Chapter 10. The investigation report of *Nature*: "publish, *then* perish" [1]

"The instincts of a journalist"

Prior to the publication of the investigation report by Nature on July 28th, 1988, there were already some rumors in Anglo-American press about information concerning the conclusions of the investigators. Thus, in *New Scientist* on July 21st, J. Randi declared that "most of these things are self-delusion." [2]

About the report itself, one could have expected a rigorous text defining the purpose of the investigation, describing the methods, presenting the data, explaining the conditions of the experiments and discussing the results obtained. In brief, a scientific paper and – why not – a peer-reviewed article. On the contrary, the titles, the style, the hint of irony and the general tone reminded of the article of a journalist trying to report a bombshell and not a scientific report. But was it surprising coming from J. Maddox? Indeed:

> "It is no secret among Nature staffers and those who know Maddox well that the former Manchester Guardian science correspondent retains the instincts of a journalist and is as anxious as the next newshound to be first with a sensational story." [3]

And questioned whether *Nature* did not plan a publicity stunt, P. Newmark, Deputy editor of *Nature* answers:

> "I wasn't directly involved in our decision about timing, and unfortunately John is not now available to answer the question. But it was quite clear from the outset that if we were to attract attention, by no means all of the publicity was likely to be good publicity." [4]

This was a skillful way to defend *Nature* and at the same time to take a slight distance from the tactics used by J. Maddox. Indeed, the decision of J. Maddox was far from unanimous support within the team of the writers of *Nature*. One remembers that the latter had expressed their mistrust through a petition when J. Maddox had returned to the commands in 1980. The direction of the magazine had nevertheless granted him full powers:

> "It is during summer 1988 that he uses his full powers, "to force through" the advice of the editor of the biology section and of four reviewers for a very particular article, according to the terms of a writer." [5]

The hypothesis according to which J. Maddox would have wanted to plan a publicity stunt is also evoked by E. Garfield:

> "Could it have been that the "story" (in the journalistic sense) was just too good – guaranteed to cause a sensation and garner publicity for Nature? The serial quality of the Nature articles, and the press releases it issued, reinforces this impression. If so, it is truly disappointing that an otherwise firstclass journal of science put its own interests above those of the community it serves.
>
> Many scientists cannot understand why the episode was handled as it was if not for the sensation of it all." [6]

« Never let these people get in your lab »

The reader who became aware of the investigation report of *Nature* concerning this "very particular article" was abundantly warned. Straightaway, he saw a catchy title playing on the sound of the words: "*High dilution experiments a delusion*", followed by this lead paragraph: "The now-celebrated report by Dr J. Benveniste and colleagues elsewhere is found, by a visiting *Nature* team, to be insubstantial basis for the claims made for them." From the onset of the text, the conclusion of the investigation was thus announced and allowed saving time for numerous readers maybe discouraged by the density of the four pages:

> "The remarkable claims made in Nature [333, 816; 1988] by Dr. Jacques Benveniste and his associates are based chiefly on an extensive series of experiments which are statistically ill-controlled, from which no substantial effort has been made to exclude systematic error, including observer bias, and whose interpretation has been clouded by the exclusion of measurements in conflict with the claim that anti-IgE at high dilution will degranulate basophils. The phenomenon described is not reproducible in the ordinary meaning of that word.
>
> We conclude that there is no substantial basis for the claims that anti-IgE at high dilution (by factors as high as 10120) retains its biological effectiveness, and that the hypothesis that water can be imprinted with the memory of past solutes is as unnecessary as it is fanciful." [7]

The unfavorable evaluation of the investigation being therefore formulated at the twentieth line of the column, the reader who nevertheless had pursued his reading could abandon by noticing that the main information was explicitly confirmed. Finally, in a paragraph of conclusion, so that no doubt remained, the authors insisted: "We conclude that the claims made by Davenas et al are not to be believed."

