Chapter 7. "I am sceptical for literary reasons"

"Please, help us to either detect the errors that we made or publish these data"

During the discussions with *Nature* concerning the first manuscript which – let us remember – concerned high dilutions of histamine, the second article was drafted with the results obtained with high dilutions of anti-IgE. J. Benveniste intended to submit this last article to *Science*, the other big international journal – but American – with a reputation and an influence comparable to *Nature*. Just after the acceptation of *Nature*'s article, J. Benveniste intented to submit this second article to *Science*, in order to take advantage of the breach that would then open. A phone call of P. Newmark however modified this strategy. This latter indeed explained to J. Benveniste that the design of the experiments reported in the article and the recent experiments of reproduction were too dissimilar. J. Benveniste recognized the rightfulness of the remark. He was however not disturbed because he knew that he could address this demand with the data from the article prepared for *Science*.

The debate on the "contamination" in Rehovot was thus at the origin of the new version of the manuscript that would be now submitted to *Nature*. One moves further away from the homeopathic products *Apis mellifica* and *Lung-histamine*.

P Newmark being absent, J. Benveniste sent a long answer to J. Maddox at the beginning of July about the brief remarks expressed by the expert.

> "[…] the suggestion from Mr Newmark to "incorporate the new information into the manuscript" is perfectly well-taken. In fact, since a long time elapsed from the beginning of our discussion with Nature, much more work has been accumulated on the anti-IgE trigger itself than on its inhibition by histamine. Therefore it is logical to publish the former information first. A manuscript is now completely ready. It will be co-signed by the participating laboratory in Israël. After approval by them you should receive this new version within two weeks." [1]

Then he suggested to J. Maddox that – as an editor – he must now take the responsibility of a decision:

> "It is clear that all consulted referees don't want to see these disturbing data (you can trust me that they are disturbing for us too !) to be released, but they fail to find any flaw in these very stringent experimental conditions. I am afraid the responsibility of the publication must be taken at the level of the editors. I remind

> you my suggestion of an editorial from you (or if you wish from myself) along the line: "We don't understand how this works, nobody can detect any error or wrong doing, so we present the work for the scientific community to judge."

In his very long answer to the brief report of the expert, J. Benveniste reacted first to the question concerning the reproduction by the other laboratories: "[…] the usual procedure for publishing new, even controversial, results is to publish them first and then let the scientific community reproduce them." Then he explained that he nevertheless complied with the requirements of *Nature* and he described how he was successful in spite of the difficulties inherent to this sort of initiative to reproduce the experiments in Israel. About the so-callled "unintelligible" results, one guesses the irritation of J. Benveniste in front of the obvious bad faith of the expert. He resumed the results point by point with a touch of irritation:

> « Here I do not understand why the numbers of basophils are "undefined" when they are under the heading "numbers of basophils"; I do not understand either why the referee find these data "literally unintelligible". He has had in hands the article itself which gives the methodology and everything is explained in these data sheets. […] Feb 27: 85, 82, 82 basophils in the control tubes (83.0 ± 1.0) vs 39, 37, 38 (38.0 ± 0.6) in the 1×10^{-34} anti-IgE dilution. What is unintelligible in these data ? Please look at these remarkably small variation of these counts, done completely blind. […] These conditions of experiments are particularly stringent and very seldom found in any biological experiment published in Nature or elsewhere. All these experiments were analysed by the scientists in Israel and not at all, as mentioned by the referee, by one of the original team. »

Finally, he asked not to try to explain a phenomenon before admitting that he exists:

> "May I ask the referee (and the staff of the Journal) to consider these puzzling but indisputable data in cold blood ? We have the feeling that these experiments cannot be accepted in the first place and therefore must be declared unintelligible. I and the other scientists involved are "classical experimentators" with, in our respective field, strong international reputation. As the discoverer of the platelet-activating factor (paf-acether), now a fully-grown field of research, my results have never been contradicted. Thus it is not our interest to put ourselves in the middle of a controversy.

