On Doing Science: A Speech by Professor Antonio Coutinho[1]

It is a great honor for me to be chosen as patron for the first "promotion" of the PGDB.[2] For some time, I hesitated and very seriously considered the alternative of declining this honor. *Vanitas, vanitas*… I had thought that the PGDB had nominated me, but I finally understood that it was the whole PGDBM[3] that was being honored. I am acting here, therefore, as a mere PGDBM representative, for we would be too many to stand behind the podium. And I am certain that I speak in name of all of us at the PGDBM in entrusting you, students and Direction of the PGDB, with all our support and confidence. We are sure that the PGDB can only be better than the PGDBM and we are proud of being thus associated with it, of "patronizing" it, if I am allowed. Hence, the reputation of the Gulbenkian PhD Program – whatever its acronym – can only be strengthened by the quality of your work, students and staff, such that "belonging in the Programme" will increasingly be a mark of excellence and of a serious stand in science.

When the PGDBM started, my primary (only ?) motivation was a matter of justice: there should be no reason why Portuguese students had less

1 Excerto de discurso do professor Antonio Coutinho aos doutorandos do Instituto Gulbenkian de Ciência. Os editores da *Economia* agradecem ao Professor Coutinho a autorização de publicá-lo.

2 Programa de Doutorado em Biomedicina do Instituto Gulbenkian de Ciência, Oeiras, Portugal.

3 Programa de Doutorado em Biologia e Medicina, antecessor imediato do PGDB.

opportunities in science than they would have if born in London, Paris or New York. They are not better or worse than their "age-matched controls", and should have equal chances of contributing to our common future. Hence, the first thing we had to ensure in the Program was equalitarian access, that interested students could simply come up "com a cara e a coragem" to manifest their interest and compete for admission, on equal basis with all others. The Program should then provide all we could to help them find their own way. These were the principles of the PGDBM, where we anchored individual freedom of choice and full responsibility, and from which we automatically gained our greatest asset. This is, beyond doubt, individual diversity. I know that the same principles are kept in the PGDB, and this is one of the many reasons to fully endorse it. We care about the Program, but the Program exists to help individuals to find their own ways. For everything that is done, all the headaches and worries, disillusions and disappointments, everything would have been worth it, even if it had been for a single student. Very fortunately for all of us, there are now nearly 140 who are on the way to find their own ways. This is the greatest reward I can think of, even greater than being the patron of the PGDB's first year.

Science and what is important about doing it.

In his talk, as always, Dan Holmberg was very kind to me, and certainly exaggerated my contributions and qualities.[4] I must forgive him for that: we have been looking at each other growing old and wise for nearly 22 years, but this is obviously not enough. I owe many things to Dan, not the least the fact that, not being my first student, he was the first to give me a "scientific grandchild". Some of you know how important this is. In addition, for completely independent reasons, a student of the PGDBM will actually be my first "great-grand-child in science", for she is completing the Thesis with one of Dan's "children".

4 O Professor Holmberg foi orador anterior ao Professor Coutinho nessa cerimônia, sendo responsável por introduzi-lo à audiência.

Within this familial context, I felt it more appropriate that, rather than telling you about the science I did, I would try to convey to you what I have learned on the way to go about doing it. You will forgive me for the paternalistic tone that my words will often have. This is, however, only a matter of age, and it reflects no intention whatsoever that you take my own way as an example, for you will have to find your own. This will obviously be a very personal view of things: as Pessoa wrote "what we see is not what we see but what we are". But I have learned with my father and with his father that a man is what he does and not what he says, even less what he owns. Juan de Mairena – whom you should all read – says, "a man needs to be what he is, to do what he does". And, as if this thought was not sufficient to open our eyes, he adds "and vice versa."

