Chapter 4. The beginning of the *Nature*gate

Homeopathy gives way to "high dilutions"

At the beginning of year 1986, a manuscript intended for *Nature* was drafted; then it began to circulate in the laboratory. This article concerned the inhibition of basophil degranulation by histamine at high dilution and by homeopathic products named *Apis mellifica* and *Poumon-Histamine*. At the end of May 1986, a first version of the article was presented to all the researchers of the laboratory accompanied with another manuscript on the effect of silica at high dilutions in mouse.[1]

This procedure was rather unusual at Inserm U200. Generally, only the team members having an expertise on the subject reviewed a manuscript from another research group. Consent of the whole laboratory was never asked for each article submitted for publication. For the articles on high dilutions, J. Benveniste made an exception. In a note accompanying both texts, he specified: "[…] it is important, in my opinion that a consensus is made among the researchers of the laboratory around these articles."

The unanimity was indeed far from being acquired within the laboratory about the legitimacy to undertake this type of research. The fact that this reseach was a "risky business" was clear to everyone. As long as this work remained confidential and was limited to a small team of the laboratory, there was not much to criticize. Some half smiles or a sarcastic allusion served to evacuate the awkwardness that some team members felt for this theme of research. It was in a way the "dancing girl" of J. Benveniste, a "curiosity" of the laboratory, which would eventually tire. As soon as the affair expanded, was widely made public and, furthermore, that J. Benveniste looked for the support of the entire laboratory, the situation changed. It would be then necessary to justify each personal position and to face the requests of explanation and ironic questions of the scientists not belonging to the laboratory. In his note J. Benveniste pursued:

> "It is important that these papers be of the usual level of the articles from the laboratory. However, it is also necessary to consider that they have a specificity which does not allow applying them strictly the usual assessment criteria. Indeed, given the massive and revolutionary character of the observed effects, one

> should not get lost in detail but convey the main message which is the existence of an effect and one not should try, at first, to explain everything. Within the framework of high scientific quality, we must be the most operational possible for these papers. Besides, you will see that we decided not to begin these articles by speaking about homeopathy but by introducing the concept as the consequence of the experiments. It is a little bit hypocritical, but psychologically certainly more effective for classic scientists." [2]

Having read the manuscript concerning basophil degranulation, a researcher of the laboratory pointed out its "voodoo" (*sic*) characteristics because of the presence of the homeopathic products *Apis mellifica* and *Lung-histamine*. It seemed to him that the article would gain credibility if it would include only histamine at high dilutions. Indeed, *Apis mellifica* and *Lung-histamine* are obtained by grinding, maceration and filtration of whole bees or lung of guinea pig having had an allergic shock. But, reporting only the results with high dilutions of histamine decreased noticeably the number and the diversity of the experiments described in the article. Nevertheless, this suggestion was well received. It was decided to split the article: the results with histamine at high dilutions would be sent to *Nature*, whereas the results with the homeopathic products would be submitted to another journal. [3]

It should be noted that this approach was integrated into a progressive process of "purification" of homeopathy. Throughout this text one will notice how the confrontation with the detractors, the experts, the journal *Nature*, the scientific community in general, gradually modified the initial program which was to assess the effect of homeopathic products, namely medicines that are prescribed by homeopaths. This "purification" easily occured since J. Benveniste and the whole laboratory shared the same "scientific values". B. Poitevin who introduced the theme of research on homoeopathy in the laboratory was an exception. He navigated between two worlds which were culturally very different: the world of homeopathy and the world of scientific and medical research. Thus, a first shift occured with the choice to speak only of histamine, to avoid the word "homeopathy" and to focus on "high dilutions". The second shift occured later when, under the pressure of *Nature* asking for a reproduction of the experiments in other laboratories, the manuscript did not concern any more histamine at high dilutions (which, by the way, was nevertheless too a homeopathic product marketed under the name of "*Histaminum*"…), but only anti-IgE at high dilutions.

Without anticipating the next episodes, it is important to know that J. Benveniste gradually escaped from high dilutions and became the defender of "electromagnetic" and then "digital" biology. What builds under our eyes is thus the consequence of the confrontation of the upholders of homeopathy/high dilutions and of their opponents. Often J. Benveniste anticipated the critics of the latter; partially by tactics – as we saw in the above internal note – but essentially because he belonged in fact to the same world as his opponents. The "homeopathic" authors of the *Nature* article gradually became distant with Inserm U200, often criticized the experiments of J. Benveniste and did not feel in tune with him.