> But we are lead by these results that undoubtedly exist and will, sooner or later, be accepted. Please, help us to either detect the errors that we made (nobody until now has been able to detect them) or publish these data. But you cannot ask us to understand how things work before admitting that they exist. In this way each issue of Nature and other scientific publication would have 1 page and a half."

Then, at the end of August, J. Benveniste sent the new manuscript to J. Maddox. One more time, J. Benveniste pointed out that he complied with the requests of Nature: "As you will see, the submission of the new manuscript corresponds exactly to the demand of Dr. Newmark in his last letter to "incorporate… the new information into the manuscript" "[2]

"People who advance extraordinary claims must go to extraordinary lengths in their support"

The text of the manuscript that was then sent to *Nature* was very close to the one that was published in June 1988. Except for one figure, which illustrated the need of shaking between each dilution to obtain active high dilutions, the results of which were simply mentioned in the text, the rest of the manuscript underwent only minor changes. But almost one year have been nevertheless necessary before the publication. During this lapse of time, an epistolary (and phone) arm-wrestling took place. For the first months however, J. Maddox did not give news anymore.

At the end of September, good news arrived to Clamart. An Italian team had reproduced the experiment of degranulation with high dilutions and sent the results of 6 experiments. Of course, J. Maddox was informed: "These results from totally independent investigators will confirm you that the phenomenon is real and should be published." [3] These results had been obtained from Antonio Miadonna's Italian team to which Alberto Tedeschi belonged. The latter stayed in Clamart within the framework of a scientific collaboration (independently of high dilutions) and he maintained a friendly relationship with the team. But more importantly, he wrote several publications in the field of basophils and histamine release. He had already used the test of degranulation of basophils and therefore did not have to learn the technique. The weight of his results was thus important: he was an expert in this field and he performed experiments with total independence.

At the end of October, J. Benveniste telephoned and sent faxes asking to J. Maddox when he would take his decision concerning the article. J. Maddox finally answered:

> "Thank you for having been so patient with us. As you will have notice, I have not been able to come to grips with your manuscript as quickly as I had hoped when you telephoned.
> Bus now, alas, I have decided that we cannot publish your manuscript. The simple explanation would be to say that people who advance extraordinary claims must go to extraordinary lengths in their support. I would, on this occasion, be fairer to say that I am sceptical for literary reasons.
> You claim an astonishing set of observations, but then do almost nothing to discuss the possible explanations. We know, of course, that Galileo was more than anything excited by the implications of his surprising observations.
> I am sorry to send you these disappointing news." [4]

Thus, J. Benveniste was back to square one. Obviously, J. Maddox did not even consider necessary to submit the new version of the manuscript to the experts. Why did he ask for so many additional experiments since only "literary" reasons prevented him to publish the manuscript? With the intent of making fall J. Benveniste? With the intent that J. Benveniste would be finally get tired? For J. Benveniste, it was too much. On November 13th, he wrote to J. Maddox. There was no more room for kindnesses:

> "I must be a matter of langage but I do not understand your letter of November 4. After a first review of our paper you asked us to verify these results in an independent laboratory. This was done with our cooperation in one set of experiments in Israel and without any intervention from our part in another sert in Israel, Milano and in Marseille. The latter result is remarkable since this experiment was specifically aimed at showing that we were wrong. Thus we have fulfilled your demand and now you refuse the paper for "literary reasons". The were are in foreign country since I cannot scientific results on a literary basis. […].
> I am certain that Galileo would be proud to be compared to me. He was, just as I am, excited by the implications of his surprising observations but he did not solve the problem. Newton and Einstein did when they got the means for it. Would Nature have accepted a paper from Galileo? […] I expected you to wish to meet the people who did the experiments, see the lab books, in other words to examine (or send an expert to examine) the facts to help us bring them to the judgment of the scientific community or detect the bug. Instead of this, you dismiss the important effort on the basis of "skepticism for literary reasons"." [5]

