

## Chapter 19. A blue bottle “for the use of beginner chemists”

*“Results are always finally published if the work is performed with a correct methodology”*

An unexpected “blue bottle” allowed writing a new chapter of the “memory of water” story. In April 1990, a short article appeared in the *Comptes Rendus de l'Académie des Sciences* (Proceedings of the French Academy of Sciences) entitled “‘Memory of water’: remarks on the test used”<sup>1</sup>. The article was signed by Jean Jacques, a chemist from the CNRS (*National Center for Scientific Research*). In his article, he explained that the results published in 1988 in *Nature* could have a simple explanation without resorting to “memory of water”. The author of this note had the merit to tackle the question of high dilutions from an experimental standpoint and not simply to suggest a hypothesis. By realizing an experiment and publishing the results, he thus recognized – at least implicitly – that the issue of high dilutions had the status of a scientific question deserving to be raised (even if in his mind this explanation should close the debate). We were thus in the onset of a scientific controversy.

This note was “presented” by the chemist and Nobel prize laureate J.M. Lehn in the section “Biological Organic Chemistry” of the *Comptes Rendus*. This journal – an offshoot of the Academy of Sciences – required indeed that each article be endorsed by an academician.

One remembers that J.M. Lehn declared in June 1988 after the publication in *Nature* that he was “disturbed” by these results. He had then clarified his thought by adding:

“I would like to finish by underlining the fact that, after all, the witch-hunt does not exist in science. There is obviously here a very passionate domain. The thesis that scientists who try to do things rejected by the so-called official science could not be heard does not hold water. This can be true, during one year or two, but the results are always finally published if the work is performed with a correct methodology”<sup>2</sup>.

In spite of this masterful lecture revealing a kind of “Rousseauist” vision of the scientific community, the practical works did not fit with these great principles when the occasion to apply them appeared.

In his note, J. Jacques explained that the phenomena of staining/discoloration observed on basophils in the presence of high dilutions could be explained by the redox properties of the staining agent used, namely

toluidine blue. Thus, he made a reference to an experiment “often described in textbooks of practical class for the use of beginning chemists”.

This experiment, named “experiment of the blue bottle”, requires three ingredients: a staining agent with properties of redox indicator such as methylene blue or toluidine blue, a reducing compound (glucose for example) and an oxidizer, oxygen of air in the present case. In this experiment, the solution is made alkaline with sodium hydroxide and the solution becomes colorless (the staining agent is then reduced) and, if the solution is shaken, the blue color reappears because of the dissolution of oxygen from the air into the solution.

It was an ingenious hypothesis. Would the issue of the effects of high dilutions on basophils be resolved? It would thus be only a rough artefact and its explanation would be accessible to “beginner chemists”? The explanation proposed by J. Jacques would be all the more remarkable given that none of the scientists who had the article in hands has ever suggested this explanation which had the merit of the simplicity.

*“I did not know that the control tubes were shaken”*

But J. Jacques did not correctly understand the technique used in the article of *Nature*. Or maybe it was badly explained to him. On one hand, in the model of the blue bottle, the oxygen of air *colors* the liquid in blue after shaking whereas, for high dilutions, shaking during the dilution process causes a *discoloration* of basophils when the dilution is added to the cells. Moreover, the experiment on basophils can be performed without glucose. But finally – and above all – tube controls were of course diluted and shaken in the same conditions as the test tubes. It is the basics of experimental methodology. It is difficult to imagine that one discussed about possible effects of high dilutions during all these years if such an elementary and fundamental control had not been performed.

