Chapter 18. "Were the investigators even qualified to do professional statistical analysis?"

"I am deeply sceptical of your claimed result."

In order to publish these results, J. Benveniste naturally considered that only a high-level journal was suitable to give an echo sufficient to erase the fatal consequences of the investigation of *Nature*. Therefore, he first asked to *Nature*. J. Benveniste suspected that J. Maddox did not probably change his mind. He nevertheless wanted him to face up to his own responsibilities. However the strategy of J. Benveniste was to try without insisting too much and, as soon as the refusal of *Nature* would be confirmed, to submit the manuscript to *Science* – the US competitor of *Nature* – which criticized the attitude of J. Maddox in 1988. In the meantime, the correspondence between J. Benveniste and J. Maddox could start again!

In February 1990, J. Benveniste took the temperature on the side of the journal of London. As expected, the same arguments were developed by J. Maddox:

> "If I understand it correctly you are saying that your original experiments have been carefully repeated, and that all necessary controls have been done. You must not be dismayed if, nevertheless, the referees think of others that appear to them crucial.
> […] As to my personal prejudices, I must tell you frankly that I am deeply sceptical of your claimed result, but that there is no reason why that should interfere with our consideration of a well-balanced research report. You must appreciate that I believe my scepticism of 1988 was justified by the statistical analysis of your data, but that data free from the same confusion would be a different kettle of fish.
> I have also a profound scepticism about homeopathy, but we agree hat there is not strictly relevant to your work (but the converse, as events have shown, is incorrect." [1]

In his letter, J. Maddox came back to the idea that results alone were not sufficient and that it was necessary to go farther in the explanation of the phenomenon:

> "A crucial question is that of the internal reproducibility of the experiments, to put it crudely, do these peaks lie always at the same dilutions and, if not, what variables might account for their

> displacements ? What is the role of wortexing ? if it 'works' with 30 seconds vortexing but not without vortexing at all, what happens at 15 seconds, for example ?"

To what J. Benveniste answered :

> " […] if you want us to explore the phenomenon, i.e. the influence of the length of agitation and many other variables, we certainly can do it but once the basic phenomenon has been accepted as real. It makes no point to work on a phenomenon that is supposed not to exist. I can readily furnish you with a list of about a hundred questions about this phenomenon. […] The question we had to answer in the forthcoming paper was: can we observe a statistically significant difference between control solutions and diluted and agitated solutions ? And nothing else. The answer is: undoubtedly, yes. Now, if you want to ask what happens with glass tubes, at night, during full moon, with or without gusty winds, etc., we will be pleased to answer these interesting questions. But this will be the subject of our next paper to Nature. Let's first establish a new phenomenon then ask how? and why?" [2]

The manuscript was nevertheless sent to the journal on March 6th.[3]

"It doesn't matter whether you withdraw your paper or we reject it"

At the end of April, J. Benveniste was getting impatient and he was decided to publish in another scientific journal. He could not however do that as long as the refusal of *Nature* was not explicit. He then sent an ultimatum by fax to J. Maddox where he explained that he could wait if necessary for the decision till the end of the month but no more: "No news from you within the next 48 hours will mean that you are implicitly rejecting the article". [4]

The answer was overdue a little more than forty eight hours, but when it came – on early May – the verdict was severe:

> "It doesn't matter whether you withdraw your paper or we reject it – I'm afraid it is the second course that we would in any case have followed. The reasons are explained in the enclosed report of one referee. Briefly, as you will see, there appear still to be errors of a statistical character in your work". [5]

The statement that there were flawed statistical analysis required to be solidly supported! On one hand, the statistics necessary for the analysis of this study were simple. On the other hand, it was implicitly accusing of incompetence the researchers from a unit of Inserm who were specifically statisticians.

On two and a half pages in simple line spacing and small characters, the expert accumulated remarks and questions which contributed to flood the main result. Thus, this latter was surprised by the variability of some counts, but he confused the standard deviation with the variance (which is the square of the latter) and complained about the absence of readility of the result tables. Especially, the quality control described above appeared highly dubious to him because he saw a way to select only the experiments that fit the expected results: "the primary flaw in these studies is the method of discarding the experiments. […] This amounts of throwing out data because it doesn't fit the conclusion."

Even if it did not make any change to *Nature*'s decision, J. Benveniste and A. Spira made an effort to answer every point raised by the expert, but they bluntly answered when his bad faith or his incompetence – feigned for tactical reasons or real – were obvious. The affair with *Nature* being close anyway, clear and frank explanations could be given.

First of all in the cover letter intended to J. Maddox:

> "As you should have noticed by yourself, and will see on this answer, there is not one point raised by the referee (Metzger? at least it is his prose with the usual errors and fantasies) that can sustain a minimal scientific discussion. Some of them […] are such crass errors that it is unlikely they were written by a scientist, even of the worst level. […] I suppose, no doubt that, faced with an arbitrary behaviour attempting to suppress free scientific information, and after all my numerous attempts to establish normal scientific relationship with you, I shall make this outrageous "critique" available of my colleagues all over the world. I indeed believe, and I am not, fortunately, the only one, that no one should be allowed to abuse his power to cynically dismiss data that must not exist by his own decision. The only means I am now left with, confronted with people who do not abide by their own rules, is to call upon the opinion of my peers and, if necessary, on the public opinion." [6]

