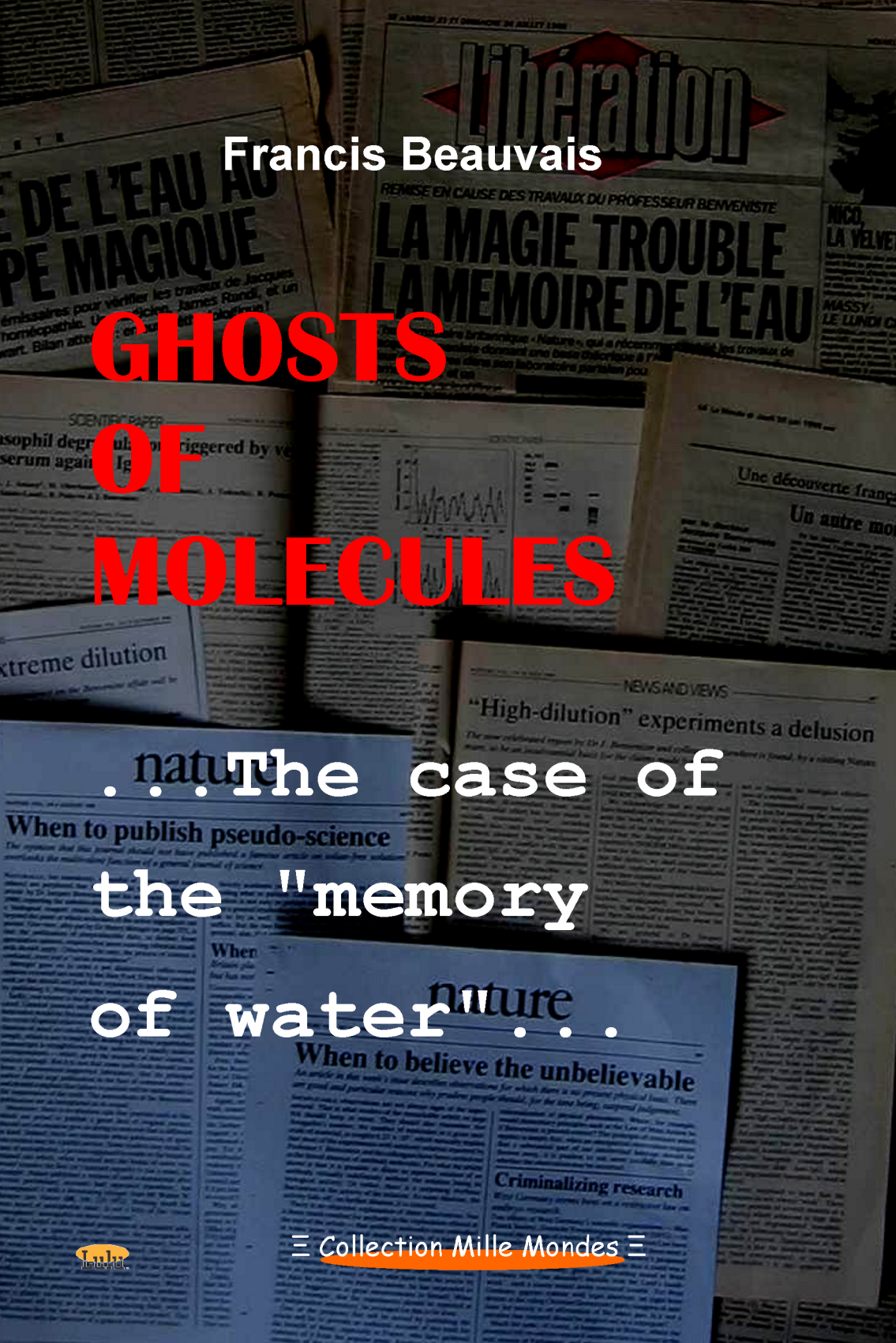
Francis Beauvais
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« *One of the most fascinating scientific affairs of the past few years.* »

Jean-Yves Nau. *Le Monde*, August 9th, 1988.

In 1988, a prestigious scientific journal – *Nature* – published an article that reported odd results. In these biology experiments performed in a well-reputed laboratory, it was as if water was able to keep memory of molecules that had been dissolved and then eliminated after serial dilutions.

Many hypotheses flourished and one began to dream. Was it a new state of matter? Was a new mechanism of cell communication discovered? These results had been obtained by a team managed by Jacques Benveniste who was not a newcomer in science. Director of a laboratory of Inserm, he could have been – according to the rumor – a Nobel prize recipient.

The story became trickier when the journal *Nature* sent a team of investigators in the laboratory to examine these experiments. The surprising composition and the unusual methods of this squad shocked even those who were not favorable to the claims of J. Benveniste.

Over the next years, J. Benveniste gave further developments to "memory of water" which were even more bizarre such as "electromagnetic transmission" and "digital biology".

Based on primary sources and experimental facts, this text tries to go out of the reducing and vain debate – for or against "memory of water" – which fuelled the controversy. It also attempts to put an end to the many rumors, approximations, preconceived ideas and untruths about this story.

In the course of the narrative, another story gradually takes shape: and if homeopathic high dilutions, "memory of water", "digital biology" had been trees which hid the forest? And if the fascination for water had diverted the attention from another phenomenon which was even more fascinating and unexpected?

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Translation of :
L'Âme des Molécules – Une histoire de la "Mémoire de l'Eau"
ISBN : 978-1-4116-6875-1

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First Edition of English translation
First trimester 2016
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ISBN: 978-1-326-45874-4

Francis BEAUVAIS

GHOSTS OF MOLECULES

The case of the "memory of water"

Ξ Collection Mille Mondes Ξ

To Anne, Diane and David

Foreword

The circumstances that guided the elaboration and the writing of this book deserve some explanations. I entered in 1984 as thesis student in the laboratory of J. Benveniste (Unit 200 of Inserm in Clamart) after studies of medicine and biology; my area of research concerned polymorphonuclear basophils, a type of white blood cells involved in allergic phenomena. It was thus quite naturally that I spent a part of my time with the team "high dilutions" of the laboratory.

During this period the case "*Nature* vs. Benveniste" occurred as told in the first part of this book. Left in 1992 towards other horizons, I had then the opportunity to work from 1996 to 2000 in the immediate vicinity of the team of J. Benveniste. Great changes had taken place in a few years. Indeed, the "high dilutions" had given way to the "electromagnetic transmissions". Without being a member of the team, but having kept a friendly relationship with all members, I was in a favored position to observe the surprising experiments of my former colleagues, coming occasionally to help for a "blind" experiment. Nevertheless, I was not a team member any more, but spectator of a fascinating phenomenon. I had the feeling – whatever would be the outcome – that with these singular experiments a chapter of the history of science was written under my eyes. From this moment, I tried to understand, I questioned, I noted. Initially actor, I became an observer. Quickly, the object of my interest slid from "memory of water" towards "the phenomena observed by the researchers who study memory of the water".

Throughout these years – about twenty years – many people who knew my interest for this subject spontaneously transmitted to me information, which added to data from my previous personal work and to my own notes and observations. The classification of the documents and the progressive reanalysis of the experimental results eventually revealed a history which had its coherence and its *raison d'être*. The drafting of this story was becoming imperative. But questioning appeared for referencing some primary documents such as reports of experiments or correspondences. Indeed, for some correspondences – those of J. Benveniste for example – whose knowledge I had had because of my functions or by another channel of information, was I authorized to state them? The content of these letters of which I had copy, did it belong to Inserm? To their addressee? To the legal successors of J. Benveniste? To his co-workers? To the private law company that J. Benveniste funded? Not retranscribing in its entirety these correspondences, I took the view that the usual right of quotation could be granted to me.

The issue of the experiments was more delicate. Did I have the right to describe them? There is a not written principle that considers that an experiment belongs to the researcher who designed and performed it. J. Benveniste not being any more among us, the same questions of "inheritance" could nevertheless arise. Could I describe only experiments with my participation? The narrative risked to be strangely abbreviated. Was it necessary for each experiment to ask for authorization to his/her author or to his "moral heir" in the absence of a "scientific heir"? By doing so – notwithstanding the heaviness of the initiative – was there not a risk to derive towards an "authorized" narrative, but amputated by some quite enlightening episodes?

A beginning of answer appeared by considering the numerous documents that J. Benveniste always widely spread. Indeed, all those who were familiar with him know that J. Benveniste wrote extensively and maintained a dense network of correspondents to whom he sent many letters. In particular, he regularly sent detailed reports of his experiments to French and foreign scientists by means of large mailings to inform them about the progress of his work. Furthermore, a large part of the results of these experiments were already described, at least in their main lines, for example in Schiff's book[1] or on the web site of the laboratory of J. Benveniste. Other results were in the public domain, having been reported at congresses in the form of "posters"; these results are available in the scientific libraries or on line.

A lot of information was also available in texts of patents on "digital biology". These patents are now public and describe in detail the experimental devices and the results obtained with them. Besides, an American multidisciplinary team appointed by an agency of the American Army evaluated an automatic analyzer designed by J. Benveniste and his collaborators. This device was intended to demonstrate the principles of "digital biology". The methodology and the experiments that were then performed for this expertise were described in details in a scientific article published in 2006. And, despite new information that I give on the genesis and the developments of "digital biology", it agrees with the conclusion of this expertise.

