there was a meteoric expansion of the neocortex, which may

have caused the imbalance in question between cognitive capacity and a happy social life.

This alone justifies the establishment of strong ethical rules and fair institutions.

*The question is: should we retain the value system that prevails today?*

This value system is that of the market economy, on a global scale. The basic value is the pursuit of profit. An American philosopher and economist, John Eustice O'Brien, whom I met by chance in Paris, writes the following (*A Critique of Rationality*, 2016) : "We identified what appeared to be a serious gap in the rationalist world's ability to explain processes related to social cognition [...]. From this assessment we felt strengthened in the fundamental assertion that 'aesthetic consciousness', as we conceive it, establishes the predisposition to meaning necessary for the continuous unfolding of the intersubjective field of action within which social relations are possible." He adds: "More than in the form of a metaphor, is it justified to consider the state of society and every individual life within it as works of art?"

The question raised is that of a new system of values based on this "aesthetic consciousness". Ricoeur spoke of the "acceptability" of ethical rules, and of the fact that they can be rejected, even when they appear justified in terms of a certain rational humanism. It seems to me that, through its ability to awaken and strengthen social bonds, the *exemplum* delivered by the work of art could, as O'Brien suggests, contribute not only to the dissemination of the ethical message, but also to its acceptability. In short, art could contribute, with its symbolic imagination, to the establishment of a more "acceptable" system of ethical regulation.

There have been few attempts to create a supranational aesthetic - the Convention, with Louis David, had formed the project of a "national" aesthetic in place of a religious one. So why not entertain the idea of one day instituting an aesthetic common to the inhabitants of the planet that would carry a new system of values, thereby making them acceptable?

*Without accusing you of being a Platonist, we might wonder whether this analysis doesn't result in a new conjunction of the Good, the True and the Beautiful... The Beautiful and the splendor of the True!*

Why not? For me, this is not a Platonist position, as I've discussed at length: their pro-active *conjunction* stems from their common cerebral origin<sup>13</sup>. What is certain, in any case, is that our societies have not sought to create an esthetic social consciousness which would replace the established value of maximum profit with that of a *consensus partium* on the scale of the world and its institutions.

Michel Foucault recommended making one's life a work of art, so why not make it our wish that humanity as a whole should become a work of art?

## Conclusion

### The tree of knowledge

The myth of the "Garden of Eden" in *Genesis* mentions the presence of two trees: "The tree of life in the middle of the garden, and the tree of the knowledge of good and evil [...]. Eve then ate a piece of fruit from the tree of knowledge of good and evil, and gave it to her husband." Then "both their eyes were opened, and they knew that they were naked".

The parable can be interpreted as follows: out of blind obedience, their eyes were opened to understanding the world. We know that exploration of the world began long *before* *Homo sapiens* appeared on our planet. The first stone tools are associated with the remains of *Homo habilis*, bifaces with those of *Homo erectus*, while *Homo heidelbergensis* practiced the cult of the dead, a possible sign of religious sentiment. This exploration continues, with the discovery of the universe of living beings and the starry sky. As hunters, man gradually began to classify, plan strategies and attempt to understand both the physical world and social life. He established knowledge, linked it together and created a tree of knowledge that merges with the tree of life, which becomes above all a tree of survival in a world that is on the whole hostile to it. It's interesting to note that these early myths assign a central place to the tree. Not so much as a plant species, but as a branching



structure rooted in the reality of the soil and continually giving birth to new branches. This should be seen as a metaphor for the development of knowledge in the form of multiple, open and limitless arborizations: the tree of knowledge.