"We find the data hard to believee"

The article was thus sent to *Nature* on June 19th, 1986 which acknowledged receipt of it on 23rd. J. Benveniste joined the manuscript on the effect of silica at high dilutions in mouse which would be submitted in parallel to another journal. It is indeed frequent to inform – under the seal of the confidentiality – the editorial team of a journal to which a manuscript is submitted that another article is being published on the same subject. Anticipating the reactions of the experts, J. Benveniste took care of specifying in a cover letter that the exceptional character of these results did not escape him. Moreover, he spontaneously suggested an audit of the results on the place where they were produced, namely in the laboratory:

> "[…] I would like to propose you to send your representatives to visit the laboratory and consult our books of experiments. It is also very easy to organize a demonstration of the effects of the ultra-high dilutions that could be performed by anybody capable of counting cells under a microscope." [4]

One could hardly be more cooperative and transparent. On August 18th, *Nature* asked to be patient because of "some difficulties" with the experts who had been asked to judge the article. On September 11th, the expertise finally reached Clamart with a surprise. The comments of the experts were there, but they did not correspond to the correct manuscript! It is certainly difficult to believe, but it was the manuscript on silica at high dilutions that was reviewed by mistake! Three months of waiting for nothing.

On September 16th, the manuscript was again sent to *Nature*, but alone this time in order to avoid any confusion. J. Benveniste decided nevertheless to answer the questions of the experts concerning the manuscript evaluated by mistake. The experts of this last manuscript indeed judged straightaway that having no explanation for a phenomenon that they thought impossible, it was not necessary to discuss the experiments. J. Benveniste considered that the same questions would again be asked for the article on basophils. Consequently, he sent to *Nature* a text where he answered the questions of the experts point by point.

On November 24th, the answer of *Nature* arrived to the laboratory. It was a negative answer – as it is very often the case at first for demanding journals – but Peter Newmark's letter, a member of the editorial team of the journal, was not completely discouraging and appeared rather open-minded; he made some proposals:

> "I am afraid that, perhaps inevitably, the referees of your paper are highly sceptical of the data; only one of them is even prepared to make formal comments, which are enclosed. We too find the data hard to believe, as I am sure you did, and impossible to understand." [5]

He then made some suggestions of experiments: to make sure that the observed effect was not simply related to a contamination from tube to tube during the process of serial dilutions[6] and to measure histamine concentrations at least in the first tubes[7]. The third experiment that he suggested was rather curious and missed the point; it consisted in directly adding the powder of histamine in water to obtain the solution to be tested and not to prepare it after serial dilutions. More interesting, he suggested performing the same experiments in other laboratories:

> "My second suggestion is that you persuade another laboratory to try and reproduce your data *before* publication. That is an unusual request but I believe the circumstances warrant it."

It was P. Newmark himself who underscored "before". Thus, at that time, it seemed obvious for *Nature* that the logic was to verify before publishing… The comments of the expert who agreed to report his opinion in writing accompanied the letter. The manuscript was quickly handled in fifteen lines in an ironic manner. The results were not discussed because from the outset they were considered as impossible:

> "[The authors] state that "information has been transmitted to isolated cells from a solution *where no molecules could possibly be present*" [8]. Are they, then, invoking the paranormal (or some other unusual phenomenon) to explain their findings?
>
> In view of such outlandish claims, it behoves them to provide far more convincing experimental evidence to justify publication of their findings in Nature!"

January 13th, 1987, J. Benveniste announced to P. Newmark that the experiments were being reproduced in two "internationally recognized" laboratories. He also invited him again to come to observe the phenomenon:

> "I would be pleased to invite you to visit the lab for one day or so, consult our log book and even, if you desire, participate in an actual experiment. This is obviously independent from the final decision that the editorial staff of Nature could take but it is clear that in such a controversial matter it is important to see things in the real life. Otherwise, I could show you our laboratory books during my next coming to London. Sorry for all the turmoil."[9]

