Chapter 8. “When to believe the unbelievable”

“Inexplicable observations are not always signs of the supernatural”

What seemed impossible a few months ago was finally achieved: the article on high dilutions was going to be published. The proofs of the article arrived to Clamart. The usual typos were pursued and minor corrections were made. With emotion, still not daring to believe it, the team contemplated these few pages scribbled with ultimate corrections.

However, in the issue of *Nature* of June 30th, 1988, a kind of editorial cordon sanitaire surrounded the publication signed by thirteen authors.[1] First of all, an editorial of J. Maddox entitled “When to believe the unbelievable”[2] was dedicated to these results. In this text, J. Maddox called for caution and restraint:

> “Inexplicable observations are not always signs of the supernatural. This is what readers of the remarkable article on page 816 should keep in mind. They should also remember that Avogadro's number, the number of molecules in a gram molecule of material, is roughly 6.23×10^{23} (*sic*) [3], which naturally implies that most of the experiments with antibody solution reported by Professor J. Benveniste and his colleagues have been carried out in the literal absence of antibody molecules. For what the article shows is that it is possible to dilute an aqueous solution of an antibody virtually indefinitely without the solution losing its biological activity. Or rather there is a surprising rhythmic fluctuation in the activity of the solution. At some dilutions the activity falls off; on further dilution, it is restored.”

Concerning the mechanism mentioned in the article to explain this phenomenon, J. Maddox expressed his incredulity:

> “There is no objective explanation of these observations. Nor is there much comfort for anybody in the explanation offered at the end of the article – that antibody molecules once embodied in water leave their internal marks, as ghosts of a kind, on its molecular structure – for there is no evidence of any other kind to suggest that such behaviour may be within the bounds of possibility.”

J Maddox also reported the willingness of J. Benveniste who complied with all requests of *Nature:*

> "Indeed, during the long period since this article was first submitted to Nature, it has been plain that Benveniste has been puzzled as many of those who have read his article by the data he reports. On many occasions, he has responded to referees' suggestions at great inconvenience to himself. When told, for example, that the experiments should be repeated at an independent laboratory, he arranged for this to be done."

Then the Director of *Nature* justified the reasons for publishing this article all the while remaining careful:

> "One of the purposes that will be served by publishing the article will be to provide an authentic account of this work for the benefit of those, especially in France, who have gathered rumours of it from the popular press. Another is vigilant members of the scientific community with a flair for picking holes in other people's work may be able to suggest further tests of the validity of the conclusions."

In particular, for J. Maddox, the danger to publish these results was that the upholders of homeopathy could feel comforted:

> "Certainly, there can be no justification, at this stage, for an attempt to use Benveniste's conclusions for the malign purposes to which they might be put. There are some obvious dangers. In homeopathic medicine, for example, which works on the principle that very small concentrations of appropriate products may have consequences that far outweigh those expected of them, there will be a natural inclination to welcome Benveniste's article as aid and comfort, but that would be premature, probably mistaken. It will be time for celebrations of that kind only when a lot more water has run underneath this bridge."

J. Maddox ended his editorial by renewing calls for caution towards those who might take the results of the article at face value:

> "But, those of supernatural inclinations will protest, is it not grossly unfair that science should put aside, even temporarily, some surprising and unexpected observations (such as these) while apparently welcoming others which are no less surprising (such as the recent suggestion that there may be a 'fifth force' between material objects)? The explanation is simple, but, perhaps for that reason, not widely understood. It is entirely possible for physicists to welcome that notion of the fifth force because it would be a

> novel happening which could nevertheless be accommodated within the accepted framework of science. Benveniste's observations, on the other hand, are startling nor merely because they point to a novel phenomenon, but because they strike at the roots of two centuries of observation and rationalization of physical phenomena.[4] Where, for example would elementary principles such as Law of Mass Action be if Benveniste is proved correct? The principle of restraint which applies is simply that, when an unexpected observation requires that a substantial part of our intellectual heritage should be thrown away, it is prudent to ask more carefully than usual whether the observation may be incorrect."