These examples thus show that a large part of information concerning the experiments performed by J. Benveniste and his team, either within the framework of "high dilutions" or in that of "electromagnetic transmissions", is available, but in a scattered way and says little for people who are not familiar with this subject.

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[1] M. Schiff. Un cas de censure dans la science (1994). *Albin Michel*

The scenario would have been quite different if these experiments had been performed in a discreet and confidential small circle not wishing to communicate with the outside world. Indeed – to say the least – J. Benveniste wished that his results benefited from a maximal "visibility". This attitude that ended in the arm-wrestling with the journal *Nature* had for consequence to raise high expectation in the public. The counterpart of this publicity that was made around "memory of water" is that the same public retains today a feeling of unfinished story and is still wondering "if Benveniste was right". For the sake of fairness, it would seem thus normal to bring to our contemporaries – scientists, amateurs of sciences, curious persons or simple citizens – all the elements available on this story. Furthermore, these experiments were performed – at least partially and even if it was against its will – thanks to infrastructures and to financing of a public institution on which every citizen holds a legitimate right to inspect.

Finally, not leaving any point in the shadow is also the best way to finish with a number of rumors, approximations, preconceived ideas and untruths of which this story was rich. It is for all these reasons that I adopted an attitude that seemed to me the most reasonable, the most honest and the most relevant at the same time from a scientific point of view, but also towards the history of science to which belongs now this famous episode. To do so, I included in the text any document or information about the only basis of its scientific interest or for the understanding of the story.

As I could not quote everyone, I thank all those – in particular my former friends and colleagues of Inserm – who, sometimes playing "Mark Felt", brought regularly documents or information to my attention; I thank more particularly Jamal Aïssa and Larbi Kahhak who were always opened to my questions and were also pleasant "bench mates". I keep a particular gratitude towards Peter Jurgens with whom I had frequent and passionate discussions during which we shared our perplexity in front of the "phenomena of Clamart". He drew my attention on certain illuminating details. If he had not left us too early, I would have been happy to have his comments on this text.

First part

The *Nature*gate

"What can a fact against a theory? Most of those who know a bit of epistemology will answer: nothing."

L. Chertok and I. Stengers[1]

[1] L'hypnose, blessure narcissique. *Les Empêcheurs de Penser en Rond.* 1999.

Chapter 1. "It is scandalous, you stifle the discovery of the century"

June 29th, 1988

On that day, the readers of the French daily newspaper *Le Monde* discovered an intriguing title on the front page of their favorite journal: "The memory of matter." [1] A promising comment accompanied it: "A French discovery could upset the foundations of physics." Nothing but the best.

The reading of the article could only shock every person having a minimum of scientific knowledge. Indeed, "the question is no more and no less of discovering if some of the current foundations of physics, chemistry and biology must be questioned." The bar was directly set very high!

In inner pages – an entire page was dedicated to the subject – the authors of the article Jean-Yves Nau and Franck Nouchi described the stages which led to this publication. The article of both journalists was enlightened by three texts: a text of J. Benveniste himself, an interview of Jean-Marie Lehn, French Nobel prize laureate in Chemistry, as well as a portrait of J. Benveniste qualified as "*enfant terrible* of the research world."

For the reader in a hurry, the words of J.M. Lehn – as reported by *Le Monde* – could nearly be considered as an approval. The Nobel prize laureate in Chemistry conjugated the verb to disturb in all tenses: "Disturbed, that's the least you can say. These results are disturbing, very, very disturbing." An attentive reading showed, however, that J.M. Lehn had rather mixed feelings. Indeed, even if there was a publication in *Nature* and even if "five laboratories joined to sign such a work", he cautiously added: "In the current knowledge […] I do not see how in biology, in the absence of molecules, one can transmit information."

The text of J. Benveniste entitled "Another conceptual world" did not bother about language precautions. "As usual", those who knew him would have been tempted to say. For this latter "The change of the way of thinking is not less big when one gave up the flatness of the earth for the roundness." And pushing the metaphor to its paroxysm, he did not hesitate to state that "the used procedure is similar to shaking the key of a car in the Seine at the *Pont-Neuf* [a bridge in Paris] and then collect at Le Havre some drops of water to get the same car started and not another one". Having expressed the doubt that suits to every good scientist – "Ourselves, from the observation of the first results, throughout this research […] felt and will feel an anxiety, a tiny quantity of

doubt present somewhere" – he described the exceptional precautions that were taken so that this doubt would be the smallest (replication of the experiments by other laboratories, blind procedures). He could thus give free rein to his innate taste of the metaphor in a kind of final bouquet. He began then to dream and wondered if one day one could not, for example "transport our electromagnetic copy at the other end of the world or in another planet? […] with the information passing under the *Pont-Neuf*, reconstitute a diplodocus or more simply catch here an electromagnetic fish without bones?"

Without showing the slightest scoffing attitude, we cannot refrain from reminding the statement of the French humorist Pierre Dac: "When bounds are crossed, there are no limits anymore"…

On the same day, Inserm – the public institute of research which was the supervisory authority of the laboratory of J. Benveniste – published a rather unusual press release in which, after having briefly described the content of the publication, it reminded:

> "Any real discovery inevitably arouses the temporary incredulity of the scientific community. It is this community that must select, by its usual methods of evaluation where the scientific controversy has its place, between what will be finally considered as only illusion and what will constitute a real advance of knowledge. It is clear in such a situation that the Administration of Inserm must trust in the judgment of this community. It considers that the publication, by a journal as prestigious as Nature, of the mentioned results constitutes an important first stage in the process of evaluation."[2]

As in the very old times of the chivalry, Inserm thus invited the researchers to compete together in a tournament where God would know his own. For *Le Monde*, this text evidenced "the embarrassment of the Institute towards this publication."

However, some details suggested to the attentive reader of *Le Monde* – regardless of any scientific concern – that there was something unusual concerning these results when he learned that "*Nature* decided not only to accompany the publication of the article by an "editorial reserve" but also to appoint a commission of inquiry which would take place early July in the laboratory of J. Benveniste." Why to commission investigators after the publication probably wondered some readers? Wouldn't the opposite have been more logical? But according to *Le Monde*, this sudden haste of the journal suggested that it was "worried, doubtless, not to miss a "historical" publication".

The publication was indeed historical. However, not exactly in the meaning seemingly understood by the journalists of *Le Monde*.

A month before

In fact the information published by *Le Monde* on that day was not really new. The sensational peculiarity was the publication of the results of J. Benveniste in *Nature*, one of the most prestigious – if not the most prestigious – scientific journals. Contrary to numerous journals that publish results in a specialized area, *Nature* is one of the rare high-level journals to be multidisciplinary. In addition to the scientific studies which are reported, the journal also contains numerous sections – pleasant and easy to read – on scientific news, comments on the articles of the week, policy of research, life of laboratories as well as job offers. It is consequently much read and is present in all laboratories and university libraries. Even if they do not sometimes hesitate to criticize the journal for its bias and its taste of the scoop, most of scientists and thesis students would give much for having an article in *Nature*. It is – besides a respected trophy in a list of publications – the guarantee of a certain visibility.

A month before, the journal *Le Monde* addressed the issue of the research of J. Benveniste on high dilutions. Indeed, on May 27th, the latter presented the results of his laboratory to the National congress of homeopathy in Strasbourg. A journalist of *Le Monde* was there.

The results of J. Benveniste were then reported by the daily paper in a way of rehearsal before the edition of June 30th.[3] The catch phrase of front page efficiently attracted the eye by evoking "The "ghost molecules" of homeopathy" and by being preceded by the title: "a scientific basis for a controversial discipline?" The comments of J. Benveniste already reflected the importance of the event: "either we regularly made a mistake for three years […], or we are in front of a completely extraordinary discovery, the consequences and the upheavals of which we cannot yet measure". In inner pages, another subtitle was written in the same vein ("a mysterious phenomenon") and the words of J. Benveniste pronounced at this conference reinforced the rather esoteric general tone:

> "We are thus led to speak of "ghost molecules", of "molecular imprints" in water having kept the "memory" of substances with which it was in contact."

As we see the "memory of water" was not very far. Moreover, it was on this occasion that the daily paper *Liberation* titled a short article: "Homeopathy: Pr J. Benveniste verifies the memory of water".[4] It was apparently the first use of this expression which became famous.