He also answered the suggestions of P. Newmark in his last letter by describing recent experiments. Thus, radioactive histamine was serially diluted (in order to measure the decrease of its concentration with dilution). The results showed that the process of dilution occured as one could expect (at least for the first dilutions because the limits of detection were quickly achieved). In fact, scientifically speaking, this experiment did not bring anything new. But J. Benveniste did not want to offer to *Nature* the slightest possibility of asserting that he did not completely answer some objections. Then he patiently explained to P. Newmark that the idea to add directly powder of histamine was hardly realistic, not to say absurd:

> "However, I must say that I do not understand the meaning of your second suggestion which is "adding solute" rather than serially. If this means to make the final dilution by adding directly the compounds to the water, I am afraid this is completely impossible given the low concentration of the compounds or even their complete absence. Anyhow, the experiment is useless because we do need the shaking for the effect to appear."

In support of his assertions, he reported results of a recent experiment, which showed that shaking every dilution was necessary (Figure 4.1). Indeed, if one made only a simple dilution by gently mixing the solution, then high dilutions had no effect on basophils. Everything happened as if shaking was necessary to allow the "transmission of information".

J. Benveniste also reported the other experiments that illustrated the first steps of an exploration of the physico-chemical properties of the high dilutions. In these experiments, anti-IgE was diluted until $1/10^{33}$ in a classic way except that the dilutions from $1/10^{15}$ to $1/10^{22}$ were performed with dimethyl sulfoxyde (DMSO) and then the following dilutions until $1/10^{33}$ were again performed in usual conditions, namely in aqueous medium (Figure 4.2). The dilutions from $1/10^{26}$ to $1/10^{33}$ were then tested on basophils. The purpose of these experiments was to study the effect of a "barrier" of DMSO on the "transmission of the biological information" during the dilution process. DMSO is a liquid, which efficiently dissolves many compounds, much more efficiently than water or other solvents. Several series of dilutions were thus performed with barriers of DMSO at various concentrations. When water was replaced by 100% of DMSO, the effect with high dilutions disapeared. By introducing water gradually (10, 50 and 90%), the degranulating effect of the high dilutions of anti-IgE progressively appeared again.

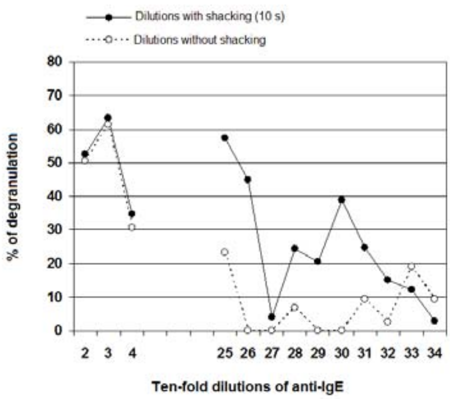

Figure 4.1. This experiment shows the role of 10 seconde-shaking using a rotating shaker to obtain active high dilutions. As expected, the first peak of degranulation (dilutions of anti-IgE $1/10^2$ to $1/10^4$) is obtained with or without ahaking between each dilution. In contrast, high dilutions of anti-IgE diliuted without shaking are not active at high dilutions (from $1/10^{25}$ to $1/10^{34}$).

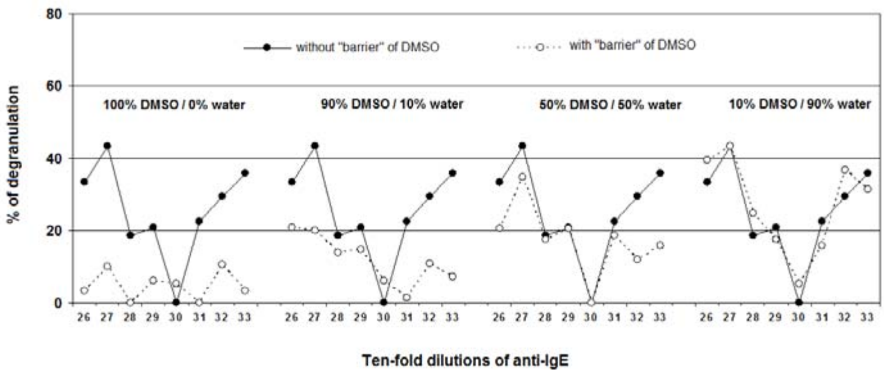

Figure 4.2. For these experiments, the dilutions of anti-IgE were performed up to $1/10^{33}$ but a "barrier" was inserted from $1/10^{15}$ to $1/10^{22}$ with dimethyl sulfoxide (DMSO); the next dilutions up to $1/10^{33}$ were performed again in the usual medium (buffered saline solution). The aim of these experiments was to "control" the passage of the "biological information" through the successive dilutions. The conclusion was that water was necessary to observe the biological effect.