Francis Bacon, in his work *De dignitate et augmentis scientiarum* (On the dignity and increase of knowledge, 1605), sketches out an initial definition of the scientific method, which is empirically based on the search for facts, the observation of invariant forms. "True science is the science of causes", he wrote. On this basis, he drew up an initial classification of the knowledge of his time, pointing out its shortcomings. He divided all types of knowledge into three general groups: history, poetry and philosophy. He did so on the basis of his own understanding of the mechanisms of information processing - memory, imagination and reason, respectively. The *Encyclopédie*, with its seventeen volumes of text (1751-1772), continued Bacon's enterprise. The "*Discours Préliminaire des Éditeurs*" ("Preliminary Discourse") ends with a double folio fold-out table, presenting *Le système figuré des connaissances humaines*, directly inspired by Bacon. The said system takes the form of a tree whose three branches stem from the Entendement and are intitled "Memory" (history: sacred, civil, natural, including celestial history), "Reason" (philosophy: metaphysics, human sciences, including logic, morality and natural sciences, of which mathematics is a part), "Imagination" (secular and sacred poetry). In the article "Encyclopédie", Diderot emphasizes the collective nature of the work, combining different disciplines represented by "men bound by the general interest of the human race and by a feeling of mutual benevolence". He insists that, while "in scientific treatises, it is the sequence of ideas or phenomena that directs the progression", in the *Encyclopedia*, "the coordination of the articles [...] will be indebted to the *cross-*

*references*, the most important part of the encyclopedic order". The notes that accompany each article in the *Encyclopédie* weave links with other articles, creating for the first time a unique and open "knowledge network". Diderot thus introduced a secularization of knowledge that caused him a great deal of trouble. One fact is of particular interest to the neuroscientist: the table in the "Preliminary Discourse" distinguishes three fundamental constituents of human understanding - "memory, reason and imagination". These represent the most eminent features of human brain function, the common trunk of which is conscious processing (*see* Chapter 7). The tree of knowledge is rooted in the very nature of the human brain. The unity of knowledge has its origins in the unity of the brain. Johann Sulzer, in a supplement to the *Encyclopédie* (1776), simply stated that, while there is a unity of knowledge mentioned in the "Preliminary Discourse", there is also a diversity of "modes" of knowledge, including the true, the good and the beautiful. All are relevant features of human brain activity, and must be analyzed in concomitant manner (Chapters 8 and 9).

*You often refer to certain Greek atomist thinkers before Socrates...*

The thesis I wanted to defend in these interviews is in fact in the tradition of the pre-Socratic philosophers, but also Spinoza and Diderot, and secular humanism, for whom natural laws explain the nature of the universe and, in particular, how the brain works. The idea that there is a common set of brain processes that explain the production and diversity of ways of knowing becomes plausible in the light of recent developments in the neurosciences of cognition (chapter 6). They offer opportunities, albeit still fragmentary, to build concrete

"bridges" between the so-called "neuronal" and the "mental", and to establish a reciprocal cause-and-effect relationship between structure and function. The nervous system is not a single-level machine, like conventional computers. It is highly complex, combining several "interlocking levels of functional organization" and strong "parallel architectures" (Chapters 5 and 6). I have tried to show that the higher functions of our brain - consciousness, reason, emotion, aesthetic efficacy, moral judgment, value systems - might be described in terms of brain activity.

No one can deny that what was once part of the "mysteries of life" is now interpreted in molecular terms. This is not to be regretted, as "precision medicine" is an immediate consequence, among many others - it is also responsible for many drugs... It is to be expected that, in the years to come, the "mysteries of the brain" will also be interpreted in terms of neuronal and glial activities, provided, of course, that we take into account the multiple interactions of the human brain with its physical, social and cultural environment, past - with history - and present - with postnatal development. We have discussed this at length (Chapters 5, 8 and 9). This is neither reductionism nor hegemony of neuroscience. Indeed, the human "mind" should not, as a matter of principle, escape scientific study. We are confronted with the facts, as I stressed in the conclusion to *The Man of Truth* : "A better knowledge of man and humanity will make it possible to value the diversity of personal experience, the richness of different cultures, the multiplicity of their conception of the world", fostering "tolerance and mutual respect based on the recognition of others as other selves..". (chapter 8).