Did these articles in the press – in *Le Monde* particularly with its audience and its reputation of "leading newspaper" – played a role in the decision of John Maddox, director of *Nature*, to publish the article, which was for two years in discussion between the editorial team of the journal and the laboratory of Clamart managed by J. Benveniste? It was according to Jean-Yves Nau "too great an honor for *Le Monde*". [5] But Bernard Poitevin – who, as we will see, was at the origin of the introduction of this research on homeopathy in the laboratory of J. Benveniste – did not hold this view:

> "It is clear that the commission of inquiry should have taken place before the publication of the article, to avoid what, one way or another, will have an air of scandal. One does not understand why the Director of *Nature* proceeded in this way. The hypothesis which I personally retain as being the most likely is that he was irritated by the publication of the information in the newspaper *Le Monde* after the congress of Strasbourg. I was personally a bit shocked by this premature "publication" of the information by journalists to whom silence had been required. But it does not reduce the responsibility of *Nature* that should have decided to refuse the publication of the article and not to set this trap to the Unit 200 and to its director." [6]s

After this article in *Le Monde* by the end of May, J. Benveniste wrote to both journalists Franck Nouchi and Jean-Yves Nau:

> "I was reluctant, as you know, to make public my scientific communication, dedicated to a congress of specialists. Only the publication in an undisputed international journal will not only allow moving forward, but describing all results in detail. Having said that, the article reflects rather exactly the issues raised by these experimental facts. I thank you particularly to have reported our doubts and fears in front of phenomena so disturbing, especially as the French official research leaves us in an absolute material and mental solitude." [7]

As we see, the reluctance was rather moderate. The friendly tone of the article seems rather to suit to J. Benveniste. Indeed, he never hated reading favorable comments on his work. Very fussy, he did not hesitate however to write to journalists if he considered that they related facts concerning him with vagueness or inaccuracy. Nevertheless, the interesting point here is the clear expression of the only purpose of J. Benveniste, namely: to publish these results in a high-level scientific journal, the only solution according to him that would allow opening a new field of research intended to study these "disturbing

phenomena". It is this line of conduct, which he never broke, that could explain the sequence of events and could constitute a second explanation for the decision of *Nature* to let publish the "scandalous" manuscript. J. Maddox indeed declared that when he wrote to J. Benveniste that he would not publish the article in spite of the checks made by other laboratories, the French scientist called him:

> "It is scandalous, you stifle the discovery of the century. You make as the Church with Galilee". He accused me of being against the truth. I answered "why you do not propose an explanation for these results that are contrary to normal science (*sic*)?" And two or three days later, he sent me the theory of the memory of water.[8] I was surprised that a director of a unit of Inserm could build such a theory so fast! And I was irritated. I decided to publish the paper." [9, 10]

"The fight of his life against false science"?

According to this version of the facts, the harassment of J. Benveniste in a kind of "epistemological blackmail" would have overcome the resistance of J. Maddox who, disheartened would have decided to publish the work. One can question such an explanation. One does not become the director of a publication such as *Nature* accidentally and one badly imagines somebody at this level of responsibility taking an important decision simply because he is "irritated". J. Benveniste wondered about another possible interpretation [11]:

> "[…] maybe the aim of John Maddox was to let take off what he considered as a pseudo-scientific theory supporting the heretic homeopathy in order to blow up it in flight. I always wondered if Maddox did not wish to do the fight of his life, supported by the scientific establishment, against "false science." " [12]

And in another circumstance :

> "[They] had decided that it should not work. Maddox said himself in front of the cameras of the British TV: [13] homeopathy is dangerous and the fact that physicians are frequently encouraged to prescribe homeopathy is a very serious situation. And he adds literally: "I had examples in my own family". I really have the feeling that he identified our research with stakes related to homeopathy and that he came in our laboratory as a crusader, to extirpate this pseudo-science." [14]

This third explanation – a "crusade against false sciences" – has perhaps a slight flavor of paranoia, but today it appears that this explanation is the closest

to the reality. Indeed, twelve years after the facts, in an interview about the release of his book "What remains to be discovered [15] ", J. Maddox gave this explanation:

> "We published the work of J. Benveniste for several reasons. At first, *we were sure that he was wrong*, but it is also an interesting example of the way the researchers could make a mistake. The inquiries which we performed in his laboratory showed how an honest scientist could persuade himself that he had made an overwhelming discovery." [16]

Hence, it was a kind of a punishment as an example administered by the director of *Nature* and in any case an effective warning for other "honest scientists". Already in September, 1988 – just after the tumult of the summer – a journalist of the *Journal International de Médicine* questioned J. Maddox on the reason for having published before investigating:

> "We did not wait until the conclusions of our investigation to publish the article of J. Benveniste, because I think that this one would not have admitted that his article would be published at the same time as a report criticizing it." [17]

J. Maddox here mistreated the logic. If the survey was unfavorable, one does not understand for which reasons the article must be published! In fact, as soon as June 30th, i.e. just at the time of the publication of the article, but before the coming of the investigators to Clamart, P. Newmark, Deputy Editor of *Nature*, explicitly admitted that – with full knowledge of the facts – his journal had published results that the editorial team considered to be forgery:

> "The head researchers in this work are reputable scientists and their results have been independently confirmed by several laboratories. *We are certain that the results must be wrong*, but we have been unable to disprove them. We are sending a team of experts to Paris to observe the research at first hand, but meanwhile, because for the publicity this work has already had in France, we feel it is appropriate to publish this paper."[18]

Nature moves its pieces

What were then the reasons explaining the attitude of *Nature*? Irritation to see the results released in the press? Exasperation due to the permanent pressure of J. Benveniste? Personal fight against homoeopathy and "false sciences"? What is certain is that J. Maddox took the offensive at early June 1988. On June 3rd, a rather obscure fax from P. Newmark put a first milestone with caution,

approaching on tiptoe the question of a possible check on the site of Clamart where worked the team of J. Benveniste:

> "[…] John Maddox has requested to me to contact you to ask whether it would be acceptable for Walter Stewart to spend a day or so in your laboratory observing the experimental procedure by which your data are obtained. It is Walter Stewart who is from NIH, that we had asked to write a comment on your paper should we publish it. He would probably be accompanied by James Rondi (*sic*) who has some expertise in examining extraordinary phenomena."[19]

It is important to note that the issue was an inquiry *before* a possible publication. The presence of J. Randi was notified in the conditional tense with a typo. There was no additional detail on the competences of the future investigators. Internet did not still exist in the state where we know it today and J. Benveniste could only speculate. Expert in extraordinary phenomena? Not easy to find such a skill in directories of scientists or among members of scientific associations! Who were then these "Rondi" and "Stewart"? Stewart is a very common name. It was probably the same W. Stewart who previously reviewed the manuscript, but we had no additional information about him. As for "Rondi", this name vaguely echoed something to me.

I finally found a reference about a man named Randi and not "Rondi" in the book of W. Broad and N. Wade, "Betrayers of Truth" [20] which I had read some time ago. Randi was a "magician". He was a professional "skeptic". He boasted of having unmasked Uri Geller which – according to the time-honored expression – "twisted teaspoons".

J. Benveniste then questioned J. Maddox about the reasons of this rather disturbing and unexpected presence, possibly related to hidden intentions of the survey commission:

> "Maddox answers me that our experiments require numerous manipulations, therefore a conjurer would be able to detect a possible error during the manipulations. At no time, I insist, he suggests, as he will do later, the possibility of a cheating – because in this case, I would obviously have got angry." [21]

It was – we must admit – a brilliant exercise in the art of casuistry from J. Maddox. It was especially a white lie. Indeed, according to M. de Pracontal who questioned J. Maddox after the investigation about the incongruous presence of the magician in the laboratory of Clamart [22]:

> "Maddox frankly declared to me that because he suspected a fraud he made this unusual choice: "I thought sincerely that somebody played a trick on J. Benveniste. That's why I asked Randi to come"." [23]

It was only on June 30th – on the day of the publication of the article on high dilutions – that J. Benveniste understood who Stewart was. As an ironic coincidence, it was indeed in an article of the same issue of *Nature* that he learnt that W. Stewart was an "investigator" in the "Baltimore case", from the name of an American Nobel prize laureate charged with fraud (and exonerated afterward). Strangely, J. Maddox introduced then W. Stewart (as well as Feder, the colleague and boss of the latter) in rather depreciating terms:

> "Feder and Stewart's activities have been much resented on several grounds, partly because they have no substantial scientific published records, partly because they are self-appointed keepers of the scientific conscience and partly because of what often seems their nitpicking persistence." [24]

It was only at this moment – when the article was published after a battle of two years – that J. Benveniste began to understand that he had fallen in a case of scientific misconduct. This suspicion on the intention of the investigators –- namely, to investigate on a presumed misconduct – took shape when the qualifications of the investigators were known. Indeed, the experts were not professional biologists, but one of them was a self-proclaimed investigator in scientific frauds and the other one a conjurer specialized in the denunciation of "false sciences". This escapade was managed by J. Maddox undoubtedly Director of *Nature* but whose specialty was formerly physics. It was however too late to move back.