J. Benveniste met J. Jacques shortly after the publication of the article:

“I pointed out his error to Jean Jacques some time later in a meeting where the fate gathered us together. “Ah well, I did not know that control tubes were shaken”, he answered me with a devastated look whereas sweat beads dripped from his forehead.”<sup>3</sup>

After the meeting with J. Jacques, J. Benveniste wrote a long letter to J.M. Lehn who presented the note:

“I regret that you expressed your opinion publicly so often without ever having taken the initiative of a direct dialogue. Therefore I am doing so now. If one wants to see the positive aspect of the

situation, your previous statements, and now your presentation of Jean Jacques's note (whose error of interpretation would have been avoided by a discussion of a few minutes, what I have just done with him), underline your interest for this phenomenon.”<sup>4</sup>

Having told again the history of the publication cosigned with A. Spira, he asked J.M. Lehn to present the article that was successively refused by *Nature* and *Science*:

“It is obviously an imposture to state that a study signed by A. Spira and approved by Daniel Schwartz and Philippe Lazar is statistically insufficient [...] Don't you think that it would be a credit to the Academy and yourself to take an initiative allowing to moderate the exaggerated privilege of the Anglo-American journal editors to have the power of life or death over researches, in this particular case of French origin? [...] I thus come to ask you to present to the Academy a condensed note of the new article refused by *Nature*.”

One week later, the answer – short and abrupt – of J.M. Lehn came to J. Benveniste:

“If I agreed to present the note of Mister Jean Jacques for publication in the Reports of the Academy of Sciences, it is because it was entirely about chemical data. Since it is absolutely not the case for your text, I do not feel that I can present it to the Reports of the Academy of Sciences.”<sup>5</sup>

What J. Benveniste answered with the same abrupt tone:

“I am not surprised with your answer which however saddens me. I hope at least that your proclaimed incompetence in biology will forbid you in the future any inopportune statement on my research.”<sup>6</sup>

M. Schiff summarized this episode in a very enlightening manner:

“The refusal of this chemist exemplifies the relationship between scientific censorship and balance of power. Having declared that “the results are always finally published if the work is performed with a correct methodology”, the eminent chemist found refuge behind a formal alibi related to his area of expertise. Thus, he would have been competent enough to judge the relevance of Jacques's article as criticism of the experiments on high dilutions.

On the other hand, he would not have been competent to judge the experiments themselves!”<sup>7</sup>

*“Who is the f... who dared to present this text?”*

Discouraged by these refusals for a while, J. Benveniste finally contacted a member of the Academy of Sciences, Pierre Potier, whom he knows well. Indeed, during conversations, an idea of strategy germinated. It consisted to base on the note of J. Jacques in order to publish the results obtained in association with A. Spira:

“I received the advice – seemingly idiotic but not in reality – to write a note to the academy in response to the note of Jean Jacques. It is perfectly academic [...] Are you ready? Or do you know anybody who would do it?”<sup>8</sup>

Pierre Potier was then Director of the Natural Product Chemistry Institute of the CNRS at Gif-sur-Yvette. He was an internationally recognized scientist – he was in particular the co-discoverer of two anticancer drugs – and he was also known for his outspokenness. He knew J. Benveniste well and there were scientific collaborations between their respective laboratories. P. Potter agreed to present the note. This note was a summary of the article previously sent to *Nature* and *Science* – meanwhile the results had gained in clarity – and was then entitled “The shaking of highly diluted solutions does not induce specific biologic activity” in order to directly answer the note of J. Jacques. Benveniste sent the note to P. Lazar for information and he explained the new strategy:

“As you can see, I completely inverted the logic of the text of *Nature/Science*: we verified the absence of effect of the diluted and shaken distilled water, by showing, almost as a series of controls, the effect of the dilutions of anti-IgE antiserum. The trick is perhaps a bit too apparent, but it addresses exactly the note of Jean Jacques presented by our Nobel prize-winner, incompetent in biology, in the section “*Biological Organic Chemistry*”. There is no chance in my opinion that they will accept it and they will raise many questions beside the point as did the referees of *Nature* and *Science*. I hope I am wrong.”<sup>9</sup>

The note was finally sent during summer. It was returned on September 5<sup>th</sup>, 1990 due to a routing error according to Marc Julia, the president of the Chemistry department of the Academy of Sciences. The note was again sent to the *Comptes Rendus* and it was submitted to the experts early October.