Furthermore, the article was itself the only one in this issue to be placed in an unusual section entitled "*Scientific Paper*", which was created for the occasion! "Normal" articles were placed under the simple usual title "*Article*" or "*Letter*" Finally, an unusual "editorial reserve" had been added at the end of the article, indicating:

> "Readers of this article may share the incredulity of the many referees who have commented on several versions of it during the past several months. The essence of the result is that an aqueous solution of an antibody retains its ability to evoke a biological response even when diluted to such an extent that there is negligible chance of there being a single molecule in the sample. There is no physical basis for such an activity. With the kind collaboration of Professor Benveniste, Nature has therefore arranged for independent investigators to observe repetitions of the experiment. A report of this investigation will appear shortly."

What the article contained that attacked "the roots of two centuries of observations and rationalization of physical phenomena"

Compared with the initial manuscript that had been sent to *Nature* two years before, the published article reminds the famous knife with handle and blade that had been successively replaced. Indeed, the initial "inhibition" experiments with histamine had been replaced by the "activation" experiments with anti-IgE at high dilutions. This was the consequence of the successive requests of *Nature* to make reproduce the experiments and of the stay of E. Davenas in Israel and its consequences. We described in the previous chapters the various experiments and the circumstances of their achievement. It is nevertheless interesting to see how these results had been integrated into the article of *Nature* and how the various ideas had been articulated.

The article began with the description of the effects with high dilutions observed until $1/10^{60}$ and $1/10^{120}$ and the absence of anti-IgG antiserum effect (Figure 1 of the article reproduced below). We have already described these experiments in Chapter 3 (Figure 3.8). The text specified that similar results were obtained, also with "waves", by using other substances that had a degranulating effect on basophils: monoclonal anti-IgE antibodies, specific antigens in allergic patients or in rabbits (immunized with peroxydase), phospholipase A2, sodium ionophore or calcium ionophore.

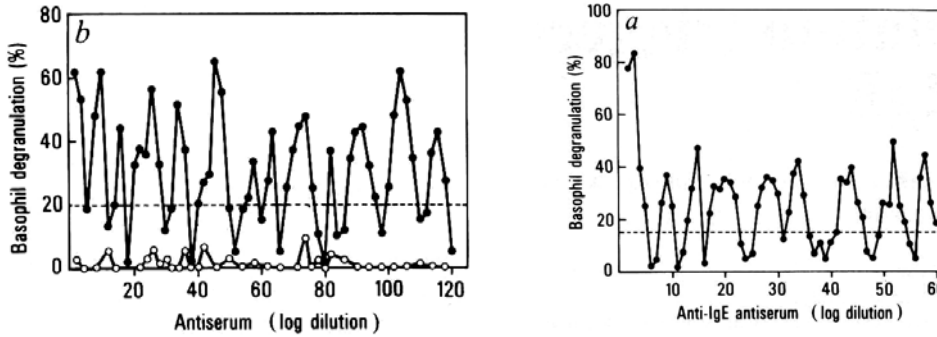

Figure 8.1. Reproduction of Figure 1 of the article of *Nature* of June 30th, 1988, p. 817. The black circles correspond to anti-IgE and white circles to anti-IgG (inactive control).

The article added that in order to confirm these experiments, four other *blind* experiments had been performed (Table 1 of the article reproduced below). They were the first four blind experiments performed in Israel. We have already presented them in Chapter 5 (Figure 5.1).

Table 1 Basophil counts after exposure to anti-IgE antiserum at low and high dilutions

Samples	Experiment 1	Experiment 2	Experiment 3	Experiment 4
Tyrode's-HSA*	81.3±1.2†	89.0±3.1	81.7±2.2	106.7±1.8
Tyrode's-HSA	81.6±1.4	87.7±1.4	83.0±1.0	105.0±1.2
Tyrode's-HSA	80.0±1.5	88.0±2.3	81.7±1.8	105.7±0.9
aIgE $1 \times 10^{1*}$	35.5±1.8 (56)‡	42.3±4.8 (53)	27.7±0.7 (66)	40.0±1.5 (62)
aIgE 2×10^{12}	77.6±0.8 (4)	87.3±1.2 (3)	66.3±2.3 (18)	93.7±1.9 (12)
aIgE 1×10^{13}	76.0±1.1 (6)	88.7±1.8 (1)	77.7±1.8 (4)	74.7±2.8 (30)
aIgE 1×10^{14}	53.6±1.4 (33)	52.7±1.4 (41)	38.0±0.6 (53)	48.3±2.4 (55)
aIgE 1×10^{15}	45.0±0.5 (44)	35.0±1.0 (61)	41.3±1.8 (49)	49.3±1.2 (54)
aIgE 1×10^{16}	49.0±1.7 (40)	50.3±0.7 (44)	55.0±2.1 (32)	74.3±2.3 (31)
aIgE 1×10^{17}	79.0±2.3 (2)	85.3±0.7 (5)	73.3±1.7 (10)	105.3±0.7 (0)