But let us return at early June. On June 13th, J. Maddox unexpectedly announced to J. Benveniste that he agreed to publish the results. Highly ironically, it was now J. Maddox who put pressure on J. Benveniste! The latter indeed would have preferred the article be published a bit later. He told:

> "Mid-June 1988, John Maddox, most probably titillated by press articles after my conference at the congress of homeopathy of Strasbourg, contacts me urgently while I am traveling in the United States. He suggests publishing the article at the end of the month, but imposes an additional condition: I have to accept the principle of a mission of expertise in order to verify the quality of the experiments. A delegation would be at work as early as July in Clamart. Once again I am surprised by this incredible requirement, but, caught by surprise, and not wanting to give up while I am

> reaching the target, I accept. Given the urgency, it is by fax that I send the answers to the ultimate objections of the questions of the referees of Nature after having drafted them in the plane which takes me in Canada." [25]

And somewhere else:

> "During June 1988, I call Maddox several times. On June 13th, he tells me that he is ready to publish the article. I remember a rather lively exchange on the date of publication. He proposed June 30th, but at this date it was impossible to organize the broadcasting of information, so that the press does not tell anything. I preferred September but Maddox refused." [26]

The possibility to see very soon the work published in black and white in *Nature* seems to have blunted the suspicion of J. Benveniste and of his team. Moreover, at this stage, it seemed difficult to be opposed to this investigation. To refuse would mean that there was something to hide. The scientific authority of *Nature*, which aims to be at the forefront of scientific excellence was very high and appeared as a sufficient guarantee. Furthermore, why to worry? The biological system correctly worked in the laboratory of Clamart. There were also these impressive blind experiments made under bailiff's control and described in the article of *Nature*. Two other articles on high dilutions had been accepted, of course in less prestigious scientific journals, but scientists do not spend their time to try to publish their results only in *Nature*. The procedure of checking that had been proposed appeared at this moment rather as a formality. Maybe the investigators simply wanted to verify that the laboratory notebooks were in accordance with the data reported in the article. At that time it seemed difficult to put in balance in one hand the work of several years and on the other hand an expertise of no more than a few days. If this expertise was the price to pay to get an article in *Nature*, why not. It would be a last effort before summer holidays. The fact that the checking procedure, which was previously scheduled before the publication was now planned after it did not seem to disturb many people. This was the state of mind which prevailed in the laboratory of Clamart at this time. Naivety? Certainly.

But before beginning the narrative of the legendary and disputed investigation of *Nature*, how did we arrive at this situation?

Notes of end of chapter

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[1] *Le Monde*, June 30th, 1988.

[2] Press release of Inserm on June 29th, 1988.

[3] *Le Monde,* May 29-30, 1988.

[4] *Libération*, May 30th, 1988.

[5] Michel de Pracontal. Les mystères de la mémoire de l'eau, p. 121.

[6] Le Médecin Homéopathe 1988, n°3, p. 40.

[7] Letter of J. Benveniste to J.Y. Nau and F. Nouchi on May 30th, 1988.

[8] J Maddox takes some shorcuts with the facts. The expression "memory of water" was of course never used in the article; the term was coined later. Furthermore, J. Maddox seems to suggest that J. Benveniste elaborated a complex theory such as the theory of relativity. In fact, there was never any theory at all. We will see in a next chapter that some sentences were simply added at the end of the article to propose possible directions for future studies.

[9] J Maddox gave reasons of his decision a number of times. In 1997, he explained it in these terms to a journalist of *La Recherche*: "Here is how things took place. I took home the complete file during a weekend, and I wrote what seemed to me a courteous letter of refusal to Benveniste, and I sent it. Some days later, Benveniste called me and asked me if I realized that I was stifling the biggest discovery of this century. He was furious. I answered him that his article did not consider how the data could find an explanation within the framework of classical physics and chemistry […]. He answered me: "No problem", and he sent me a fax on the "memory of water" as early as the next day. Then he again phoned me to ask if I was going to publish him this time. I answered him that it was ridiculous, that his new explanation was even more fanciful than the article itself. After that, I lost patience, and he then began comparing himself with Galilee. Then, I said to him: "OK, we will publish the article, but with a warning and if you let us visit your laboratory" ". When the journalist of *La Recherche* asked him: "But once again, why to have published the article?", J. Maddox answered: "I said it to you, the extravagant claims made me lose my cool" (*in* J. Maurice. L'hebdomadaire « Nature ». Un sanctuaire de la science en marche. *La Recherche*, July-August, 1997).

[10] M. Pracontal. Les mystères de la mémoire de l'eau, p.13.

[11] It is also possible that J. Maddox had in mind the initiative of Robert W. Wood, an English physicist who reported in *Nature* at the beginning of the twentieth century his visit in France in the laboratory of R. Blondlot who claimed having discovered a new type of rays. The experiments to show the hypothetical N-rays were performed in the darkness. Indeed, the method used by R. Blondlot was based on the variations of the brightness of an electric spark, which was a very subjective method. Having put away a prism that played an important role in an experiment, the same positive results continued nevertheless to be imperturbably announced by R. Blondlot and his assistant. The report made by R.W. Wood in *Nature* marked the end of the N-rays. This episode of the history of science is now an archetype, which allows illustrating the bias that the

subjectivity of the experimenter can introduce into experimental results. Blind experiments eliminate this bias. The story of N-rays was told and analyzed by P. Thuillier (La triste histoire des rayons N *in* Le petit savant illustré. *Seuil*. 1980).

J Maddox alluded to this episode one year after the visit to the laboratory of Clamart: "In September 1904, we (*sic*) asked the distinguished specialist in physics R.W. Wood to visit one of the laboratories that claimed having detected N-rays, a more powerful type of X-rays. The latter wrote: "I went there not without skepticism, but with the hope that I could be convinced of the phenomenon." He was not convinced. Pure coincidence, the laboratory was also in Paris" (*in* J. Maddox. Plus vrai que « Nature ». *Le Monde*, July 26th, 1989). Swept along by its own momentum to draw a parallel between both cases, J. Maddox made an error of geography. The laboratory of R. Blondlot was situated not in Paris but in Nancy. It was precisely a tribute to his city that Blondlot called N-rays this "new" radiation.

[12] J. Benveniste. Ma vérité sur la mémoire de l'eau, p. 63.

[13] J Maddox had then declared: "I thought that it was important, in the current context, that there was no delay for publication. Among other considerations, the more the comment on the report of Benveniste would be delayed, the more we would be in danger – because it is, in my opinion, a danger – to see the partisans of the homeopathic medicine spreading in declarations, asserting that their curious way to cure was legitimized." (P. Alfonsi. Au nom de la Science, p. 72).

[14] Philippe Alfonsi. Au nom de la science, p. 34.

[15] The title of the book of J. Maddox "What it remains to be discovered" is curious. A real discovery is precisely not scheduled.

[16] Cyrille Vanlerberghe. Qui sera le prochain Einstein ? *Le Figaro*, May 2nd, 2000 (emphasized by me).

[17] Joël Le Moigne. Interview of John Maddox. *Le Journal International de Médecine*, 1988, September 15–30, n°117, p. 15.

[18] M.W. Browne. Journal publishes theory in disbelief. *New York Times*, 30 juin 1988 (emphasized by me).

[19] Fax of Peter Newmark to J. Benveniste on June 3rd, 1988.

[20] William Broad and Nicolas Wade. La souris truquée. *Seuil* (1987) [Translation of "Betrayers of Truth". Simon & Schuster: New York. 1982].

[21] P. Alfonsi. Au nom de la science, p. 27.

[22] It seems that the initial proposal to integrate J. Randi to the group of investigators came from W. Stewart.

[23] Michel de Pracontal. L'imposture scientifique en 10 leçons. *La Découverte* (2001), p. 91.

[24] J. Maddox. Can a greek tragedy be avoided? *Nature* 1988 ; 333 : 795.

[25] J. Benveniste. Ma vérité sur la mémoire de l'eau, p. 57.

[26] P. Alfonsi. Au nom de la science, p. 24.

Crossed portrait #1

by Franck Nouchi

"The *enfant terrible* of the French medical and scientific community"

"At fifty three years old, Doctor Jacques Benveniste is still, under teenager's look, the *enfant terrible* of the French medical and scientific community. Poorly known by the general public, he cultivates not without elegance or naivety an outstanding character, halfway between a member of the generation of May 68 and a member of the Establishment that he hopes never to become.

"Immigrated of the first generation" – his father, native of Salonika, arrived to Paris in 1925 – this Parisian, son of local doctor is, in his young age, seduced by racing cars and wishes only one thing: becoming an automobile engineer. Having passed his "baccalaureate" at fifteen years, "too bad in mathematics", he takes refuge within medicine.

It was what was called the "royal road". Medicine student, resident of the hospitals of Paris and staff physician, the future mandarin put an end to this academic career to enter the world of the research. After the thunderstorm of 68, he leaves France for California. At La Jolla he discovers the PAF […] Then he decides to return in France, in 1973, in Professor Jean Hamburger's team and, finally, he obtains autonomy in Clamart, with the creation of the Unit 200 of Inserm that he manages since 1980 and where fifty people work on the fundamental mechanisms of allergy and inflammation today."

(*Le Monde*, June 29th, 1988)

Chapter 2. "It is a debate that will probably overwhelm me"

First quakings

The introduction of high dilutions in Unit 200 of Inserm led by J. Benveniste was due to Bernard Poitevin. This latter was a homeopathic physician, but he had also a "classical" scientific training. In 1980, he met J. Benveniste to ask him to direct his thesis. J. Benveniste – who had moved to a new location in Clamart near hospital Antoine Béclère – accepted. At the beginning, it was not question of homeopathy. The subject of the thesis of B. Poitevin concerned the production of free radicals by inflammatory cells.