Although the review process was confidential, an information leak worried J. Benveniste because his previous fears seemed to be confirmed:

“I learnt from Philippe Lazar himself the possible argument justifying the rejection of the note. It would be asked for a control of the control, namely what occurs if one does not shake the active dilutions? It is rather curious, because the purpose of the note is to show that the agitation has no effect”.<sup>10</sup>

J. Benveniste finally heard about the manuscript early December. Despite the waiting time, there was good news since the comments of the experts “are insignificant and the general tone is rather friendly.”<sup>11</sup>

The initial fears of J. Benveniste were thus unwarranted and the publication of the results in the *Comptes Rendus* appeared then possible. Nevertheless this perspective was apparently not everyone's cup of tea:

“Potier reported later to me the funny scene which occurred during the examination of texts proposed for the *Comptes Rendus*:

“Who is the f... who dared to present this text? asked Jean-Pierre Changeux, an eminent professor of neurobiology at the *Collège de France* and wild opponent to my research.

– It's me, Sir. Do you have any comments?”, answers Potier who pays no attention to the power of the mandarins.”<sup>12</sup>

Even if the note was not accepted without some changes, the questions and the comments of both experts who assessed the manuscript strangely contrasted with the aggressiveness of the previous experts of *Nature* and *Science* and corresponded to the more usual tone for this kind of exercise.

*“On the pallet, ready to leave”... but destroyed*

On January 30<sup>th</sup>, 1991, the article was accepted. The editorial process then seemed to continue with the usual corrections of the printer's proofs. But the story of the blue bottle did not stop there. Indeed, the following precision was printed as a footnote of the front page of the article,<sup>13</sup> without the knowledge of the authors:

“The Perpetual Secretaries indicate that this Note is published in accordance with the right of reply to the Note of Mr Joan Jacques entitled “*Memory of water*”: *Remarks on the test used*, the reference of which is given in [2] of the present article.”

If the sense of this footnote escaped some readers, a press release from *Agence France Presse* confirmed the intention of the Academy:

“The Academy specifies however on Friday that it concerns an answer to a criticism of the research of Mister Benveniste concerning the “high dilutions”.”<sup>14</sup>

Nevertheless, as we have seen, the article followed the usual process with a review from experts. Furthermore, the right of reply such as it is understood for the press is never applied to original scientific results. Publishing results different from those of a colleague or contradicting them is not considered as a personal attack or as defamation. It is the usual scientific process.

In fact, this note was added at the last minute. The attentive reader has perhaps noted the typo on the first name of “Joan Jacques”, probable witness of the haste with which this note was added. M. Schiff indeed told:

“According to the person in charge of the printing office consulted by phone, all copies of the issue of the *Comptes Rendus de l'Académie des Sciences* were "on the pallet, ready to leave" as the printer received the order to add the paragraph above. In order to add the paragraph, the whole issue which was ready to leave had to be destroyed. Therefore the article on high dilutions had the honors of a traditional rite which had a little bit fallen into disuse since the Inquisition. As everybody knows, the function of the Academies is to defend the traditions.”<sup>15</sup>

*“It seems that it is neither a plain artifact nor a simple error of manipulation”*

The publication of these results on February 28<sup>th</sup>, 1991 had however only a limited impact in the press. The same plays on words were trotted out again (it was admittedly rather difficult to resist) such as “When the memory of the water resurfaces”<sup>16</sup> or more macabre: “ "Ghost molecules" theory back from the dead.”<sup>17</sup> The journal *Le Monde* quoted A. Spira:

“Professor Spira, who said at the beginning that he was very "perplexed", states today to be "very disturbed". "In the light of the last experiments, he says, it seems that it is neither a plain artefact nor a simple error of manipulation. In these conditions, either we are in the presence of a much more subtle bias which, until now, had totally slipped our minds, or there is actually something." [...]