J. Maddox replied to this letter only on January 21st. A negotiation gradually set up between both protagonists – on the initiative of J. Maddox – about mechanisms involved in the claimed phenomena. In the mind of J. Benveniste, it was necessary to first publish and then only an international cooperation with biologists and physicists alerted by the publication would allow casting some light on the described phenomena. For J. Maddox on the contrary, the publication had sense only if one explained what was observed. This suggestion to progress in the clarification of the phenomenon before publishing could be obviously interpreted as a new delaying operation of *Nature*:

> "I do honestly appreciate the puzzlement you must feel that we should first have asked for independent verification of your results and then that I should have written a frankly discouraging and sceptical letter. I do think, however, that this sequence of events is explicable by the conversation we had on the telephone in which I asked that you should speculate about possible explanations.
>
> At that stage, you said, if I understood correctly, that it might be something to do with the way in which macromolecules might leave their imprint on the structure of liquid water long after they themselves had been made to vanish by dilution, which is so much at odds with what we all believe (perhaps wrongly) to be the properties of liquid water that I could not help wondering why you appeared not to regard that as an issue as central as the one with which your paper dealt.
>
> Generally, we are for the publication of observations, however surprising, but when they are both surprising and inexplicable, I think it is fair that we should ask not merely for verification but also for an attempt at explanation or alternatively an acknowledgement of defeat in that direction." [6]

This idea that molecules would leave an "imprint" in water – what was popularized under the term of "memory of water" – was in fact not new. The reading of the letter of J. Maddox gives the feeling that he heard this "interpretation" for the first time during a phone conversation with J. Benveniste. In fact, this concept, which was far from being a highly-developed theory as one sometimes suggests, was already mentioned in the first versions of the article submitted to *Nature*.

Always faithful to his line of conduct, which consisted in not leaving the slightest chance of wrong footing him to *Nature*, J. Benveniste suggested integrating some experiments that began to explore the physical properties of the high dilutions into the future version of the article, what should allow establishing the mechanism of the observed effects (or at least should allow drawing some avenues of research):

> "[…] we have started the job and I will briefly give you an outline of what we have obtained. By four physical means, we have, I believe, definitely answered to the criticism (that was as awkward as the results themselves) that after the first dilutions there was no more dilution thus still leaving molecules in the suspension. Heating, ultrasonication, freeze-thawing and filtration show that the activities at low vs high dilution, although identical in their biological effect, are different in their physical behaviour. The most impressive experiment is the following: a 150 kD IgG molecule does not, as expected, sneak its way through a 10kD filter whereas its ghost counterpart is, just a good honest ghost, found in the filtrate, demonstrating that these ghost molecules have no real structural presence in space but are most probably "composed" of a rearrangement of water molecules. Also quite impressive are the results of the heating experiment: whereas regular molecules react according to their thermal sensitivity all ghost molecules disappear at 80°C. […]" [7]

Finally, he asked to J. Maddox to take a clear position on a possible acceptance of the manuscript if these new results were to be integrated into the last version:

> "We believe that we have gone an other step forward in the explanation of the phenomena. You cannot, in the present stage of knowledge and technology, ask us to go much forward since finding the whole answer to these data might take 20, 50 years or more. We do have now to present these results to interested scientists, in order to start the cooperative process.
>
> Be kind enough to drop a short note to indicate me if on this basis you are willing to reconsider the acceptability of the paper. It should now reach the volume of a full article. In this way, we will not waste time if you are definitively opposed – whatever our new evidence – to publish the paper. It will have to find its way somewhere. Many people believe that these experiments will change our vision of the world, with immense consequence. Nature is the vehicle for such an endeavour. I maintain my proposal of an introductory editorial from your staff or from myself. […]"