B. Poitevin afterwards got in touch with Michel Aubin, the scientific director of the *Laboratoires Homéopathiques de France* (LHF). A first contract was signed in 1982 between LHF and the laboratory of J. Benveniste to assess the effect of homeopathic products on some biological models of the laboratory. In 1983, B. Poitevin became scientific director of LHF.

In 1982, J. Benveniste was approached by Boiron Laboratories to reproduce results that had been obtained by Jean Sainte-Laudy on basophil degranulation. The latter was a physician who managed a private laboratory of medical analysis in Paris, specialized in medical immunology. He particularly used the "test of degranulation of basophils" – developed by J. Benveniste – as an *in vitro* method for the diagnosis of allergies. Besides, J. Sainte-Laudy was interested in homeopathic high dilutions and he worked on this subject with Boiron Laboratories for several years. A first contract with Boiron was signed by J. Benveniste in 1983.

Two research programs intended to assess homeopathic products on *in vitro* biological models were thus simultaneously led during several years in the laboratory of J. Benveniste for two rival firms, LHF and Boiron (they merged in 1988), sometimes on identical models, on the test of degranulation of basophils in particular. This biological test will be detailed in the next chapters (see also Appendix 1).

During the next years, the most significant results obtained in the Unit 200 concerned the reproduction of some of the results of J. Sainte-Laudy, namely the inhibitory effect of histamine at high dilutions on basophil degranulation. Another study managed by B. Poitevin concerned the effect of silica at high dilutions in mouse. Besides, B. Poitevin also obtained significant results with *Apis Mellifica* – a homeopathic product – on basophil degranulation. The latter

presented his results to the "Forum of the young researchers" in Lille in September 1984 and these results were published in January 1986 in a journal which – it must be underscored – was not a "journal of homeopaths", but a journal that published studies concerning new biomedical technologies. This first "breakthrough" was perceived by J. Benveniste and B. Poitevin as an encouragement to persist in their attempts to go out of the "ghetto" of journals dedicated to homeopathy, which – we must admit – are not very demanding on the level of proof and the quality of the submitted results.

In these experiments, homeopathic dilutions of *Apis Mellifica* decreased basophil degranulation. *Apis Mellifica* is a homeopathic medicine sold in pharmacy for the treatment of acute inflammation. There was some publicity around these results in the media before their publication. The reactions that these experiments aroused deserve to be described because they anticipated the repercussions that the publication in *Nature* induced a few years later.

Apis mellifica, *queen for a day*

On January 17th, 1985, a round table on homeopathy was organized in Puteaux in the suburb of Paris by the medical journal *Impact-Médecin*. Physicians – homeopaths or "skeptics" – representatives of associations of homeopaths or representatives of the homeopathic industry participated, as well as J. Benveniste.[1] Public and journalists were present during the exchanges of views. During the discussion, J. Benveniste reported that now the question of high dilutions – a major obstacle which prevents the recognition of homeopathy by scientists – was no more a problem. To support his statements, he described the results obtained in his laboratory that evidenced a biological effect with *Apis Mellifica* at dilutions where no molecule of the initial compound could in principle be present.

Impact-Médecin published a report of this debate on February 23rd and this information was widely covered by the media. J. Benveniste denied then to have wanted this publicity and asserted that the results were published "without his agreement and in a premature way".[2] He nevertheless distributed photocopies, which summarized these results during the meeting. B. Poitevin himself regretted this diffusion, not understanding why J. Benveniste displayed these experimental data in such a detailed manner.

In any case, the reading of the press articles that reported this information is interesting because homeopathy and its possible therapeutic properties were then pointed out. One did not yet speak of revolutionizing physics and biology. J. Benveniste, at that moment, seemed careful and he did not make audacious extrapolations as he did a few years later:

> "When I agreed to test these various homeopathic products, I was very skeptical […]. I knew nothing about homeopathy, and my scientific culture – I would say even scientistic – incited me rather to think that homeopathy was only a placebo. Hence my great surprise when I saw the first results. […]
> We must certainly not draw conclusions on the therapeutic efficacy of these various products. A biological effect was observed. Neither more nor less. " [3]

And, when one pointed out to him that it was the first time that a "team of international reputation" published such results, he added, auguring without knowing it:

> "You know, that is the way it is, there is nothing we can do about it. It is a debate that will probably overwhelm me, which already overwhelm me maybe. But the facts are there."

Even though there was some suspicion coming from skeptics, it concerned rather the manufacturer who supplied the tested solutions and who would have been able "according to some committed opponents of homoeopathy […] to replace *Apis Mellifica* by corticoids" [4,5]. But the sincerity of the researchers of Clamart was not questioned.

Although these results seemed promising, nevertheless they remained preliminary and J. Benveniste took a lot of risks by advancing so openly. The results were then not published and had not been submitted to the "judgment of peers". Furthermore they had not been reproduced in other laboratories and some control experiments to eliminate experimental biases had not been yet performed (blind experiments for example).

The friendly, and sometimes accommodating, welcome which was granted to these results in the media was probably due to the climate at that time. Homeopathy as therapeutics came to national attention in 1984. The Minister of Social Affairs, Georgina Dufoix, was favorable to "alternative medicines" and the reimbursement of homeopathic medicines by Social Security was agreed that year. Contrary to the other medicines that have to give evidence of their efficacy, it is enough for the homeopathic specialties to refer to the "tradition" to be recognized. Besides this political determination to promote what some people considered as quackery, the Academy of medicine denounced a return to irrationality explaining that "in the present state of science, the homeopathic prescription is not an act of reason, but an act of faith" and wondered with some irony if it would be necessary in the future "to consider the dowsing rod

as an official tool of diagnosis besides the stethoscope and the laying-on of hands as a therapeutic process?" [6]

Away from the media, however, when the researchers of Inserm U200 experimented at the bench, they noticed that the effects of the homeopathic products, if they existed, were nevertheless variable and capricious. The exploration of the physico-chemical properties of the homeopathic high dilutions appeared thus difficult without an experimental model working more regularly. In the absence of such a model, the bet of J. Benveniste would be probably very adventurous.

Notes of end of chapter

[1] Among the "skeptics", H. Gounelle of Pontanel of the Academy of medicine, C. Laroche of the National council of the Order of Doctors, M.F. Kahn, Professor of medicine, specialist in rheumatology, were present; among "pro-homoeopathy", there were P. Cornillot, dean of the faculty of Medicine of Bobigny, M. Tétaut and F. Buraud, both representatives of societies of homeopaths and Jean Boiron, co-founder and director of laboratories Boiron (from M. Rouzé. Mieux connaître l'homéopathie. *La Découverte* 1989, p. 185).

[2] *Le Nouvel Observateur*, April 12th, 1985.

[3] F. Nouchi. Certains produits homéopathiques ont des effets biologiques *[Some homeopathic products have biological effects]*. *Le Monde,* March 6th, 1985.

[4] Incidentally, corticosteroids have no effect on basophil degranulation in the *in vitro* experimental conditions to assess the effect of *Apis mellifica*. Degranulation of basophils and histamine release are too fast phenomena to be inhibited by corticosteroids the action of which requires protein synthesis. In order to inhibit basophil degranulation with a corticosteroid, an incubation of 24 hours is necessary.

[5] F. Nouchi. *Ibid.*

[6] Gounelle de Pontanel H, Tuchmann-Duplessis H. Non à la délivrance d'un diplôme d'homéopathie par les facultés de médicine *[No for the delivery of a diploma of homoeopathy by the faculties of medicine]*. *Bull Acad Nat Méd* 1984; l68: 429.

Crossed portrait #2

By Philippe Alfonsi

"The profile of the perfect mandarin"

"The man through whom the scandal arrives", Jacques Benveniste, is one of the most renowned French immunologists. He has the profile of the perfect mandarin, he says himself with a smile. Ironic with ease, caustic, iconoclast, he manages a laboratory, the prestigious Unit 200 of the *Institut national de la santé et de la recherche médicale* (Inserm). He has an international reputation since he discovered paf-acether, a mediator involved in some allergic mechanisms. Before "the affair", he was frequently presented as one of the rare French who could win the Nobel prize in his area of research."

(*Au Nom de la Science*, 1989, p.11)

Chapter 3. An uncharted continent

Before continuing, the reader who is not biologist or not familiar with this area of research can refer to Appendix n°1. Information about the experimental model and interpretation of the results are given.

An unexplored peak is observed

It is tempting to believe that the god of the scientists watched then over J. Benveniste. Indeed, a modification of the experimental conditions performed at the end of 1985 timely arrived. It is the spark which sets fire to powder and propelled this research subject towards unhoped and unexpected summits.

On November 5th, 1985, there was a meeting in the Unit 200 of Inserm in Clamart with some people – including the author of this text – who worked in the laboratory on high dilutions. J. Sainte-Laudy who has been mentioned in the previous chapter, also participated in the meeting.