In J. Benveniste's answer to the report published in the same issue of the journal, the appreciation of the events was of course quite different. However, while the report of *Nature* was accompanied with figures, thus strengthening the impact of the arguments on statistical topics, the text of J. Benveniste was devoid of tables and figures of experimental results and was emotionally charged with many *ad hominem* attacks: [8]

> "Amazingly, J. Maddox, with all his experience, fell with us into the trap set by a squad of 'self-appointed keepers of the scientific conscience', 'with no substantial scientific published record' [J. Maddox, Nature 333, 795; 1988]. Their amateurism, the climate they created in the five days of our ordeal, their inability to get to grips with our biological system and their judgment based on *one* dilution series dismiss this inquiry altogether. Who, with event he slightest research background, would blot out five years of our work and that of five other laboratories on such grounds?" [9]

He thus commented on the famous fourth experiment which upset the investigators very much:

> "The fourth (counted blind upon our insistence) was 'incredible': 70-75% degranulation at dilution 10, 16/18, 22, similar to Fig. 1b of the article, controls varying by the usual 15. Then Stewart, with his typical know-it-all attitude, called these results, blind though they were, valueless; that implies fraud before counting."

Then J. Benveniste gave some insights of the atmosphere due to essentially to the presence of W. Stewart:

> "The next day [thursday], the hysteria was such that Maddox and I had to ask Stewart not to scream. He had decided also to blind the counting (an overkill) and to fill the chambers, using a modified untested method (two other serious errors). Referees must respect experimental design and not take part in it. This one was untrained and knew both codes (dilution and counts).
>
> Here is another hard-to-believe incident: Stewart imposed a deadly silence in the counting room, yet loud laughter was heard where he was filling chambers. There, during this critical process, was Randi playing tricks, distracting the technician in charge of its supervision."

He ended his objections by an appeal to all scientists:

> "More, I believe this kind of inquiry must immediately be stopped throughout the world. Salem witch-hunts or McCarthy-like prosecutions will kill science. Science flourishes only in freedom. We must not let, at any price, fear, blackmail, anonymous accusation, libel and deceit nest in our labs. Our colleagues are overwhelmingly utmost decent people, not criminals. To them, I say: never, but never, let anything like this happen—never let these people get in your lab. The only way definitively to establish conflicting results is to reproduce them. It may be that all of us are wrong in good faith. This is no crime but science as usual and only the future knows".

Small manipulations between friends

However, J. Benveniste had built his answer from the printer's proofs transmitted by *Nature*. The comparison, on one hand, concerning both successive versions of the proofs of the investigation report intended for the printer of *Nature* and, on the other hand, the text published on July 28th, 1988 reveals modifications which are far from being unimportant. In the version of the proofs of July 25th which are nevertheless called "final version", the following sentence was absent in the published text:

> "Thus we believe that many of the experiments whose results are regarded as significant are artefacts of statistical noise. But plainly this does not apply to all the data (for example, the fourth experiment of the study."

If this sentence had been kept, this meant that either there was a real effect, or the results had been "made up". [10] Let us remind that the 4th experiment is the only one with blind counting of basophils (nevertheless watched closely when the experiment was performed). The consequence of this deletion was that J. Benveniste in his answer used this assertion in his reasoning. But for the reader, it was difficult to understand to what he referred to:

> "Then, the report auto destroys the statistical bias declaring it "not applicable to all […] data, for example in the 4th experiment." [11]

For a good measure, if J. Maddox removed some sentences, he also added other ones at the last minute! A whole paragraph titled "Collaborations" was indeed not present in the proofs transmitted to Inserm U200. Therefore, in his answer, J. Benveniste could give the feeling to avoid some questions. In this added paragraph, J. Maddox reviewed the respective contributions of the participants from other laboratories who signed the article. About the results obtained by the Israeli team, he wrote:

> "The first trials were in March 1987, during a visit to Rehovot by Dr Davenas. The most remarkable of several successful trials was her correct identification of seven high-dilution tubes out of ten presented to her blind. Even so, the report (to Benveniste) was cautious. Later analysis of the tubes which had tested positive in this trial revealed not merely immunogobulins but other protein contaminants apparently identical with materials in the original IgE (*sic*) vial." [12]

These comments did not clearly accuse, but nevertheless contributed to cast doubts in the mind of the reader who could not judge. If this "contamination" really raised a problem, why to speak about it at this moment while *Nature* knew this information well before the publication of the article? What was the reason to prevent J. Benveniste from answering?