P Newmark made no comment on these experiments, but he answered to J. Benveniste about the reproduction of the experiments by other laboratories:

> "I am glad to hear that two other laboratories are in the course of trying to reproduce your data and look forward to the results. I am sure that is a better way to confirm the phenomenon than by inspecting your lab books or participating in an experiment (but thank you for the offer." [10]

As we can see, the wisdom prevailed at this moment in the editorial team of *Nature*. P. Newmark clearly expressed here his desire of not wanting to go out of the traditional role of the scientific journals.

Notes of end of chapter

[1] In the experiments described in this article, mice drank water in which a solution prepared with silica according to the conditions of the homeopathic pharmacopoeia had been added. There is indeed a homeopathic product which is sold in pharmacy under the name of *Silicea*. These experiments were performed blind, the experimenter did not know the nature of the treatment which she administered to mice. After 25 days of treatment, mice had been sacrificed and the capacity of peritoneal macrophages to synthesize a mediator of the inflammation (paf-acether) was measured. The results showed that the synthesis of paf-acether was increased for the mice which had received *Silicea*. The controls were mice which had received a control solution (three types of different controls had been performed during 3 series of successive experiments). These results were published in 1987 (Davenas E, Poitevin B, Benveniste J. Effect of mouse peritoneal macrophages of orally administered very high dilutions of silica. *Eur J Pharmacol* 1987; 135: 313–9).

[2] J. Benveniste. Internal memo of May 20th, 1986.

[3] They were published in 1988 (Poitevin B, Davenas E, Benveniste J. In vitro immunological degranulation of human basophils is modulated by lung histamine and Apis mellifica. *Br J Clin Pharmacol* 1988 ; 25 : 439–44).

[4] Letter of J. Benveniste to *Nature* of June 10th, 1986.

[5] Lettre of P. Newmark to J. Benveniste of November 24th, 1986.

[6] Needless to say that the tip of the pipette was changed between each dilution. Only aerial contaminanation was theoretically possibe. Although often suggested to explain the results with high dilutions, this type of contamination could not however achieve the minimal concentration inducing the biological effect (see Chapter 15).

[7] In order to show that the decline was as expected. Of course, after 6–7 ten-fold dilutions, there is no method sufficiently sensitive to measure histamine.

[8] Underscored by the expert in his report.

[9] Letter of J. Benveniste to P. Newmark of January 13th, 1987.

[10] Letter (no date) of P. Newmark to J. Benveniste.

Crossed portrait #4

By Judith Mandelbaum-Schmid

"Someone who has always had an inner need to remain at the fringe"

"[*on his return to France*] he also began to develop his now well-established reputation as an outspoken critic of French science, revealing himself as a man who relishes the limelight. In flamboyant speeches and interviews with the press, he would refer to himself as the sole discover of PAF (an absurd contention) and one of the few biological researchers with any imagination in the entire country. He would denigrate French research as stagnant, unproductive, and controlled by a scientific oligarchy.

During the 1970's, at a time when left-wing politics had gone out of fashion and the new right held sway over France's political life, Benveniste resumed his activities as a militant in the Socialist Party. He allied himself with the influential politicians who would shape the government of socialist leader François Mitterrand when he came to power in 1981. Soon after the election, Benveniste was appointed to an advisory post, conseiller d'état, by Jean-Pierre Chevènement, then minister of research. He stayed only briefly, returning to INSERM soon after his nomination.

Benveniste says he left the government to return to his true calling – research. But a high-level official in the national health administration (who requested anonymity) thinks there are other reasons as well. "Benveniste is someone who has always had an inner need to remain at the fringe – even with the Socialist Party. He has the qualifications and the contacts to become very influential in shaping government research policy. But he chose not to – I think because he cherished his marginality. He needed to be on the outside, where he could openly criticize the government and, at the same time, feel like a martyr."»

(*MD* avril 1990)[1].

[1] Dilutions of grandeur: is water anamnestic? *MD*; avril 1990 (*MD* is a New Yorker monthly magazine for physicians).