J Sainte-Laudy explained us that he often observed a second peak of basophil degranulation when he diluted an allergen more than usual. Our interest was raised, but we pointed out to him that this type of phenomenon was more or less already described and could be explained because allergens are complex molecules (they have several epitopes the immunologists say). J. Sainte-Laudy agreed, but he immediately added that he had observed this effect not only with allergens but also with anti-IgE antibodies, what was more difficult to explain. More importantly, he said that he noticed that high dilutions of histamine "flattened" this second peak. He specified that this inhibitory effect exceeded by far the effect on the first peak of degranulation that both laboratories used until now to assess the effect of homeopathic substances.

We were torn between doubt and desire to believe him. On one side, we knew well J. Sainte-Laudy; we appreciated him for his imagination and his creativity. But getting details on the precise experimental conditions, how many experiments had been performed and what was the reproducibility was often a challenge.

On the other hand, if this story of second peak was true, maybe it was the perfect model to assess high dilutions with obvious effects, in white or black.

We dreamed about such an experimental model, because we could then advance further in the understanding of the physico-chemical characteristics of high dilutions.

In any event, checking the reality of this "second peak" was very simple and the experiment was immediately performed. In contrast with J. Sainte-Laudy, we had only rarely at our disposal samples of blood from allergic subjects and we thus used blood cells from not allergic donors that were stimulated with anti-IgE antiserum. Indeed, anti-IgE antiserum plays the role of a "universal allergen" (see Appendix n°1).

After counting the stained basophils under a microscope, we noticed, with a mixture of surprise and excitement, a rise of the curve of degranulation with the low concentrations of anti-IgE antiserum (Figure 3.1).

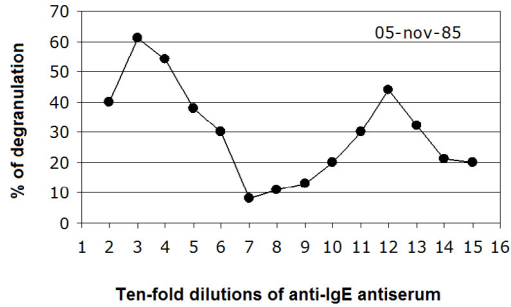

Figure 3.1. First attempt at Inserm Unit 200 to get basophil degranulation with low concentrations of anti-IgE. Samples were obtained after serial ten-fold dilutions. Between each dilution, the tube was shaken for 10 seconds using rotating shaker. The left "peak" is the classical degranulation curve; the right peak is the "second" peak the observation of which was unexpected. Note that the "left" peak could be also obtained without shaking between each dilution.

In the weeks that followed November 5th, 1985, we explored this new avenue which unexpectedly appeared under our feet. We had the feeling that an important lock had been broken. We were in the state of mind of somebody who would discover a hidden door in his own house for new rooms that he would explore gradually. From November 6th, we repeated the experiment and the second peak (which we improperly called the "second curve") was still there (Figure 3.2)

From November 5th, 1985 to April 11th, 1986, 39 double peaks of degranulation in various experimental conditions were obtained as depicted in Figure 3.3.

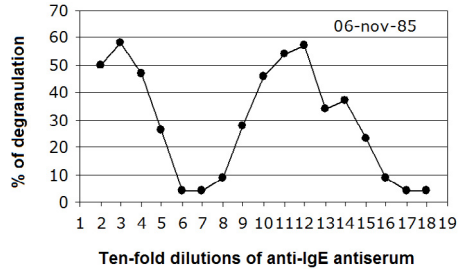

Figure 3.2. Repetition of the experiment of November 5th, 1985.

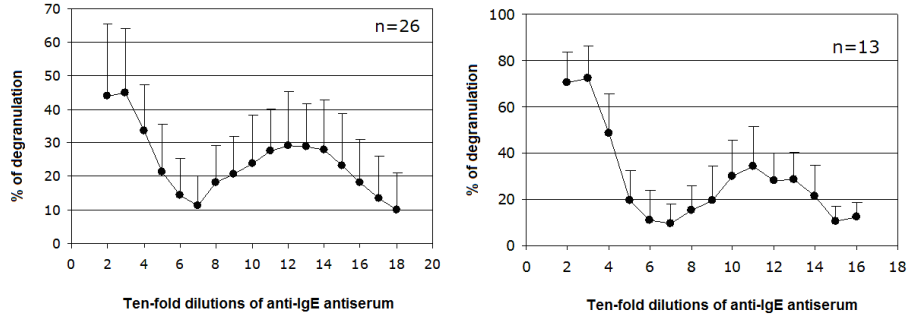

Figure 3.3. Summary of 39 experiments confirming the existence of a second peak of basophil degranulation. Results are presented with mean ± standard error of the mean. The experiments were performed with two different saline buffered-solutions: 26 experiments for the first one and 13 for the second one.

The second peak keeps its promises

But, for the moment, we were impatient to assess the effect of high dilutions of histamine on the second peak. Histamine indeed is not only released by basophils, but it can also inhibit its own release. This phenomenon was known for histamine at "classic" concentrations and in previous experiments on the "first peak", the same inhibitory phenomenon was observed with histamine at high dilutions.

We thus chose the dilution "18 C" of histamine with which we had already observed inhibitory effects on the first peak. Traditionally, homeopathic dilutions are performed by factor 100 and are named "C" (it is this "C" that we can read on the tubes of homeopathic pills; cf. Appendix 1). Therefore, the 18th

1/100-dilution – that is a dilution $1/10^{36}$ – "theoretically" contains 10^{-36} mol/L of histamine. We also decided to test this "18 C" dilution on all dilutions of anti-IgE to kill two birds with one stone: to accumulate results with the second peak and to begin exploring the possible inhibitory effect of histamine at high dilutions. We decided to perform these experiments in blind conditions to convince ourselves of the reality of the results.

During November 1985, four blind experiments were performed that compared the effect of 18 C dilution of histamine and a control dilution obtained exactly in the same conditions, but without histamine in the first tube. Control samples and samples of histamine at high dilution were given to the experimenter under a code label. We then noted with pleasure that a moderate inhibition of the first peak was obtained – thus reinforcing our previous results – and most importantly that a very large inhibition of the second peak was obtained (Figure 3.4 A).

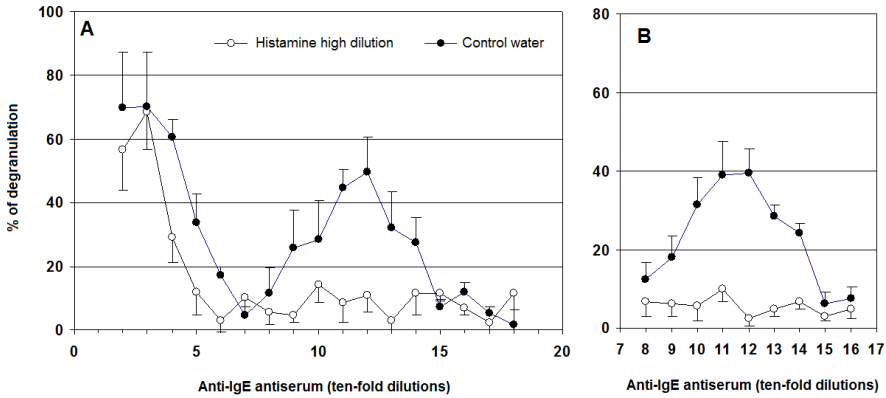

Figure 3.4. This figure shows the effect of high dilution of histamine on the first and second peaks (figure A) and on the second peak alone (figure B). High dilutions of histamine were obtained by performing 18 serial 1/100-fold dilutions with 10 seconds-shaking between each dilution (dilution $1/10^{36}$). The "theoretical concentration" of histamine was about 10^{-38} mol/L. "Water control" was obtained with the same process without histamine at the onset. Results are presented as mean ± standard error of the mean of 4 experiments for A and 8 experiments for B. All these experiments were performed blind: the tube containing high dilution of histamine and the tube containing its control were given under a code.

Then, in order to save time, we focused on the second curve and 8 new blind experiments were performed with similar results (Figure 3.4 B). We then assessed the effect of a series of dilutions of histamine on the "top" of the second peak. The results of three experiments confirmed the results that we had previously obtained on experiments restricted to the first curve with two zones of inhibition the first one around 5–6 C and the second around 17–18 C.

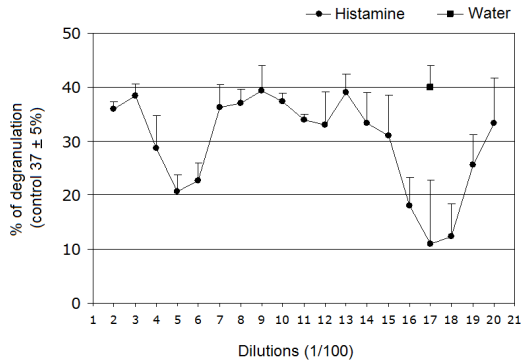

Figure 3.5. For these experiments, a solution of histamine was 1/100-fold serially diluted with 10-second shaking between each dilution (mean ± standard error of the mean of 3 experiments). The effect of these solutions was assessed on the second peak of degranulation. A control "water in water" diluted in the same conditions had no effect (square).