The answers to the specific points followed. The tone was not friendly, what is rather unusual in this type of correspondence. Thus, if a reviewer who evaluated a manuscript made a stupid error or did not understand a point (it is possible), it is better to explain the point in a courteous and diplomatic way. But obviously there was no more any time for this kind of courtesy for J. Benveniste and, having nothing to lose now with *Nature*, he answered – with the help of A. Spira the questions about statistics – without taking the usual wording intending to care for the susceptibility of the expert. Here are some extracts that give the general tone of this text:

> "It is rather difficult to answer these three pages since they contain almost no substantiated arguments, and numerous blatant errors indicating either an incompetent reviewer or a will to engineer the document so as to reject the paper whatever its content. […]
>
> If the "referee" did not understand this, which is the basic of the most elementary statistics, no wonder that tables appeared "quite unclear" to him!
>
> […] the "referee" completely misunderstood the last criteria. It is too long to describe why, and anyhow it is not the job of authors to make referees understand what is written in plain English. These errors in interpretation being the main basis for rejecting the paper, it is a good measure of the seriousness, or lack of it, of this review process."
>
> […] Numbers (or counts) are number (or counts) and percentages are percentages. In the new version of the paper, we precise "absolute numbers (or counts)".
>
> Is this easier to understand, even by somebody who does not want to understand, than "numbers (or counts)"? "

And he concluded by addressing not only to he expert but also to J. Maddox:

> "[…] To say the truth, we are quite ashamed that a "referee" and an editor of a journal which claims to be the epitome of scientific excellence presented us with such a dreadfully sloppy critique, so full of elementary errors and so blatantly biased. These men jeopardize the very peer-review system of which they are supposed to be the guardians. Their fears of these indisputable data, and/or the external pressure, must be enormous to push them to such extremities, especially knowing that they cannot win and that they are heading straight towards a "Naturegate". Indeed, the most severe professional error a scientific editor can do is to deliberately suppress information, under fuzzy excuses. On our part, we have honesty played the game according to the rules. We have met the demands, especially on the statistics. And we got in return no sense literature, in fact indirectly ascertaining the soundness of our work: they could find anything to criticize. We are awaiting, in confidence the judgment of the majority of scientists all over the world who have kept in mind the interest of science and not personal beliefs or the influence of pressure groups."

"We do not know what were the results obtained"

All ties with *Nature* being broken off, J. Benveniste then addressed to *Science*. In April, he had already contacted Daniel Koshland, the editor of *Science*, to test his state of mind about the research on high dilutions and to inform him that he would receive a manuscript. He told to D. Koshland the complete story with *Nature* and asked him if he agreed on the principle to put the manuscript in the chain of expertise. He called for his conscience of scientist:

> "As a scientist, Dr. Koshland, you will certainly share my feelings that it is not possible to see a biological activity repeatedly appear, for five years, way beyond the limit of the Avogadro number, to simply put the data back into the drawer and go to the movie. If these data are real, and I have not heard one sound argument in favor of a demonstrable artefact, they must be shown to our colleagues for them to judge. If they are wrong, for reasons nobody presently understand why, let them live their own life, and should they be unearthly monsters, meet their doom." [7]

The manuscript was sent to *Science* on May 4th, 1990. In the cover letter to the editor, it was specified that the director of Inserm, P. Lazar, "himself a statistician of the Schwartz school in Villejuif" [8] was among the scientists who reviewed the manuscript.

But it was not enough to address the manuscript to the competitor of *Nature* to suppress all difficulties; it was not enough also to be supported by specialists of biomedical methodology and statistics. Indeed on June 13th, J. Benveniste received a letter of *Science* reporting that: "our reviewers perceive basic problems in the design and execution of the study that lead us to conclude that this paper does not resolve the questions posed in your earlier publications."[9]

The comments of two experts who reviewed the article were joined to the letter. As regards the text of one of the experts, J. Benveniste was furious and asked to the Managing Editor of *Science* if he maintained this comment which "is not in line with the respect of has peer-review system that we should expect has newspaper such have Science".[10] Indeed, this expert – protected by his anonymity – coldly wrote in his report:

> "We do not know what were the results obtained – we see no data. […] Were the investigators even qualified to do professional statistical analysis?"

A very frightening comment also for the "statisticians of the Schwartz School in Villejuif" including P. Lazar….

The report of the second expert had a more classic style without hostility or sarcasms. Questions were essentially raised on the presentation of the results and on statistical analysis. J. Benveniste and A. Spira answered to the latter, although not being formally obliged to do; the decision of *Science* was indeed not subject to appeal.

At one time, they thought of making public the article, the comments of the experts and their answers in order to expose publicly the process of expertise which usually operates behind the scene and under the cover of anonymity.

An event, seemingly insignificant, offered to J. Benveniste and A. Spira the unexpected opportunity to publish these results.

Notes of end of chapter

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[1] Letter of J. Maddox to J. Benveniste of February 27th, 1990.

[2] Letter of J. Benveniste to J. Maddox of February 27th, 1990.

[3] The manuscript was entitled: « Basophil modulation by very dilute ligands: a reappraisal ».

[4] Fax of J. Benveniste to J. Maddox of April 23rd, 1990.

[5] Letter of J. Maddox to J. Benveniste of May 4th, 1990.

[6] Letter of J. Benveniste to J. Maddox of May 21th, 1990 (accompanied by the answer to the expert by J. Benveniste and A. Spira).

[7] Letter of J. Benveniste to D. Koshland of April 18th, 1990.

[8] Letter of J. Benveniste to the *Managing Editor* of *Science* of May 4th, 1990.

[9] Letter of Patricia Morgan, *Managing Editor* of *Science*, to J. Benveniste of June 13th, 1990.

[10] Letter of J. Benveniste to P. Morgan of June 18th, 1990.