Blind experiments: test tubes were randomly coded twice by two independent pairs of observers and assayed. The codes were simultaneously broken at the end of all experiments. Dilutions of anti-IgE antiserum were performed as described in legend to Fig. 1.
* Uncoded additional tubes for negative (Tyrode's-HSA) or positive (aIgE 1×10^{-1}) controls. † Data represent the mean ± s.e. of basophil number actually counted in triplicate (see legend to Fig. 1 for methods). ‡ Number in parenthesis indicates percentage degranulation compared with Tyrode's-HSA.

Figure 8.2. Reproduction of Table 1 of the article of *Nature* of June 30th, 1988, p. 816. These results correspond to Figure 5.1 of chapter 5. These results are the experiments performed in Israel from February 23rd to March 1st, 1987. It should be noted that the results are presented here as counts of basophils and as percentages of degranulation for Figure 5.1. The raw data are reported in Appendix 2.

Then the results of the fifth experiment made in Israel were described. These results have been detailed in Chapter 5 (Table 5.1). The article then described the two blind experiments made in Clamart after the controversy related to the 5th Israeli experiment. We described these experiments in Chapter 6 (Figure 6.1 and Table 6.1).

Table 2 Comparison of basophil degranulation with the presence of immunoglobulins and anti-IgE activity in dilutions performed in HSA-containing Tyrode's

Samples	Basophil degranulation (%)*			Gel electrophoresis†		Anti-IgE activity
	I	II	III	*A*	*B*	μml^{-1}
Tyrode's-HSA	0	0	0	—	—	$< 1 \times 10^{-3}$
Tyrode's-HSA	0	0	0	—	—	$< 1 \times 10^{-3}$
Tyrode's-HSA	0	0	0	—	—	$< 1 \times 10^{-3}$
Tyrode's-HSA	0	0	0	—	—	$< 1 \times 10^{-3}$
aIgE 1×10^{-2}‡	53	50	33	++§	++	ND
aIgE 1×10^{-2}	51	44	37	++	++	10.6
aIgE 1×10^{-3}	65	38	45	+?	—	1.1
aIgE 1×10^{-32}	7	26	22	—	—	$< 1 \times 10^{-3}$
aIgE 1×10^{-33}	37	0	13	—	—	$< 1 \times 10^{-3}$
aIgE 1×10^{-34}	45	37	20	—	—	$< 1 \times 10^{-3}$
aIgE 1×10^{-35}	39	41	34	—	—	$< 1 \times 10^{-3}$
aIgE 1×10^{-36}	31	29	39	—	—	$< 1 \times 10^{-3}$
aIgE 1×10^{-37}	23	12	29	—	—	$< 1 \times 10^{-3}$

Blind experiments and dilution protocols as in Table 1. —, Lack of strained bands. ND, not determined. A faint band corresponding to IgG appeared after reduction by 2-mercaptoethanol.
* Basophil degranulation tests I, II, III were performed using 3 different blood samples (see Fig. 1). Percentage basophil degranulation induced by aIgE, as compared to Tyrode's HSA, was calculated from duplicates.
† Electrophoresis (polyacrylamide 7-15%, revealed by silver staining) was carried out in Rehovot (*A*) and at INSERM U 200 (*B*).
‡ Uncoded additional tube for positive control.
§ ++, + Bands correspond to IgG present in large or small amounts.

Table 3 Comparison of basophil degranulation with the presence of immunoglobulins and anti-IgE activity in dilutions performed in Tyrode's without HSA.