Une proposition de J. Maddox

On March 14th, J. Benveniste and J. Maddox had a phone conversation, which led to the sending of the new manuscript to *Nature* on March 19th integrating the results mentioned by J. Benveniste in his last letter. These results were however only briefly described. Their complete description would indeed have weighed down the article. J. Benveniste renewed his proposal once more to accompany the article with an explanation by the editorial staff of *Nature*:

> "I would like to remind you my proposal of having this paper preceded by an editorial that would absorb the shock that any scientist will feel when reading these results (I can assure you that we feel this shock every day when looking at them). It should in my opinion explain why we are showing these data to the scientific community that is mainly to trigger experiments on other biological systems and international cooperation between chemists, physicists and biologists. It could also indicate that the editorial staff has seen the experiments mentioned in the text "to be published", that could not possibly be presented in a single article. […] As you will certainly agree, the challenge is enormous since the results might be among the most fascinating in recent times. Please answer as fast as possible." [8]

One month later, in his inimitable British style where understatement competed with litotes, J. Maddox answered to J. Benveniste by expressing once more time his skepticism. The last version of the article again had been not reviewed by experts. But J. Maddox made a proposal of publication – admittedly an amended publication – but a publication nevertheless!:

> "Many thanks for your revised manuscript, but I am afraid that my colleagues and I are still rather sceptical of it. For example, I am not convinced that the dilution procedure fully guards against the possibility of contamination.
>
> But I do have this proposal to make. We would send your article to Dr Walter Stewart, who acted as a referee for an earlier version. I believe you may not have seen his comments of 15 July, so they are enclosed. Obviously, some of his criticisms are outdated, but they will give a flavour of how he is likely to approach any new manuscript. We would show you his report on this occasion and then discuss with you the question whether we should publish an amended version of your manuscript together with a no-doubt amended version of Stewart's report.

> If that attracts you, I suggest that we have a word on the telephone. Otherwise, I fear that we are not able to publish your manuscript." [9]

J. Benveniste was thus invited to answer to a comment dating almost one year. Contrary to the previous comments, the expertise report had several pages and obviously W. Stewart had carefully read the text. The tone of the report was not aggressive, even if W. Stewart expressed his skepticism very clearly. Having in hand the report of the experiments made in Israel by E. Davenas, W. Stewart also commented about them. Thus, the low variability of the counts of basophils in these experiments amazed him:

> "The low variability of the three repetitions on each page of the data supplied with the supporting letter strikes me as quite extraordinary from a biological point of view. The authors of the letter, however presumably know the characteristics of their system. How do they explain the extraordinarily low variability? Does this cause them to question the validity of the data."

Then, comparing the results of the manuscript and those of Israel, W. Stewart wrote:

> "The results obtained in Israel, however, appear to be of outstanding statistical significance. […] How do the authors explain the difference."

J. Benveniste thus must react to a report that was irrelevant at this time and must answer to numerous groundless questions. However, concerning the question of low variability, J. Benveniste answered with pragmatic arguments to statistical ones. We notice in the comment of W. Stewart what will constitute the main criticism of the future report of *Nature*, namely "too good" results:

> "??? are our results too good ? May we remind the referee that all counts were performed "blind" (if I may say so). Dr. Davenas did not know what she was counting. She had been in a foreign laboratory, under an extraordinary pressure, with a lot of people accusing her for cheating (for what purpose ?). She kept her calm, giving repeatedly the same results even when tricks were used (announcing 5 control tubes when there were 7). This shows that: 1) the method for counting is simple and reliable, 2) Dr. Davenas is one of the best experimentators seen in ages. Her extraordinary log books, the photocopies of which were sent to Dr. Maddox, are there to witness this. You are free, as repeatedly offered by us to

> Dr. Maddox, to come and examine them at length, at our expenses […]"[10]

This debate which became central a few months later – with all its insinuations – is thus only sketched here but each of the protagonists is already in his future posture. On one side, W. Stewart for whom two plus two will always equal four. On the other side, J. Benveniste, more pragmatic, who did not understand how he could be blamed for having a too precise measuring instrument. We will return in detail during Chapters 10 to 12 on the arguments from both sides. Indeed, under the appearance of simplicity, this question deserves developments and detailed explanations.