*In André Comte-Sponville's Dictionnaire philosophique (PUF, 2021), there's an entry that directly concerns you, entitled "Le démon de Changeux". By analogy with the "devil of Laplace", the author proposes a fiction, that of, and I quote: "A gifted neurologist who, in ten thousand years' time, could know everything about the brains of his contemporaries, to the point of reading them with an open book." Let's imagine," he says, "that he observes the brains of two individuals: in the first, he sees that Mr. X is convinced that 10,000 years ago there was a mass extermination, known as the Shoah. In the second, he reads that Mr. Y is convinced of the opposite. Which of the two is right? To decide, "the neurobiologist will have to do something other than neurobiology, in this case history". A. Comte-Sponville, who is not at all hostile to the neurosciences, concludes that "neurobiological knowledge of a true idea can know everything about it, except its truth". In a nutshell, "Changeux's devil can know everything about our values except their value. What does this objection inspire in you ?*

Readers need look no further than Chapters 8 and 9 to realize the extent to which "value systems" play a key role in my vision of the world as a neurobiologist. These "value systems", produced by man's brain in society over the course of history, form the foundations of all ethical and scientific reflection. The "Changeux devil", as A. Comte-Sponville presents it, is little more than a "paper tiger"...

*Shouldn't the voice of scientists be heard more?*

Yes, and if their voices were more concerted, they would be better heard. The reflection begun at the end of chapter 9

deserves to be continued. It is precisely about the responsibility of scientists for the future of mankind; yet scientists too rarely speak out in public. Around me, I can think of André Lwoff, who has loudly declared his affiliation with the Pugwash<sup>1</sup> movement, and Jean Dausset, who is at the origin of the Universal Movement for Scientific Responsibility. This responsibility is well expressed by the German-born philosopher Günther Anders, in his book *The Obsolescence of Man* (1956). He clearly saw that scientific and technological progress is at the service of a "civilization of leisure, in which machines would have taken all the drudgery out of human existence, and media would replace individual reflection". He notes that, after Hiroshima, the gap widened between the ability to produce science and make new technologies and the ability to represent the end product of this manufacture. He questions the reasons for our "aveuglement face à l'apocalypse" (blindness to the apocalypse). As a result of the division of labor and our inability to control the exponential growth of the knowledge, man runs the risk of no longer recognizing his actions. There is a "Promethean gap" between our faculties of fabrication and imagination. Anders formulates an imperative: "Expand the limits of your imagination to know what you're doing."

In *Hiroshima is everywhere* (1995) - his correspondence with Claude Eatherly, the pilot of the weather reconnaissance plane who gave the go-ahead before the first atomic bomb was dropped - he develops a reflection on the inability of our brains to measure up to the destructing power conferred by technology. When it comes to 200,000 deaths, it becomes impossible for anyone to feel pain commensurate with the scale of the massacre. Such is the case today with the war in Ukraine or in Israel-Gaza, with its daily toll of hundreds of deaths, the result of the technical development of new missiles

or new fragmentation bombs.

In his book on the Vietnam War, which is still relevant today, the author also blames "the industry, which does not produce weapons for wars, but provokes wars for weapons".

Günther Anders' despair, however lucid, does not detract from the urgency of exhortation and action. He quotes Marx's famous motto from *The German Ideology*: "Philosophers have only interpreted the world in different ways; what matters is to transform it". At the end of his life, he even went so far as to justify the use of force. In chapter 8, I mentioned the concrete possibility of creating a World ethics committee, through the United Nations, which would have the means to enforce its recommendations.

More importantly, this broadening of the limits of our imagination, which Anders calls for, cannot be developed in isolation.

This means training in the latest research findings, ongoing multidisciplinary secular education, and mutual information for the general public and the political world, both nationally and worldwide. Existing institutions need to be reorganized. They will ensure that scientists keep each other and themselves informed, as well as political leaders, in situ and during their training.

*If the atomic threat is more present than ever, as is the vertiginous degradation of our environment, what are we to think of the ongoing development of brain sciences and artificial intelligence?*

There is much to look forward to from the application of brain sciences to the development of new drugs and new ways of dealing with the brain pathologies that plague so many women and men (chapter 4). We can also look forward to new

educational procedures and more harmonious social living conditions.

What can we say about the creation of an “augmented human being”? Do we want to "immortalize" the human being, giving way to a world of ultra-performing robots and irresistibly alienating media? Let's systematically and concretely return to our values. An exhortation to reflection and action is called for...

Let's join forces - and our imaginations - to strengthen and update the tree of knowledge on which our humanity rests!