Professor Spira, who considers to have done his best to ascertain the methodological validity of the experiments – he even asked a biostatistician to oversee his own work – appeals now to the international community of scientists to try to clarify this mystery.”<sup>18</sup>

J. Benveniste hoped to be back in the saddle on the occasion of the publication of this article and in a letter to P. Lazar just before the publication in the *Comptes Rendus*, he anticipated the reactions by the media:

"No doubt that this publication and its impact, easily predictable, in the media will obviously relaunch the debates. I hope that the Administration will take place, as much as possible, on the good side, for example by declaring that what could have been only an "illusion" appears as a set of solid scientific facts about which the scientific community should seriously start to wonder about." <sup>19</sup>

P Lazar answered not long after this new request for support. He also mentioned the benefits, according to him, of the reserve towards the media observed by J. Benveniste at the request of Inserm:

"Without any doubt, you noticed yourself, in these conditions, that the publication of your article in the *Comptes Rendus* did not trigger the general outcry as formerly among your "peers". Personally, I think that this mutual reserve can favor the normal functioning of the scientific community and this slow settling of facts and hypotheses which constitutes the essence of science. I do not understand – I ask you to take these words literally – your request of endorsement of your results by the administration of INSERM. As I expressed to you, on numerous occasions, I do not believe that it is the role of a research administration to intervene on the contents of science; there is already a high degree of responsibility to have to decide, periodically, on the future of a laboratory. And I do not think that, on this last point of view, you can blame your administration." <sup>20</sup>

Regarding the journal *Nature*, it simply ignored this article. In a correspondence with *Nature* of 1991 <sup>21</sup>, a reader was ironic about the research of J. Benveniste, referring to a comment of the latter of October 1990 promising in *The Lancet* "to publish in the month to come indisputable proof." <sup>22</sup> This reader added: "I have not seen such a paper". *Nature*, which meanwhile refused the manuscript of J. Benveniste and A. Spira, published the letter of the reader without additional precision. Then, J. Benveniste having protested in a new *Correspondence* <sup>23</sup>, *Nature* added a comment indicating that the manuscript was indeed submitted, but was rejected on the advice of two referees due to statistical problems. And taking advantage of the argument offered on a platter by the French academicians, *Nature* added that the publication "took the form of a reply to an earlier article in the *Comptes Rendus*".

*"I am still convinced that there is an artifact"*

In the years which followed this publication, A. Spira gradually took some distance from these results to which he nevertheless contributed. So, in 1997, he made the following remark:

“The results did not reproduce exactly those of 1988, but a transmission of information persisted at high dilution.”<sup>24</sup>

And a little further:

“I am still convinced that there is an artefact. The experimental procedure has a weakness”.

In 2001, while answering a journalist of *La Recherche*, A. Spira stated:

“ We did not completely confirm the first results of Benveniste on the effects of the very high dilutions [...], but we noted curious effects which we could not explain”. Nobody nevertheless succeeded to reproduce the first experiments of the researcher. What Spira agrees: "Yet, it was necessary to explore these new tracks to know that they led nowhere", he noticed by kicking the ball into touch.”<sup>25</sup>

We can perceive through these words that the one who asserted in 1989 that “It is not the logic of research to give up a problem at a crossing point” became a little disenchanted. Let us remind that in 1991, he declared: “it is neither a plain artefact nor a simple error of manipulation”. Concerning the evolution of the positions of the scientist, J. Benveniste told:

“Spira bravely fought with me to get this publication. In this occasion and afterward, he underwent strong pressures to break away.<sup>26</sup> He stood firm, for a while, then most probably he considered – with good reasons I believe – that he had done his utmost and that he did not have to risk his career and that of his team for this affair which was not really his fight. I am sorry and disappointed, but not bitter, to see him standing back today.”<sup>27</sup>

It is also true that since the publication of the article of the *Comptes Rendus*, J. Benveniste became more radical. After high dilutions, he introduced a new topic that he named “digital biology” and he continued sparing nobody, discouraging sometimes his rare supports in scientific circles (cf. second part).

At the end of the 19<sup>th</sup> century, the photoelectric effect was also considered as a “curious effect” which could not be explained with the tools of classic physics. The explanation of this phenomenon was one of the pillars of quantum physics which revolutionized physics and our vision of the world. However, unlike the high dilutions, there was no doubt for the physicists that the photoelectric effect itself was real. The issue concerned its interpretation and a theory to describe it.