I came into science for several reasons, but the easiest to identify are "the military". It would seem that scientists, biologists at least, are little inclined to shoot other people. In this very moment, a symposium is being held in London to honor Martin Raff, a great scientist of our times, member of the Scientific Advisory Board of the Gulbenkian Institute. Martin was a Canadian MD in the US during the Vietnam war and his refusal to join the shooting chased him to Europe … where he was to become a scientist. Somehow, it would seem that we appreciate life enough to respect it above many other things, including "causes" that, at some point in time, do convince the majority of people that they should not look at the means to reach the solutions they want. Sadly, only 1% or so of my male contemporaries did refuse to fight the colonial war. To me, the refusal had a simple solution that was to leave the country and, therefore, to give up medical practice and become a "mouse doctor". This period brought me a great admiration for the scientific community. I wrote to 3 great scientists, whose names I had seen in papers, explaining that I was a young and ignorant MD decided to start in science. They were immunologists or close enough to it, for my brief life as a MD had led me into this interest: John Humphrey, George Klein and Goran Moller. I have rarely been as surprised as when I got kind replies from all three of them saying that I was welcome to join their laboratories. What a difference from the small but apparently busy "bosses" of today, who closely scrutinize their students for the best potential performance !!! Of course, times were different, but

I would be surprised if those three would do it differently today. In other words, the main difference in "times" is actually a difference of the individuals who make up for the scientific community and ensure its values.

I could not possibly have entered science with a better mentor than Goran Moller. With him, I learned everything important. Many of you know my attachment to Russell's Liberal Decalogue: I learned with Goran most of the commandments, before I have read it, as well as some of the most fundamental of Blake's prophecies – another of my "meditation" preferences. The first (and most important) of Russell's commandments: "do not feel absolutely certain of anything" became obvious to me from my first conversation with Goran. I asked which books to read in order to learn immunology, and was told that the best would be the proceedings of the Brook Lodge Symposia; "you know, they print all the discussions at the meeting and thus you can quickly find out the different opinions about the problems, and things that good people do not take seriously". I was not prepared, from my University education, for this fundamental notion that science grows in the domain of doubt, in contrast with religion or technology that exist in the domain of certainty. Actually, it took me months to accept that many papers printed in the great journals were wrong.

After I had read those few volumes and thought I had some idea about the subjects, I went back to Goran, only to start learning the essence of science education. I asked for "what should I do" and got a straight answer "whatever you want". I insisted, of course, that I did not know what to do, not even the questions to ask, that I needed a "project" to start working; only to hear "fine, you go around, talk to people, read, come back to discuss whenever you want, and you will soon find out what you really want to do". Scared and insecure, I dared to insist that I would prefer to have a "project" that, coming from him, would certainly be appropriate, feasible and excellent. Goran replied what I heard several times later, and my students heard from me (and I hope yours will hear from you): "I am not here to teach technicians; my job is to educate scientists". His perception of the strict requirement for individuality and originality in serious science was so present that I am certain he would have interrupted several of this week's presentations, namely all of those who started with the sentence "our lab is interested in …". Goran would say, "I do not want to know what your lab is interested, but what YOU are interested".

This attitude of extreme protection of the students individuality, and of serious concern with her/his education into independent thinking, seems so alien to today's practices of pure exploitation of students as "hands" or "risk capital for doubtful projects", that we tend to think once again that "times are changed". And again I say: perhaps not so much, for already then, there were certainly many of the "big names" that would do it precisely like most today. Simply, I was very lucky in ending up in Moller's lab. "Some are born to sweet delight, some are born to endless night", Blake says in a beautiful sentence that gets repeated over again in one of Jarmusch's movies. Autocratic "technician-teachers" often argue that their attitude is imposed by the financial pressures on the research: it is a lot of "waste" to let students do whatever they want, for most of it is useless … for the lab and for themselves. But is it useless for the student ? Is it so certain that a few lost experiments represent a high price for fostering an independent, original mind ? Is it not a much higher cost to end-up with lots of "pseudo-scientists" who do just the same as everybody else, multiplying the real waste of parallel investments, experiments, results and "back-to-back publications" ? Is there a price for original, independent thinking ? Is there a price for diversity ? Is diversity ever expensive ? The only serious argument, I believe, concerns the straight jacket of time into which European fellowship systems force PhD students. As well as PhD Programs … and I do *mea culpa* in public, for I often have reminded you that you had only 3 years for your Thesis work. Even a good supervisor, knowing that the student has exactly 3 or 4 years to complete a Thesis work, will hesitate before telling her/him "whatever you want". Unless the supervisor trusts the abilities of the student, trusts that the group is rich enough to provide for the individual maturation and for the solution of all the problems that will come up, trusts that one head (the supervisors'), whatever exceptional it is, will always think less and less well than a few or many. When the PGDBM started, I was convinced that the "ideal career" for you was to produce a Thesis in Europe and go for a post-doc in the US. Along these years, I did change my mind for a variety of reasons and following a number of your examples. (Goran Moller also used to say, "if you are not able to change your opinion, all you will ever learn is technique"). Today I think that a PhD education in an American lab is superior to that in equivalent European groups. The US system does "protect" students. The pressure for "production" in American labs is on the shoulders of "post-docs", releasing the students from this immediate obligation and opening a space of individual freedom. In addition, there is a tradition that excellent students might take 5, 6, 7 years to complete a PhD. By transferring to the post-doctoral periods all the pressures for individual achievements in the search for "positions", studentship is the time for preparing, for "education and maturation". In addition, European labs are often smaller, with only a PI and a few students who cannot but be the (only) "work-force" in the group.