J Maddox continued about the Israeli team:

> "Since then, there have been two developments in Israël – a series of experiments carried out independently of Benveniste's laboratory and a further blinded experiment. Data from the latter are unfortunately not available. Maitre Simart, a legal official at Clamart who held the codes, is said not to have had times to decode them."

About which blind experiment did J. Maddox want to speak? The only blind experiment that Maître Simart could have blinded for the Israeli team concerned electrophoresis performed in April-May 1987. If we read *Nature*'s article again, these experiments seemed well to have been published and therefore unblinded.

Concerning this last point, B. Robinzon – the researcher of the faculty of Rehovot which had participated to the Israeli experiments – answered afterward personally to J. Maddox:

> "Not quite in accord with your report, it is well known to us that the data of our double-blind studies were decoded by Maitre Simart prior to the publication of your report."[13]

Then, about "contamination":

> "Since, in your report, it was cited that the so called "protein contaminants" were not immunoglobulin, I presume you had not seen our report to Dr. Benveniste as to the nature of this protein. I might remind you that there was no evidence whatsoever that this protein is other than the albumin which was a component of the buffer used at that time."

J. Benveniste could answer to these points not before the issue of *Nature* of October 27th, 1988 which concluded the debate in the columns of the journal. He answered in these terms to the question on the Israeli experiment which would not have been unblinded:

> "A section called "Collaborations" was also added at the last minute which is filled with "mistruths": data from Israel, twice described as not available, can be found … in our *Nature* paper (Table 2), and the corresponding raw data were given to *Nature* editors in March 1987." [14, 15]

Then about the skipped sentence concerning the "4th experiment", he added:

> "And, shamelessly, a critical sentence indicating that many (?) of our results are statistically correct was removed at the last minute, after receiving my answer (*Nature* 334, 291, column 3, paragraph 2)."

Naturally, three months after the presentation made by J. Maddox, few readers were able to follow the events in detail concerning these apparently minor manipulations. The impact of the answers of J. Benveniste was considerably decreased.

Small manipulations between friends (episode two)

About the Israeli experiment which would not have been unblinded, J. Maddox was not completely wrong to be amazed. But if he had the feeling that he put the finger on something unclear, it was not what he seemed to imagine. It was not indeed about experiments of basophil degranulation with high dilutions which would have been performed blind by the Israeli team. Here are the facts which could explain this misunderstanding.

As we said it in Chapter 5, two series of blind experiments were performed under the control of a bailiff and of J. Dormont in April-May 1987 on the return of E. Davenas from Israel. The second experiment which was not planned had been made necessary because albumin disturbed the electrophoresis and did not allow obtaining a correct picture intended to illustrate the article. Consequently the experiment had been done again in the absence of albumin.

For the first series (blinding on April 22nd), samples had been shared and attributed to the participants in the experiment for various tests: E. Davenas (basophil degranulation and electrophoresis), a researcher of a laboratory of Marseilles (dosage of anti-IgE), B. Robinzon (electrophoresis) and M. Shinitzky (electrophoresis). For the second series (coding on May 12th), samples were intended to E. Davenas (basophil degranulation and electrophoresis), the laboratory of Marseilles (dosage of anti-IgE) and B. Robinzon (electrophoresis).