Samples	Basophil degranulation (%)		Gel electrophoresis		Anti-IgE activity (μml^{-1})
	I	II	*A*	*B*	
Tyrode's	0	0	—	—	$< 1 \times 10^{-1}$
Tyrode's	0	0	—	—	$< 1 \times 10^{-1}$
aIgE 1×10^{-2}*	85	48	++	++	ND
aIgE 1×10^{-2}	81	47	++	++	32.6
aIgE 1×10^{-3}*	ND	ND	+	+	ND
aIgE 1×10^{-3}	75	53	+	+	ND
aIgE 1×10^{-35}	35	31	—	—	$< 1 \times 10^{-1}$
aIgE 1×10^{-36}	40	35	—	—	$< 1 \times 10^{-1}$

* Uncoded tubes for positive control of basophil degranulation and/or gel electrophoresis.
ND, not determined.

Figure 8.3. Reproduction of Tables 2 and 3 of the article of *Nature* of June 30th, 1988, p. 816. These blind experiments were performed at Clamart on April 22nd and May 12th, 1987, respectively.

We remember that the experiment) of May 12th, 1987 had been performed in the absence of albumin in order to obtain a "clean" and interpretable electrophoresis. The latter was reported in Figure 2 of the article (reproduced below in Figure 8.4).

The article then reviewed the precautions which had been taken and refuted the possibility that the results could be explained by a simple contamination. In particular, the results of a filtration experiment (performed twice) were briefly summarized. Through a molecular filter (which retained the molecules with a molecular weight higher than 10 000), the molecules of anti-IgE (which have a molecular weight of 150 000) at concentrations corresponding to the first peak (1/100 and 1/1000) were retained in the filter and the filtered solution had no degranulating effect. In contrast, the filtered high dilutions ($1/10^{27}$ and $1/10^{32}$) kept a degranulating activity. An identical result was obtained by using ion-exchange resin which retained immunoglobulins corresponding to the first peak but allowed passing the high dilutions.

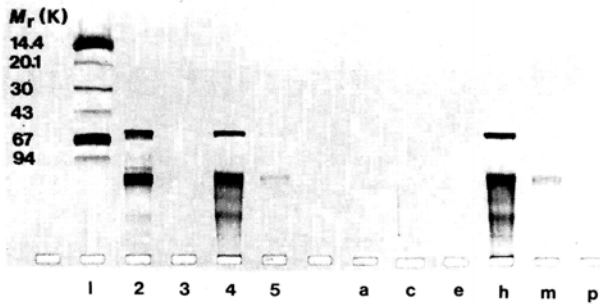

Fig. 2 Electrophoresis (polyacrylamide 7–15%, bands revealed by silver staining): samples numbered 1 to 5 are standards for the blind experiments *a*, *c*, *e*, *h*, *m*, *p*. Lane 1, Molecular weight standards for electrophoresis; lane 2, monoclonal IgG added with human serum albumin; lane 3, Tyrode's buffer without human serum albumin; lane 4, 1×10^{2} anti-IgE dilution; lane 5, 1×10^{3} dilution. Samples tested blind: *a* and *c*, buffer; *e*, 1×10^{30} anti-IgE dilution; *h*, 1×10^{2} anti-IgE dilution; *m*, 1×10^{3} anti-IgE dilution; *p*, 1×10^{35} anti-IgE dilution.

Figure 8.4. Reproduction of Figure 2 of the article of *Nature* of June 30th, 1988, p. 818. This is the electrophoresis made in Clamart and corresponding to the blind experiment that received a code on May 12th, 1987 (Chapter 6). The purpose was to show that high dilutions of anti-IgE did not contain anti-IgE at concentrations detectable with electrophoresis.

Then, when one carried on the reading of the article, the first experiments intended to explore the physico-chemical properties of the high dilutions were briefly described. For example (see Chapter 4, Figure 4.1), it was reported that shaking the solutions between every dilution during at least 10 seconds was necessary (shaking from 30 to 60 seconds did not increase the degranulating activity of the high dilutions). "Transmission of information" could be made through propanol or ethanol, but not through dimethyl sulfoxide (see Chapter 4, Figure 4.2). Heating (70–80°C), cycles of freezing-thawing or ultrasounds suppressed biological activity of high dilutions. Particularly, heating of high dilutions always suppressed their biological activity, whatever the diluted molecule, whether it was thermosensible or thermoresistant at "classic" concentrations.