Coming back to my own experience, I was indeed lost for 8 months: I worked 16 hours a day, produced large amounts of data, but could use none, absolutely none, in my Thesis. But I discovered what I wanted to know and how to find it out, such that, in the next 16 months, I could produce a Thesis with several papers published in Nature, J Exp Med and other good journals. More importantly, shortly after my Thesis, I was invited by Goran to write a review article to "the" review series of the time, of which he was the Editor. Adding that we should each write our own review, as it was obvious that we did not think the same about several important aspects of the problem.

I learned with Goran Moller many other essential things about science and its practice. For example, originality that often cannot be but heterodoxy. Russell's 7th commandment says "do not fear to be eccentric in opinion for everything that is now accepted was, once, eccentric". This has a price, of course, for the scientific community is conservative and reactionary: those in power positions – who referee our papers and decide on our grants – are in that position because they contributed to the core of the discipline, and they will always have difficulties to accept youngsters who come to falsify, bypass or minimize their contributions, thus questioning their position. *Vanitas, vanitas* … Originality also requires persistence and solidity of convictions. Blake's prophecy says, "if the fool would persist in his folly, he would become wise", which is just another way of reciting Russell's 7th.

Goran Moller is radical and sees the world in black & white. I learned that, most often, this attitude helps to see things clear. Goran had, at that "pre-PubMed and -BioMedNet time" and of no computers in the lab, a fantastic system to classify reprints and papers: he would read everything published by people he had in a "good" list, and would refuse to read anything published by scientists in the "bad" list; otherwise, he would glance through the journals and read whatever seemed interesting. Blake also wrote, "never the eagle lost so much time, as when he submitted to learn from the crow". Interestingly, some of the people in the "good list" were people with whom he would never or rarely agree. As he put it, however, "he is always wrong, but he thinks". Goran systematically encouraged us to listen carefully to one of our most active opponents; after some years, I came to realize that the latter used to say that "it is better to be clear than right" and, in the extreme argument, would throw on the table "please, do not confuse me with facts". Russell's 4th goes "do not ever discourage thinking, for you are sure to succeed".

Last but not least, Goran Moller also has another of the most important virtues of a supervisor and mentor: <u>generosity.</u> A few months after I defended my thesis, I passed public exams for "Docentur" (the equivalent in Swedish Universities to "Associate Professor", I guess), and Goran provided me, on a silver plate, with a position, a technician, and one of his own students. I had a group, and life seemed to be straight and easy all the way to the horizon. Nevertheless, having passed to give a seminar at the Basel Institute, I decided to accept the proposition of Niels Jerne to move to the Institute. I now know how it feels when a very close collaborator in whom we had invested all we had, decides to leave for other adventures. All the more so, as I was a student that had been formed from scratch by Goran, and as I left for no reason other than looking for new environments, interactions and challenges. I had everything that anybody could hope for, but rejected it all, not even realizing that it probably felt bad for Goran, and that I should have apologized to him. Yet, Goran understood, I am sure, and even encouraged me and helped me with the move and with many a difficulty in Basel. What a tremendous difference from some of our "small supervisors" of today, who take it for granted that the "investment" in the education of students and collaborators must be "paid back" (to them, of course) in the form of years of hierarchical "slave work" in their ridiculous "courts". More, when some 5 years later I decided to come back to Sweden to open a new department of immunology that would obviously be competing, for resources and relevance, with Goran's own department, he was the first to support the project and to help in any way he could. Today's science would certainly be different if there were more like him. I hope that Goran feels proud for all my 25 PhD students, for you as well, and for all others whom you will help to find their ways. He did show us how this is done and my own contribution is limited to the mistakes that were made.