The bailiff received the results of E. Davenas on May 11th (blinding of April 22nd) and on May 15th (blinding of May 12th), those of the laboratory of Marseilles on May 29th (blindings of April 22nd and May 12th) and those of B. Robinzon on June 1st (blinding of April 22nd). M. Shinitzky not having replied to the first sending, he did not receive a sample from the second blinding. Concerning B. Robinzon, he had asked to a researcher from the Weizman Institute to perform electrophoresis. For the second series, he had apparently difficulties renewing this collaboration and he obtained various reasons to explain the delays (diseased technician, unavailable material,…)

Pressed by time, J. Benveniste thus decided the unblinding of the results by the bailiff on June 11th without waiting for the results of Israel from the second series.[16] Scientifically, it changed nothing. But, psychologically, the contribution of these results would have allowed making a complete break with the controversial "contamination" of the Israeli experiments with the famous electrophoresis overloaded with proteins and consequenty not interpretable. Finally, J. Benveniste had only the electrophoresis performed at Clamart with the hope that the Israeli electrophoresis would eventually arrive.

In spite of the absence of the Israeli result, J. Benveniste decided nevertheless to send to P. Newmark on June 12th a table summarizing the results of April 28th and May 12th. For the experiment of May 12th, two columns entitled "Benveniste" and "Robinzon" reported the electrophoresis results. In the first column the results of the electrophoresis made at Clamart were described and for the second column J. Benveniste took the risk of "anticipating" the results to come which certainly would be identical to the results of Clamart..[17]

However, the results of the Israeli electrophoresis never arrived and this mention of two electrophoreses performed for the experiment of May 12th persisted in the article of *Nature* of June 30th, 1988. Nobody – including the co-authors – noticed this detail because the presentation of the results was misleading. Indeed, the experiment of April 22nd was reported in Table 2 which contained 2 columns A and B for electrophoresis; the legend of the table indicated that these electrophoreses A and B had been performed at Rehovot (Israel) and at Inserm U200, respectively, what was correct. Concerning the experiment of May 12th, it was reported in Table 3 with also two columns A and B for the results of électrophoreses. However, nothing in the legend of the table indicated to what A and B corresponded. The results of Table 3 being the logical result of those of the Table 2, the reader had the tendency to deduce that

A and B had the same meaning in both tables (see the reproduction of Tables 2 and 3 in chapter 8: Figure 8.3). In fact, one of the columns was simply a "copy and paste" of the other one.

It is thus possible that J. Maddox had knowledge of an unblinding with the Israeli team had not been performed or most probably – as he indicated in his report of July 28th – that he noticed that results were awaiting unblinding in the laboratory notebook. It is very likely also that he thought that it was about degranulation experiments (after all it was the main objective) and not simply an electrophoresis. J. Benveniste being aware of this small "manipulation" did not probably wish that the investigators dwell on this question. This version of the facts seems to be confirmed by the following extract from the text of J. Maddox of October 27th, 1988 in *Nature* where he once again discussed for a long time on the Israeli experiments because something obviously bothered him:

> "The data available from the Israeli work is the most explicit but also somewhat confusing. We know of three separate phases of investigation – an attempt to repeat the Clamart experiments (with negative results), a further trial in the presence of Elisabeth Davenas (which yielded positive results but also, unfortunately, accusations of deception by some members of the Israeli group) and a further trial organised remotely from Paris under the supervision of the Clamart bailiff, M. Simart.
>
> The data from the second trial are undoubtedly significant; we said so. There is a profound misunderstanding about the third series of measurement, whose incompleteness came to light when we failed to find the decoded data in the notebooks we had borrowed. Our recollection is that Dr Davenas said at our meeting on 8 July that M. Simart had been too busy to decode them, and that Dr Benveniste said something to the effect that "I'll will get them from him on Monday". But now, members of the Paris and the Israeli groups have said that the data were already decoded, on which case we have not seen them (or have mistaken them for other data)." [18]

In spite of a little biased presentation of the Israeli experiments (this team indeed obtained positive results independently of E. Davenas), the incomprehension of J. Maddox seems actually deep. The vague and contradictory answers of the various protagonists did not help to dissipate his perplexity. The code being the same for all laboratories, there could have been no specific unblinding/decoding for one separate laboratory. The answer that the bailiff "was too busy" was thus inconsistent. It is surprising *a posteriori* that the investigators did not push their advantage farther. It seems in fact that they did not really understand that the experiment blinded by Maître Simart was not unique but consisted of two successive experiments (April 22nd and May 12th), each with a specific code. Especially, the fact that J. Maddox placed on equal footing "three series" of experiments indicates that in his mind they were comparable and that they were degranulation experiments.