## Notes

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CONCLUSION (p. 270-277)  
THE TREE OF KNOWLEDGE

1. The Pugwash Movement, founded in 1957, brings together leading figures from the worlds of academia and politics, and aims to reduce the dangers of armed conflicts and seek counter-measures to threats to global security.

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J.-P. Changeux





## Glossary

- Acetylcholine* : One of the oldest known neurotransmitters, whose effect at the nerve-muscle junction is blocked by curare.
- Amino acid*: Organic molecule with amine and acid functions, which is a component of proteins, but also performs other functions, such as neurotransmitter. Example: glutamic acid, aspartic acid,  $\gamma$ -aminobutyric acid or GABA.
- DNA or deoxyribonucleic acid* : the material carrier of heredity, DNA is composed of a linear sequence of nucleotides, themselves made up of an organic base, a sugar (deoxyribose) and phosphate. In most cases, two complementary DNA chains are wound into a double helix.
- Affinity* : Describes the strength of a non-covalent interaction between a biological macromolecule, amino acid or protein, and a ligand that binds to a site on its surface.
- Cortical area* : Delimited area of cortex, characterized both by its cellular architecture and its function. Classically, we distinguish between *primary* sensory *areas* and secondary motor areas involved in sense organ projection and motor control respectively, and *association areas* outside them.
- Aphasia* : Deficit in the production and/or comprehension of spoken and/or written language due to a brain lesion.
- RNA or ribonucleic acid* : DNA-like linear macromolecule involved in the decoding of DNA genes into proteins.
- Axon* : A single extension of the nerve cell where nerve impulses travel from the soma to the end of the axon; it is the nerve cell's exit cable, ending in an arborization of nerve endings that contribute to the formation of synapses.
- Ion channel* : place where ions pass through the cell membrane. There are several categories of channels, defined in particular by their selectivity for ions and their sensitivity to electrical potential. The propagation of nervous influx involves sodium-selective channels.
- Category* : The smallest group of cells of the same morphological and biochemical type.
- Pyramidal cell* : Major category of neurons in the cerebral cortex whose axons emerge from the cortex.

*Cerebellum* : An ancient structure of the hindbrain specialized in motor coordination. The cerebellum contains only a small number of neuron categories, including Purkinje cells and grain cells.

*Corpus callosum* : large bundle of nerve fibers linking the two hemispheres.

*Cerebral cortex or neocortex* : layer of gray matter that forms the lining of the cerebral hemispheres, and is highly developed in mammals.

*Dopamine* : Catecholamine neurotransmitter implicated in a biological theory of schizophrenia. *Reticular formation*: Set of nerve fibers mixed with cell bodies, located in the ventral part of the brain stem, from the spinal cord to the thalamus. It is made up of discrete groups of neurons, the best-known of which contain catecholamines such as noradrenaline or dopamine.

*GABA -  $\gamma$ -Aminobutyric acid* : amino acid acting as an inhibitory neurotransmitter.

*Gene* : DNA segment with a defined function. Structural genes code for proteins. Regulatory genes regulate the activation (or locking) of structural genes.

*Genome* : All the genetic material (DNA) in a cell.

*Genotype* : genetic makeup of an individual.

*Glia* : A group of so-called "glial" cells, distinct from nerve cells, which play a supporting and nourishing role.

*Hippocampus* : Circumvolution located in the antero-medial region of the temporal lobe, resulting from the internalization, in mammals, of archaic cortex developed in reptiles and primitive mammals. It is not composed of six layers like the neocortex.

*Hypothalamus* : Set of twenty-two small nuclei located in the forebrain below the thalamus nuclei, playing a vital role in "vital" behavior despite its small size: eating, drinking, sexual behavior, sleep, temperature regulation, emotional behavior, hormone regulation, movement, etc.

*Ion* : atom or molecule carrying an electric charge.

*Isogenic* : Refers to individuals with the same genotype, such as identical twins.

*Ligand* : An atom, ion or molecule with chemical functions enabling it to bind to one or more central atoms or ions.

*Cell membrane* : A continuous film of lipids and proteins that delimits and envelops all cells, including nerve cells. Its proteins include channel molecules, pump enzymes and neurotransmitter receptors.