Moving to the Basel Institute was to come to the center of the world. And to be close to Niels Jerne. Niels and Goran shared many of their virtues and the opinion on the way science should be done. But with a different style, at least in some details. Jerne was older and enjoyed, or at least used to, surprise and provocation as a strategy to get his ideas through; but he talked from the high stand of being the father of modern immunology. Deservedly so, as he has introduced Darwinian principles in the field, against an overwhelming majority, and when it seemed impossible that his theory could possible be true. Perhaps then, by the end of the 1950's, Jerne was like Moller when I met him, who could not help it but being provocative, for his ideas were truly novel and frontally against the establishment. Jerne told me once that, as he submitted his seminal 1955 paper to PNAS, he traveled through the US giving the corresponding seminar. "Hundreds of colleagues listened to this", he said, "some voicing their opposition, most others not, but I am certain that only one (in New York) understood the relevance of what I was talking about".

Jerne also gave the absolute priority to intellectual work; in his Nobel speech, he stated that "science is more than mixing things in test tubes". To be clear in your mind, to define the questions you have, are the important requirements for a scientific approach. He repeated often that "the first thing to know is what you want to know", and the stories of Max Delbruck that he enjoyed most to report were either concerned with clarity of mind, or else, with making fun of biochemists. Jerne had a very strong sense of "school", often referring to Niels Bohr and Delbruck, and to others who had influenced his thinking. I cannot resist to transmit to you one of his stories: once in the discussion of a seminar of Delbruck on Dictyostelium, Bohr has attacked a biochemist who was concerned with the purification of light-sensitive molecules; Bohr came up with the fantastic statement that "what a stupid question; the interesting thing to discuss is the biological phenomenon, for nature will provide the molecules".

For Jerne, science was supposed to occupy all your thoughts or, rather, the question you had could not but occupy your mind all the time, even when thinking about other things and going about life in all sorts of occupations. In the book that was prepared for the anniversary of Delbruck, he writes on the influence of Kierkegaard's philosophy in the genesis of his immunological ideas, and how he came to the central notion walking over a bridge in Copenhagen. When a journalist asked him how he had come to that idea that gave him the Prize, I heard him replying "thinking about it all the time". But I knew that he thought about all sorts of other things, a very cultured man, versed in classics as in some of the latest fashions of contemporary literature. His bench neighbor and experimental partner in Caltech – Gunther Stent, who turned to philosophy at later years of his career, gave a speech at Jerne's 80th birthday party in Geneva, precisely on the interpretations of Kierkegaard that Jerne had produced in various texts. Even here, however, he enjoyed to express "surprising" opinions, in order to mark his individuality and uniqueness, I would think. In a manner that, as Cioran says of Joseph de Maistre, "raises the smallest difficulty to the dignity of a paradox". When Eco stopped writing extremely boring books in the "dead-end" subject of semiotics and became a most popular favorite with "Il nome de la rosa", I heard Niels telling that he had managed to read only as far as page 79. "Very boring. I thought first that it was because of the German translation, but then I read the English, the French and the Danish, and I never got passed page 79".

Jerne also saw the world in black & white, entirely ignoring whole areas of immunology that he simply did not consider relevant for his own thinking. Less relevant things just get your thoughts away from the essentials. On his working table in the office, he would keep a few journals open; after some time, I discovered that these would be open in the very same page for successive visits of mine. I then confirmed with other colleagues that they were always open on those pages that had intrigued him for a result, or a statement, or a question. In his discussions, we could talk about many things, science and otherwise, but sooner or later, the incisive question or comment on his current concerns would come up. Systematically. "Thinking about it all the time", of course. When I asked for his advice on whether or not I should take a position at the University of Umea, Jerne had no doubts that I should: "Here in Basel there are lots of excellent immunologists, and every one has a set of questions to which you are exposed and on which you get also interested and spend your mind on them. It is a good thing that you get isolated with your own questions, such that you can better care about them". At the time, this actually reminded me of Goran Moller who has always claimed that "good places" or "bad places" do not matter, but good and bad people do. If a good person goes to an unknown place, it will make it to be known rather quickly, but if a bad scientist goes to a well-known place, nobody will even notice that. People make the places, not the other way around.