The authors thus concluded that the molecules of the initial solution were not present any more in high dilutions beyond the limit of Avogadro and that specific information was nevertheless transmitted during the process of dilution/shaking. To explain the presence of this information, the authors suggested that: "Water could act as a 'template' for the molecule, for example by an infinite hydrogen-bonded network, or electric and magnetic fields. At present

we can only speculate on the nature of the specific activity present in the highly diluted solutions." And farther in the text, one could read:

> "The precise nature of this phenomenon remains unexplained. It was critical that we should first establish the reality of biological effects in the physical absence of molecules. The entities supporting this 'metamolecular' biology can only be explored by physical investigation of agitation causing interaction of the original molecules and water, thus yielding activity capable of specifically imitating the native molecules, though any such hypothesis is unsubstianted at present."

As we can see, we are very far from a sophisticated theory. Some avenues of research were sketched for a future research program, but there was no "theory of the memory of water".

"A new state of matter that opens unsuspected horizons"

We will not dwell upon the reactions of the press at the time of publication of the article about which we spoke about in Chapter 1. On the day of publication, June 30th, 1988, J. Benveniste planned to organize a press conference. When he learnt that the staff of Boiron Laboratories was also ready to communicate on the publication in *Nature*, he decided to anticipate the press conference on June 29th in a room of a Parisian hotel of Montparnasse district. The consequence of this haste was that only a small number of journalists were present and that the public was mostly members of Unit 200 of Inserm.

In the text given on the occasion of this press conference, J. Benveniste reviewed the steps of what he considered as "a fundamental discovery, literally bases of new mechanisms of information, perhaps a new state of matter, opening unsuspected horizon". The goal he had set for himself had been achieved and he could – by love of rhetoric – envisage the possibility that there was an error somewhere: "In front of the incredible features – which we still have difficulty in believing – of these results, we keep in mind the possibility of an error which nobody saw, as a "virus" which invaded our programs or our neurons to us all". However this careful attitude did not resist the conclusion of the document in which J. Benveniste asserted that all these experimental results "demonstrate without possible discussion that we can obtain specific biological effects with very high dilutions of active substances".

Boiron Laboratories (renamed Boiron-LHF after the merger of both companies) also wished to have their part in the scientific recognition of these works: a brochure dated June 30th was widely distributed to the pharmacists. It presented this "real "bomb" susceptible to radically transform the public

attitude towards homeopathy". In a note of introduction, Christian Boiron, CEO, explained that these studies succeeded "thanks to the close collaboration of LHF and Boiron around Dr Jacques Benveniste so illustrating the coherence of the merger of both companies" and he underlined the role played by B. Poitevin, E. Davenas, P. Belon and J. Sainte-Laudy "all being researchers of the group Boiron-LHF". One could not express more clearly the wish to be associated with this publication.

B. Poitevin wrote the explanatory text of the brochure, insisting on what constituted an important scientific event because "a breach is widely opened in the fundamental dogma of molecular biology and in the understanding of the physicochemical mechanisms of life" and because "new horizons opened in biology and in pharmacology today". The link with homeopathy – as predicted by J. Maddox – was strongly underlined: "the "infinitesimal" fact is an idea of Hahnemann which extended and propagated over time thanks to the quality of the clinical work of the Homeopath Doctors (*sic*)."

However, the results reported in the article of *Nature* did not concern a homeopathic medicine sold in pharmacy and the word homeopathy was not pronounced. Furthermore, by virtue of the homeopathic principles, we would expect that what causes an effect at low dilutions would provoke an opposite effect at high dilutions. But the article insisted in particular on the identity of the effects, that is an "activation" of basophils whatever the strength of the dilutions.

How many laboratories obtained these results? Three? Four? Five? Six?

On this matter, when one read the diverse articles or comments, there is some wavering for the number of laboratories that reproduced the experiment. Indeed, according to B. Poitevin in the same text, the results had been obtained by 6 laboratories in 5 countries: Inserm U200, Institute of Clinical Immunology of the hospital Kaplan at Rehovot (Israel), Faculty of Agriculture of Rehovot (Israel), Department of Internal Medicine of Milan (Italy), Department of Zoology and Physiology of Toronto (Canada) and Laboratory of Immunology at Paris (France).