Once again, scientifically speaking, these considerations change nothing. The purpose of the electrophoresis was to show that in controlled blind conditions there was no contamination in the tubes containing high dilutions of anti-IgE. J. Benveniste had taken nevertheless a very important risk. Pressed to answer to *Nature*, he had "anticipated" a result which never arrived. If this "dodging" which escaped the vigilance of W. Stewart and of J. Maddox had been discovered, it would have been used by the investigators and – well presented – would have had probably more impact than the questions on the funding by homeopathic industry or the "errors of sampling" that we will consider in the next paragraph.

The central argument of the report

Le Monde of August 9th, 1988 – curiously using the expression once again "memory of matter" – summarized the main reproaches made by the investigators to the authors of the article: the financing of the researches by Boiron Laboratories, first world manufacturer of homeopathic products, the technical problems related to the test of basophil degranulation and the "difficulty to reproduce the results". [19]

The attentive reading of the investigation report showed however that the central argumentation rested essentially on an attempt to demonstrate that there was a statistical bias and that consequently the results were non-existent. Indeed, among the rare objective data in the report, the issue of a supposedly too low "error of sampling" was repeated as a leitmotiv, illustrated with figures intended to convince the reader that these conclusions were obvious. In less statistical terms, the investigators expressed the idea that the precision of the counts was "too good" than allowed by chance. These comments concerned more particularly the variability of the counts reported in the laboratory notebook of E. Davenas as well as the experiments performed in Israel.

Indeed, when one counts objects such as cells, the characteristics of various samples coming from the same population of objects must – as a general rule – follow a mathematical law named Poisson distribution. The underlying idea behind this criticism of the investigators is that the researchers of Clamart systematically biased (with more or less good faith) the counts of basophils thus explaining the "too good" results or – even worse – being able to simply explain the results.

Incidentally, there was no need to spend one week in Clamart to understand that. If this issue was an irrefutable proof of poor experimental practices (not to say more), the simple reading of the article was enough to discover this fact and would be a sufficient motive to not publish the manuscript (the raw results of the counts of basophils corresponding to Table 1 of the article are listed in Appendix 2). One remembers that the question had already been raised during the expertise of the manuscript, in particular by W. Stewart. It was thus inopportune to discuss as if it was a recent discovery.

J. Benveniste told in these terms how, at the end of the investigation, W. Stewart summarized his opinion concerning the famous laboratory notebooks which – that takes the cake – seemed to him too clean to be honest:

> "Stewart had taken in his hotel room notebooks and sheets of the results of experiments. Incidentally, I must point out that we are still missing some of the original documents! Just to say the professionalism of these people who do not even leave a signed report)!
>
> I went to get back all these documents, and when I drew his attention on a page, where there was an experiment which was particularly demonstrative, he snapped the fingers and said: "*Made up!*". I told him that I should smash his face, because nobody had ever allowed himself of saying that there was fabrication of results in my laboratory. But that I would not do, because the press would immediately seize the incident…" [20]

In the report itself, this question of the variability of the counts was mentioned in rather derogatory terms. Indeed, the knowledge of the researchers of Clamart in statistics seemed rather light:

> "We were astonished to learn, in the discussion of our conclusions at the end of our visit, that neither Dr Benveniste nor his colleagues to be aware of what sampling errors are. We provided a simple explanation, complete with an account of what happens when one pulls a handful of differently coloured balls from a bag, to argue that the sampling error of any counting measurement must be of the order of the square root of the number to be counted. On several occasions, Benveniste called these "theoretical objections". " [21]

Then, in the concluding text of J. Maddox on Octobre 27th, 1988, one could read:

> "I am puzzled that Dr. Benveniste is as indifferent as appears to be the case, both in several conversations in Paris and in his two comments on our report, of the complaint that he and his colleagues were unaware of the importance of sampling errors. At our final conversation on 8 July, it was clear that the relevance of the point was simply not understood, and discounted as "theoretical objections". "[22]

The argument of the director of *Nature* seems of those that one engraves in the marble. The common sense indeed says that two and two will always make four and that the mathematical laws are a part of rare certainties the durability of which is guaranteed. Consequently the match between "Maddox-the-theoricist" and "Benveniste-the-pragmatic" seems to tilt widely in favour of the first one.

But what if J. Maddox had left out one or several details?

Notes of end of chapter

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[1] Allusion to the scientific maxim: "*publish or perish*" .

[2] Nature sends in the ghost busters to solve riddle of the antibodies, *New Scientist*, 21 juillet 1988.

[3] R. Dixon. Criticism builds over *Nature* investigation, *The Scientist*, September 5th, 1988.

[4] Ibid.

[5] J. Maurice. L'hebdomadaire « Nature ». Un sanctuaire de la science en marche. *La Recherche*, July-August 1997, p. 120.

[6] E. Garfield. Contrary to *Nature*? *The Scientist*, September 2nd, 1988.

[7] J. Maddox, J. Randi, W.W. Stewart. "High dilution" experiments a delusion. *Nature* July 28th, 1988, p. 287.

[8] The various registers of language as well as the nature of the arguments handled by J. Benveniste and J. Maddox in their exchanges in *Nature* have been analyzed by Caroline Joan S. Picart (Scientific controversy as a farce: the Benveniste-Maddox counter trials. *Social Studies in Science* 1994; 24: 7–37.

[9] J. Benveniste. Dr Benveniste replies. *Nature*, July 28th, 1988, p. 291.

[10] For his survey for the series of articles in *Le Monde* of January 1997, E. Fottorino wanted to question J. Maddox on this famous sentence which had disappeared from the report: "This precision contradicted the rest of the text and thus meant that some results were not due either to an observation bias or to erroneous calculations. John Maddox, who at first agreed to answer our questions, then became injoignable." (E. Fottorino. La mémoire de l'eau. Une vérité hautement diluée. *Le Monde*, January 23rd, 1997).

[11] J. Benveniste. Dr Jacques Benveniste replies. *Nature*, July 28th, 1988, p. 291.

[12] J. Maddox, J. Randi, W. Stewart. "High dilution" experiments a delusion. *Nature*, July 28th, 1988, p. 290.

[13] Lettre of B. Robinzon to J. Maddox of September 18th, 1988.

[14] This is an error of J. Benveniste. The results of these experiments were transmitted to *Nature* on June 12th, 1987. The experiments with electrophoresis having been performed on April 22nd and May 12th, 1987, they could not be communicated to *Nature* in March. It is the results of the experiments performed by E. Davenas in Israel (Table 1 of the article of *Nature*) were communicated to *Nature* in March 1987 (cf. Chapter 4).

[15] J. Benveniste. Benveniste on the Benveniste affair. *Nature*, October 27th, 1988, p. 759.

[16] Letter of E. Davenas to B. Robinzon of June 19th, 1987.

[17] Letter of J. Benveniste to P. Newmark of June 12th, 1987.

[18] J. Maddox. Waves caused by extreme dilution. *Nature*, October 27th, 1988, p. 763.

[19] J.Y. Nau. Nouvelles polémiques à propos de la « mémoire de la matière ». Le docteur Benveniste doit répondre à trois séries de critiques. *Le Monde*, August 9th, 1988.

[20] P. Alfonsi. Au nom de la Science, p. 35.

[21] J. Maddox, J. Randi, W.W. Stewart. "High dilution" experiments a delusion. *Nature*, July 28th, 1988, p. 288.

[22] J. Maddox. Waves caused by extreme dilutions. *Nature,* October 27th, 1988, p. 762.