*Chapter 19. A blue bottle “for the use of b chemists”*

In the case of the high dilutions, was the reality of their effects established by reproducing the experiments independently of J. Benveniste’s team?

*Notes of end of chapter*

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- <sup>1</sup> J. Jacques. La "mémoire de l'eau" : remarques sur le test utilisé. *C R Acad Sci (Paris)* vol 310 series II (1990) p. 1437.
- <sup>2</sup> J.M. Lehn. *Le Monde*, June 30<sup>th</sup>, 1988. Interview by J.Y. Nau.
- <sup>3</sup> J. Benveniste. Ma vérité sur la mémoire de l'eau, p. 103.
- <sup>4</sup> Letter of J. Benveniste to J.M. Lehn of June 14<sup>th</sup>, 1990.
- <sup>5</sup> Letter of J.M. Lehn to J. Benveniste of June 22<sup>nd</sup>, 1990.
- <sup>6</sup> Letter of J. Benveniste to J.M. Lehn of July 2<sup>nd</sup>, 1990.
- <sup>7</sup> M. Schiff. Un cas de censure dans la science, p. 144.
- <sup>8</sup> Letter of J. Benveniste to P. Potier of July 5<sup>th</sup>, 1990.
- <sup>9</sup> Letter of J. Benveniste to P. Lazar of July 10<sup>th</sup>, 1990.
- <sup>10</sup> Letter of J. Benveniste to P. Potier of September 21<sup>st</sup>, 1990.
- <sup>11</sup> Letter of J. Benveniste to P. Potier of December 3<sup>rd</sup>, 1990.
- <sup>12</sup> J. Benveniste. Ma vérité sur la mémoire de l'eau, p. 104.
- <sup>13</sup> J. Benveniste, E. Davenas, B. Ducot, B. Cornillet, B. Poitevin, A. Spira. L'agitation de solutions hautement diluées n'induit pas d'activité biologique spécifique. *C R Acad Sci (Paris)* vol 312 series II (1991) p. 461–466.
- <sup>14</sup> Press release of *Agence France Presse* of March 1<sup>st</sup>, 1991.
- <sup>15</sup> M. Schiff. Un cas de censure dans la science, p. 118.
- <sup>16</sup> M. Vigy. Quand la mémoire de l'eau refait surface. *Le Figaro*, March 1<sup>st</sup>, 1991.
- <sup>17</sup> D. Concar. "Ghost molecules" theory back from the dead. *New Scientist*, March 16<sup>th</sup>, 1991.
- <sup>18</sup> F. Nouchi. L'affaire de la "mémoire de l'eau" Deux équipes de l'INSERM constatent que des solutions hautement diluées pourraient avoir des effets biologiques. *Le Monde*, March 2<sup>nd</sup>, 1991.
- <sup>19</sup> Letter of J. Benveniste to P. Lazar of February 27<sup>th</sup>, 1991.
- <sup>20</sup> Letter of P. Lazar to J. Benveniste of March 29<sup>th</sup>, 1991.
- <sup>21</sup> H. Timmerman. *Nature*, August 29<sup>th</sup>, 1991, p. 751.
- <sup>22</sup> J. Benveniste. Publicity and controversial data. *Lancet* 1990;336:944.
- <sup>23</sup> J. Benveniste. *Nature*, October 1991, p. 787.
- <sup>24</sup> E. Fottorino, La mémoire de l'eau. Du rêve au soupçon. *Le Monde*, January 21<sup>st</sup>, 1997.
- <sup>25</sup> Julien Naël. Portrait : Alfred Spira, la santé publique en bandoulière. *La Recherche*, March 2001, p. 25.
- <sup>26</sup> What A. Spira confirmed in 1997 during the survey of E. Fottorino for *Le Monde*: "when I signed the article with Jacques Benveniste, I felt pressures. One wondered why I compromised in such an affair" (E. Fottorino. La mémoire de l'eau. Du rêve au soupçon. *Le Monde*, January 21<sup>th</sup>, 1997).

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<sup>27</sup> J. Benveniste. Ma vérité sur la mémoire de l'eau, p. 210.