Except the fact that we can only count four countries, the two laboratories in Israel concerned the same team. We thus find five teams. Nevertheless, if we consider the affiliations indicated in the article – J. Sainte-Laudy and P. Belon are "concealed" under the banner of Inserm U200 for "strategic" reasons – we find then no more than four teams. It is this number of laboratories that was also mentioned in the press release of Inserm of June 29th (Clamart, Israel, Italy and Canada).

It is however necessary to note that the laboratory of Toronto of B. Pomeranz achieved only preliminary results. Nevertheless numerous exchanges had taken place between the Canadian laboratory and that of Clamart. Patricia Fortner, assistant of B. Pomeranz, came to Clamart from 5th to 11th February 1987 to learn the technique and E. Davenas then went to Toronto from 16th to 24th May 1987. But the Canadian team did not succeed in going beyond the stage of preliminary results. As a matter of fact, the article did not hide this fact and indicated it clearly by describing the results of Toronto as "preliminary results". We thus find three laboratories including that of Clamart.

On May 30th, the article in *Le Monde* which stated for the first time a reproduction of the experiments by other laboratories mentioned four laboratories: Weizman Institute of Jerusalem (cf. note 7, Chapter 5), University of Toronto, University of Milan and… Sainte-Marguerite hospital (Professor Jacques Charpin in Marseilles). A former assistant of J. Charpin indeed tried to reproduce the experiments with high dilutions. To the great displeasure of J. Benveniste, J. Charpin still remained cautious.[5] Similarly, J.M. Pelt (Metz) announced for a while that he had obtained results which confirmed those of Clamart. Unlike the Israeli and Italian teams, these two teams never achieved – despite the insistence of J. Benveniste – to formally attest in a document that they had obtained positive results with high dilutions. It is possible that if the "victory" of J. Benveniste had taken place without ambiguity, the hesitations would have given way to less reluctant assertions and to more strengthened positions.

Therefore, strictly speaking, results comparable to those described in the article had been reproduced by the Israeli and Italian teams; overall, with Inserm U200, three laboratories. In spite of his closeness with the team of Clamart, one could add the laboratory of J. Sainte-Laudy. But everything depends if we also consider the effects "in inhibition" or on the contrary only the effects "in activation" with anti-IgE antiserum to which the last version of the article of *Nature* was limited. Indeed, we will see later that the "homeopathic" authors of the article distanced themselves from this article in which any reference to homeopathy had been carefully erased. We underscore again that the participation of the "homeopaths" of Boiron Laboratories had been masked by affiliating them to Inserm U200 and that no allusion to the funding of this work by the same laboratories appeared in the article.

Notes of end of chapter

[1] Davenas E, Beauvais F, Amara J, Oberbaum M, Robinzon B, Miadonna A, Tedeschi A, Pomeranz B, Fortner P, Belon P, Sainte-Laudy J, Poitevin B, Benveniste J. Human basophil degranulation triggered by very dilute antiserum against IgE. *Nature* 1988 ; 333 : 816–8.

[2] J. Maddox. When to believe the unbelievable. *Nature*, 30 juin 1988, p. 787.

[3] In fact, Avogadro's number is 6.023×10^{23}.

[4] J Maddox appeared to forget that these "two centuries of observation and rationalization of physical phenomena" did not wait for this "affair" for being "struck at the roots". Indeed the advent of quantum physics at the beginning of the 20th century was an incredible – and unexpected – upheaval of our vision of the physical world. Consequently, the questioning about our "intellectual heritage" has already occured.

[5] Patrick Vellieux, a biologist from Marseilles, collaborator of J. Charpin, presented the results which he had obtained with high dilutions in these terms: "We for example made the same experiments as Benveniste and we have at the moment results that confirm his results. But we consider that it is not sufficient to publish. […] We prefer to wait even if we will be undercut by other teams. This risk seems to me more tolerable than that to be denied because of haste." (E. Favereau. Les scientifiques s'en lavent les mains. *Libération*, July 29, 1988).