Simultaneously, experiments were undertaken to obtain an exit of histamine from cells ("release of histamine") in the presence of high dilutions of anti-IgE (see Appendix 1). Various experimental conditions known to favor the release of histamine were tested, but were unsuccessful. Finally, other experiments were performed to assess the effect of homeopathic products *Apis mellifica* and *Lung histamine* on the second peak.

A third peak appears and also the next ones

Only six months after the first observation of the second peak, an experiment was performed to answer the following question: what was beyond the second peak? An infinite plain? A mountain range? On May 13th, 1986, cells of a patient allergic to dust mites were incubated with allergen dilutions and waves of degranulation were observed beyond the second peak.

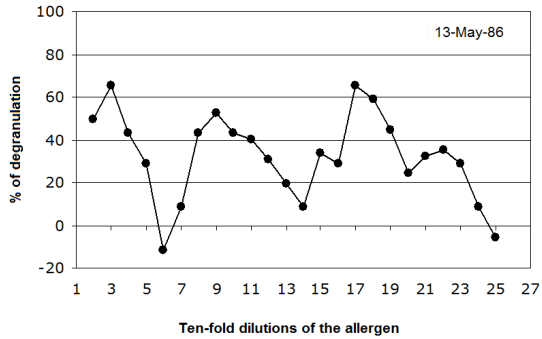

Figure 3.6. First evidence of degranulating effect after the second peak.

On June 11-12th, 1986, an attempt to activate basophils until the dilution $1/10^{60}$ of anti-IgE was performed, giving the result shown below.

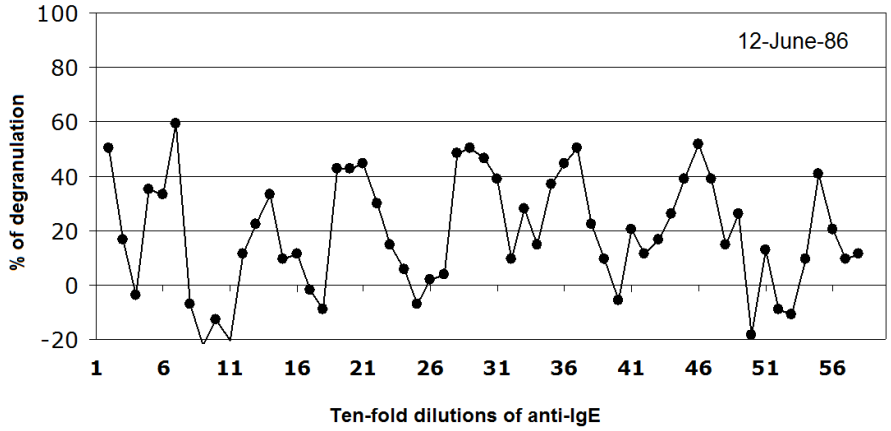

Figure 3.7. This figure shows the first attempt to dilute up to $1/10^{60}$. As soon as the phenomenon began, it seemed to self-reproduce at the infinite with successive waves of biological activity.

The dilutions of anti-IgE were continued until $1/10^{120}$ (Figure 3.8). In front of these oscillations, which seemed to continue endlessly, we were bewildered. The vertigo which seized us with the early experiments when we performed these (very) high dilutions was now a little blunted because it seemed that the same phenomenon was self-sustaining throughout the whole dilution process.

Naturally, we were also concerned about the "specificity" of this phenomenon. We observed that an anti-IgG antiserum, which did not produce a first peak, had also no effect at high dilutions.[1] This result was excessively

intriguing. Indeed, an anti-IgE immunoglobulin and an anti-IgG immunoglobulin have very similar structures. Only a small portion of the protein – the one that "recognizes" IgE or IgG – is different. Nevertheless, an immunoglobulin is a voluminous molecule and if water keeps the "memory" of this molecule, it was as if water also keeps in memory all the fine details of this big protein structure (Figures 3.8 and 3.9).

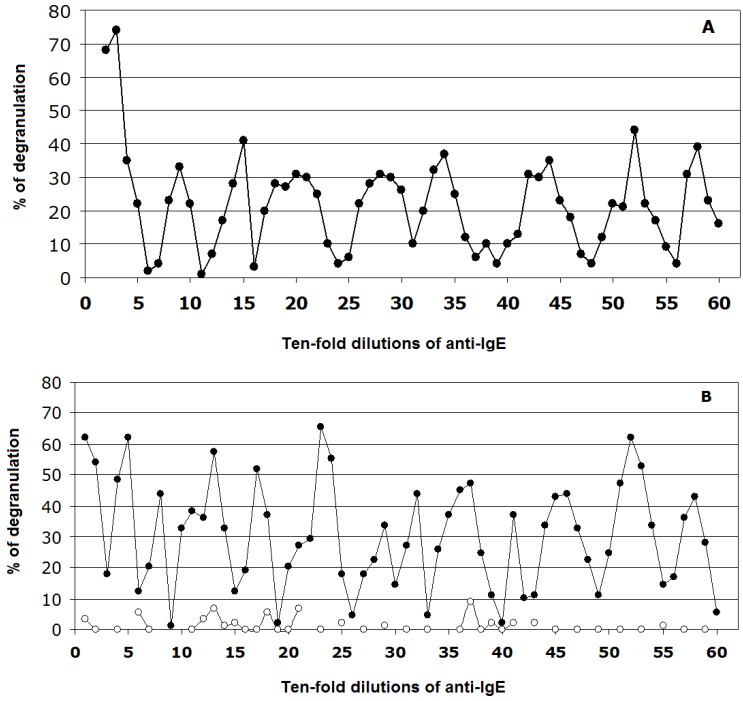

Figure 3.8. These experiments that repeat those of Figure 3.7 were published in *Nature* in 1988. They were reproduced a dozen times with anti-IgE antiserum dilutions (including four experiments with anti-IgG controls: open circles). Ten-fold dilutions were performed in experiment A and hundred-fold dilutions in experiment B. The last dilutions (60) in B is thus a $1/10^{120}$ dilution.

The apparent specificity of the high dilutions was at least as problematic as the absence of molecules. Indeed, even if one could accept that the properties of water could be modified during the successive dilutions in the absence of the starting molecules, the maintenance of the specificity was much more difficult to conceive.

We also used other basophil degranulating agents at high dilutions (calcium ionophore, phospholipase A2, etc.) and the waves of degranulation were always

there. Thus, rabbits were immunized with an antigen named peroxydase. A degranulation of their basophils was also observed in the presence of high dilutions of this antigen. But here once again, there was no release of histamine (Figure 3.10).

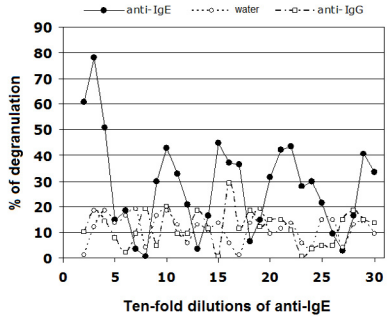

Figure 3.9. In this experiment, anti-IgE dilutions were prepared until $1/10^{30}$ before coming into contact with basophils. The controls (antiserum anti-IgG or water) were prepared in the same conditions. The "water" control showed that the shaking-dilution process alone was not sufficient to trigger the phenomenon; the "anti-IgG" control showed that diluting a protein was not sufficient – an immunoglobulin in this case – to obtain the same results as with anti-IgE.

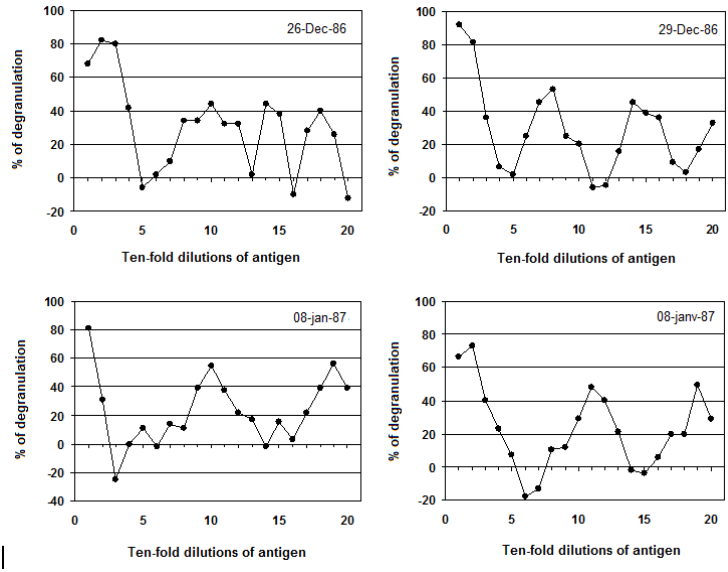

Figure 3.10. Rabbits were immunized against an allergen (peroxydase). In the presence of a series of dilutions with this allergen, rabbit basophils also degranulated with "waves" according to the strength of the dilution. Other agents that degranulated basophils at "classic" concentrations were also able to induce rabbit basophil degranulation at high dilutions.