Jerne's advices were three: first, find out what you want to know; second, think about it all the time; finally, find the "most acute continuation". As he said, "The good scientist is like a chess player: it is useless to memorize all the classical openings and mid-games; the important thing is to find the most acute continuation." He was absolutely inflexible with the quality of experimental systems and results, and many of us learned from him the importance of quantitative thinking in Biology: how many cells, how many molecules, which turn-over rates... but not "half-lives" that he insisted should be kept to physics. Like Goran, he was merciless with "toilettage" of data, let alone cheating. With Jerne, I learned the fundamental importance of "organism-centered biology". Molecules and cells are necessary but what we really want to understand is "the system" in its organization and integrity. I had thus the privilege to move from the influence of Goran – concerned with cells and molecules (of the system, nevertheless), to Jerne, who was concerned with the system (and thus with the necessary cells and molecules that "nature provides"). I could therefore very well understand the discussion between the Great Kahn and Marco Polo that was invented by Calvino in one of his beautiful books, which I will now destroy with my terrible translation. Polo is describing what is a bridge to the Kahn (who has never seen one in his rushings through the steppes) and how it is made, stones laid on each other in the form of an arch. The Kahn interrupts him to ask "of all those stones, which one supports the weight of the bridge ?" Surprised, Polo says that "the weight is not supported by this or that stone; it is the arch they form that takes the weight", only to hear from the Kahn "Why, then, do you tell me about the stones ? Only the arch is interesting". Polo reflects a moment and closes "Without stones there is no arch". Biology, particularly in modern times, has a lot to learn from this piece of Calvino. Our most successful agenda has been driven by component analysis for over 50 years, but we continue extremely ignorant as to the organisms' physiology. The major remaining questions (development, morphogenesis and size control, life span, aging, brain function, immunological tolerance, etc.) all pertain to the whole organism and we probably already know enough of components to address some of those questions in a more productive manner that to continue to isolate and describe components.

Following closely some of these principles, I have settled 6 times in 4 different countries, every time convinced it would be for good. Every time, I could not have been more wrong, such that I got used to accept that things happen and you just have to move to where you think you can do better, be more useful, have more fun. And I still feel that it can happen to me again, any time. If I had to leave permanent positions to join risky projects or to go on to fellowships or short-term contracts, it all turned out fine in the end. And this was in my time, when the possibilities in science were so much more limited than today. If this complicates life, because of all practicalities of apartments, and cars, and languages, and residence permits, if like this you end up with no or a very small "pension", I do think it is worth it, for all you gain in independence from all that. You discover that what you have in your head and in your heart, together with the people around you (and many are close to you even if they live thousands of miles away), is all you need to feel great, and you start suspecting that the more you are dependent on "things" you own, the poorer is your spirit and your heart. In essence, I would have done exactly the same if I was given the chance to repeat it all, and I actually want to close with a declaration of luck: not only I was very privileged with the people I met and led me in science, but I was also extremely lucky with the time period that I was in science, and even more privileged with the people whom I led into science myself. You know, I started in science only 20 years after Watson & Crick's discovery and, as you know, nearly everything happened since then. I understand today many more things than I did when I started, and this is the greatest blessing any one can ask for: to die a little less stupid than we were born. I must congratulate you, all of you young students and scientists, because your time in science will certainly be even better than my own. You will gain further understanding into questions that will not be solved before I die. And because you will have increased possibilities of contributing to a better society and a better world. Science produces knowledge and understanding such that the most noble product of science is actually tolerance. Your work and dedication can increase it around you and science, at large, can increase it in the world.

In the end, this is what counts more, because it has to do with people. If you ask me how happy I was for publishing a great paper, or being invited for a major lecture, I must say how excited I have been with such things. If I look back, however, I see that I have published too many papers (although I wrote every one I ever signed), including some in the great journals. I published 10 or 12 times in Nature, for example, but now I think that only 2 or 3 of those papers should have been published and really made a difference. In contrast, I helped 25 PhD students to a Thesis and, if you ask me, I think that every one of them was worth it. More, I do think that it has been worth all of this if it were for each single one of them. Simply because they are all very different and each found a unique way of going about science. As I expect that each one of you will do. Good luck and keep the principles straight.

Curia, September 22, 2001