*Mutation* : Spontaneous or induced heritable change in the structure of genetic material or DNA.

*Neuron* : Nerve cell comprising a cell body or soma, containing the nucleus,

and two types of extensions or neurites: dendrites, which converge on the soma, and the single axon, which extends from it.

*Neurotransmitter* : Chemical substance involved in nerve signal transmission at the chemical synapse. There are several dozen neurotransmitters in the brain.

*Operon* : Sequence of genes whose function depends on a regulatory protein. It comprises a coding sequence, preceded by a promoter site and an operator site. The lactose operon in *Escherichia Coli* regulates the production of lactose-degrading enzymes.

*Phenotype* : Set of apparent and observable characteristics of an individual, resulting from the interaction between the genotype and the environment in which development takes place.

*Post-synaptic* : Located on the "posterior" side of the synapse, i.e. in the dendritic (muscular or glandular) part of the synapse.

*Pre-synaptic* : Located on the anterior side of the synapse, i.e. at the axonal nerve ending.

*Protein* : Fundamental components of the cell, proteins are large molecules, or macromolecules, resulting from the linear linking of a large number (from 20 to sometimes more than 1,000) of amino acids. The sequence of these amino acids (chosen from among 20) characterizes each protein species. For example: enzymes, receptors, channel molecules and antibodies are all proteins.

*Receptor* : The term refers to two different entities: on the one hand, the sensitive cells of the sense organs (e.g. the cones and rods of the retina), and on the other, the molecules that recognize neurotransmitters or hormones (e.g. the acetylcholine receptor).

*Serotonin* : Neurotransmitter derived from the aromatic amino acid tryptophan.

*Singularity* : Distinguishes each cell belonging to the same category by the exact repertoire of connections it establishes and receives.

*Soma* : Cell body of the neuron, containing nucleus and cytoplasm as well as mitochondria and multiple biosynthetic apparatuses.

*Synapse* : Junction between neurons, but also between neurons and other cell categories (muscle cells, glandular cells). At the synapse, the cell membranes of the axonal terminal and the enervated surface are juxtaposed, but do not fuse. A distinction is made between electrical synapses, where electrical signals propagate directly, and chemical synapses, which use a neurotransmitter to cross the intercellular space.

*Limbic system* : set of primitive structures important for controlling affective behavior, including the hippocampus, septum, amygdala, olfactory bulbs,

etc.

*Thalamus* : Set of forebrain structures on which the cortex rests; pathways entering and leaving the cortex usually establish a relay in the thalamus.

*Brain stem* : Major part of the brain, extending from the medulla oblongata to the thalamus.

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## Honours and awards

### Honours

Awards Grand Cross of the Legion of Honor.

Commandeur de l'Ordre des Arts et des Lettres.

Foreign member of the Deutsche Akademie der Naturforscher Leopoldina (1974).

Foreign Associate of the US National Academy of Sciences (1983).

Foreign member of the Royal Academy of Sciences of Sweden (1985).

Member of the French Academy of Sciences (1988). Founding member of Academia Europaea (1988).

Foreign member of the Accademia Nazionale dei Lincei (2010).

*Doctor honoris causa*: Universities of Geneva, Switzerland, 1994; Stockholm, Sweden, 1994; Liège, Belgium, 1996; The Hebrew University of Jerusalem, Israel, 2004 ; University of Chile, Santiago, Chile, 2016; Weizmann Institute, Rehovoth, Israel, 2016; Monash University, Melbourne, Australia, 2017.

### Awards

Price Gairdner Award, Toronto (1978).

Richard Lounsbery Award, National Academy of Sciences (USA) and Académie des Sciences (1983).

Wolf Prize for Medicine, Jerusalem (1983). CNRS gold medal (1992).

Louis-Jeantet Prize for Medicine, Geneva (1993).

Balzan Prize for Cognitive Neuroscience (2001).

The Olav Thon International Research Award in Biomedicine, Oslo (2016).

Albert Einstein World Science Prize, Hong Kong (2018).

Erasmus Medal of the Academia Europea (2022).

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