« These results could well be the event of the century »

J. Benveniste dictated his answers to the expert report from Bermuda where he was invited to present his results to a conference from 15th to 21st April 1988 which was attented by many Nobel prize winners and also the philosopher of the sciences Karl Popper. The theme of the conference concerned the relationships of quantum physics and biology. With a limited number of participants, presentations took place in a rather informal and friendly atmosphere, often followed by passionate discussions on the beach. Naturally, J. Benveniste announced in his letter to J. Maddox his participation at this conference and the warm welcome that his presentation received among the elite of the science:

> " I was last week in Bermuda attending the conference "Overlap and Union of Quantum Theory and Biology". Here were some of the most prominent theoricians, physicists and biophysicists who invited me to present my results. A few names are Sir John Eccles, David Bohm, Finkelstein, Bryan (*sic*) D. Josephson, Cyril Smith. Something quite remarkable happened which is that, instead of my 1-hr presentation, I was asked to present and discuss these results 4 times for a total of 6–8 hrs. Most of the participants agreed that 1) they could not find any flaw in the experimental design (they were especially impressed by the filtration experiment showing the absence of "classical molecules"); 2) they could well be the event of the century and some of these men stated that they were the most important they had seen in all their life; a theory seemed to fit best that was put forward by Emilio del Guidice from Milano : the organisation of water dipoles, creating an electromagnetic field that could mimic the one originated by the original molecule." [11]

Then, J. Benveniste confronted J. Maddox with his responsibilities:

> "You will certainly think that I am putting pressure on you and try to influence you. This is certainly the case. Through more and more contact with colleagues, especially of this high level, I am gradually realizing the enormous possible impact not only on biology but on physics of water and transmission of specific informations. Since you are now on the process of reaching a decision I thought useful to bring these informations to you. […] Finkelstein offered me to publish these data in the « Journal of Theoretical Biology » but there is no doubt in my mind that – besides its scientific level – Nature is the ideal place to trigger a multidisciplinary debate."

At the beginning of this text, we reported different reasons that could have decided J. Maddox to finally publish the controversial manuscript. It is possible that this conference in Bermuda is also an element to consider. Indeed, it is likely that the director of *Nature* who continued to be skeptical (it is a euphemism) about the results about high dilutions could have been anxious to be accused of preventing the diffusion of results supposed (rightly or wrongly) to be important. Moreover, this accusation would originate not only from J. Benveniste – who after all was known only amongst biologists – but also from Nobel prize laureates and great names in physics. Indeed, one must not forget that J. Maddox, via his numerous contacts related to his position, had probably heard of this conference. This is only a hypothesis, but the possible anticipation of charge of scientific obstruction should also be probably taken into account in order to understand his subsequent attitude.

Notes of end of chapter

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[1] Letter of J. Benveniste to J. Maddox of July 6, 1987.
[2] Letter of J. Benveniste to J. Maddox of August 20, 1987.
[3] Letter of J. Benveniste to J. Maddox of September 27, 1987.
[4] Letter of J. Maddox to J. Benveniste of November 4, 1987.
[5] Letter of J. Benveniste to J. Maddox of November 13, 1987.
[6] Letter of J. Maddox to J. Benveniste of January 21, 1988.
[7] Letter of J. Benveniste to J. Maddox of February 2, 1988.
[8] Letter of J. Benveniste to J. Maddox of March 19, 1988.
[9] Letter of J. Maddox to J. Benveniste of April 21, 1988.
[10] Letter of J. Benveniste to J. Maddox of April 29, 1987.
[11] Letter of J. Benveniste to J. Maddox of April 26, 1987.