Ghosts and their footprints, predators and their preys

Such oscillations of the biological effect of a substance according to its dilution are unusual in cell biology and in pharmacology. At the most, it is sometimes reported in some biologic systems "bell-shaped" responses according to the concentration. Some opponents to high dilutions sometimes took these oscillations as an argument to state that these results were "impossible" [2]. In fact, the oscillations observed with high dilutions reminded models described in population biology describing evolution over time of two animal populations, one being a predator and the other one a prey. The variations of the numbers of preys and predators can be modeled by the classic equation of Lotka-Volterra, which was developed in the 1920s. [3] This model rests on the idea that the number of preys decreases according to the number of predators and that the number of predators increases when the number of preys increases. We can easily transpose this model in the field of the high dilutions.

Indeed, to explain these oscillations, we can suppose that water has the property to keep a kind of imprint in counter-relief by "molding" a dissolved molecule. This molding would then generate a "ghost" – a kind of copy of the initial molecule – which in turn would leave an imprint. The successive generation of these imprints (biologically inactive because in "counter-relief") and "ghosts" of the molecule (biologically active because in "relief") could in this manner explain the succession of the peaks of biological activity. It is therefore necessary that "real" molecules are present in sufficient amounts at the start of the reaction, but the process could then self-generate when the initial molecules would have disappeared during the serial dilution process.

According to the model of Lotka-Volterra, we define X_t as the number of preys and Y_t the number of predators at time t. We then obtain:

$X_{t+1} – X_t = rX – aXY$ et $Y_{t+1} – Y_t = bXY – mY$ with:
r = rate of reproduction of preys in the absence of predators
a = rate of mortality of preys due to predators
b = rate of reproduction of predators according to eaten preys
m = rate of mortality of predators in the absence of preys.

We can conceive from this model a simple mechanism to explain the oscillations observed with high dilutions (Figure 3.12). The graphic representation of the equation of Lotka-Volterra with parameters specifically chosen gives the curves depicted in Figure 3.13.

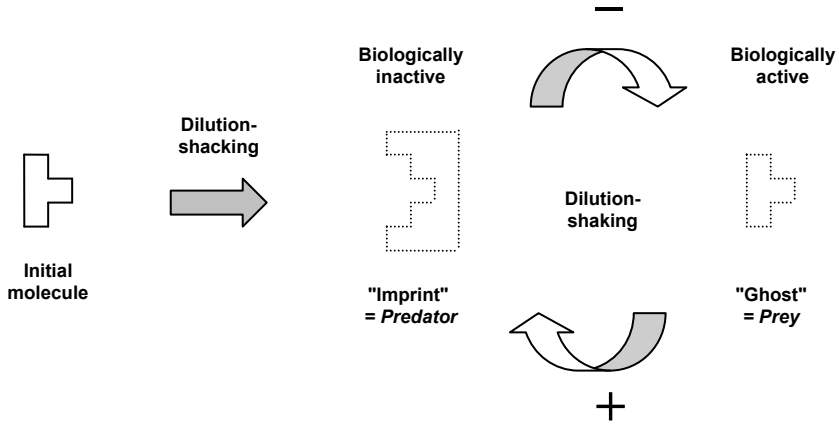

Figure 3.12. The model of Lotka-Volterra applied to high dilutions.

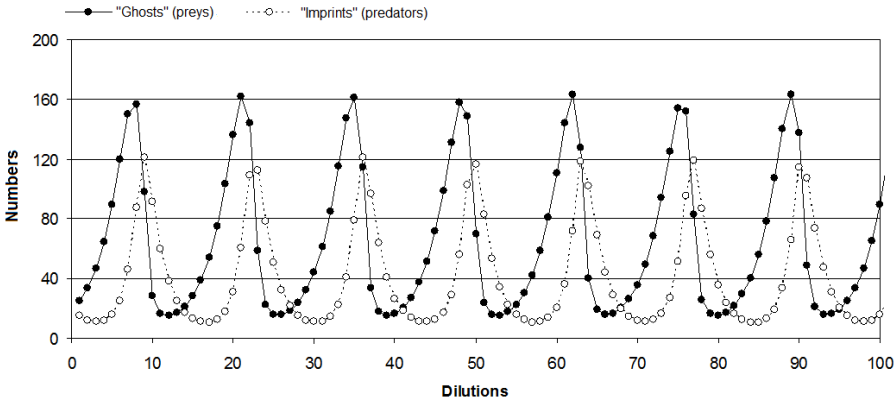

Figure 3.13. The model of Lotka-Volterra, which is usually applied in ecology to model dynamics of animal populations, can be used to model the experimental oscillations observed with high dilutions. One can indeed make the simple hypothesis of the existence of two "entities" that, as in the initial model, interact on each other as one prey and its predator do. They are "ghosts" and "imprints", respectively. Only "ghosts" have biological activity (closed circles); "imprints" (open circles) are present in the solution but are biologically inactive. During each step of the dilution-shaking process, "ghosts" produce "imprints" that in turn destroy a certain amount of "ghosts". By correctly choosing the parameters of the model, oscillations of the number of "ghosts" – biologically active because they mimic the molecular structures of the starting molecule – appear. Each step of the dilution-shaking process plays the same role as time in the model of Lotka-Volterra.

Hunted by Avogadro's ghost

Of course, this modeling is hypothetical. In spite of our difficulties in naming the underlying processes of the effects that we observed, it was however such images ("molecules ghosts", "imprints", "copies", "moldings", "virtual molecules", "structuring of water") that we had then in mind and that allowed us to dilute beyond what was *a priori* reasonable and without feeling ourselves ridiculous. It was indeed psychologically difficult – because of the nonsense of this process for someone who knows a minimum of physical chemistry – to dilute a biological substance beyond a dozen ten-fold dilutions. Indeed, every biologist knows that it is very rare to observe biological effects at concentrations below 10^{-14} mol/L. Diluting beyond the limit fixed by the Avogadro number [4] needs either an unshakable faith or a total ignorance of an elementary scientific principle. We should not bury our heads in the sand, after this limit, we diluted water in water! One might as well add zeros to zeros hoping that a non-null number would appear.

But thanks to such theoretical speculations, we could imagine when we made this strange manipulation that, in spite of the disappearance of the initial molecules, it was not impossible that the process of dilution-agitation would generate "entities" that in turn would convey biological activity. In fact, these speculations remained mechanistic and very close to a molecular description of biology. It was also by means of "structures" that cell activity would be modified. These "structures" would be as "true" biological molecules able of interacting with cell receptors. We were far from a "new state of the matter" prophesied by some people and far from the "questioning of two centuries of scientific discoveries". The law of mass action was not indeed modified in this conception. At the most it would be necessary to take into account additional interactions in some circumstances. These conceptions were hardly formalized within the framework of the experiments at Clamart, but they allowed not to be stopped by the argument of the unsurpassable limit fixed by the Avogadro number.

However, the highlighting of physical modifications of the solvent related to its possible structuring appeared as a distant objective when the experiments which we have described above were performed. In the meantime, it was necessary to convince the other scientists – including those of Inserm U200 who worked on more "classic" subjects – and especially to convince ourselves that these biological effects were very real. It was then dozens of experiments that were performed.

Michel Schiff analyzed in 1992 all the laboratory notebooks concerning the period that followed the observation of the "second peak". Scientist at the

CNRS (*National Center for Scientific Research*), initially in physics and subsequently in sociology of sciences, M. Schiff participated in 1992-1993 to the life of the laboratory of Clamart to understand the causes of the controversial debate. We will talk more about M. Schiff in the second part of this text. Firstly skeptic about the results of J. Benveniste on high dilutions and "transmission of biological signal", he ended up being convinced about the reality of the results by investigating himself and by participating in the experiments. When he began to observe the life of the laboratory and to participate in the experiments, basophils had been replaced by another biological model than we will describe in the second part. Here are some extracts of his observations:

> "What I want to underline here is the caution with which the researchers of the Unit 200 moved forward in the study of the high dilutions. Partially depending on the most qualified person for the counting of basophils (Elisabeth Davenas), they wanted to take precautions to make sure against the risks of bias in the sequence of operations. In the reports of the blind experiments of the first six months *[after the "discovery" of the second peak]*, I did not find less than twelve different names among the people involved in coding!" [5]

M. Schiff estimated that about 350 experiments had been performed before the investigation of *Nature*. And in another extract, he expressed the impoverishment of the research on high dilutions when a logic of proof had been substituted to it:

> "While an original work had begun on the physical properties of high dilutions and on the phenomenon of "waves", this work was stopped. Among 200 experiments performed after the investigation of *Nature*, less than 5% were new. So, during two years, the researchers of U200 dedicated the major part of their efforts to repeat indefatigably the two same experiments to convince their colleagues." [6]

The events that led to the publication in *Nature* in 1988 are described next chapter onwards.

Notes of end of chapter

[1] Some anti-IgG antisera can also induce basophil degranulation. The one that was chosen had no effect at usual concentrations in order to be a proper control.

[2] For example, here is what F. Jacob (French Nobel prize laureate in 1965) answered in 1996 to the journalist E. Fottorino: " […] "The curve that Benveniste showed me indicated an incredible character". François Jacob sketched in front of us the figure that Benveniste should have shown if he had really discovered an effect at high dilution. A simple straight line parallel to the x-axis and not a series of domes as depicted by Benveniste." (E. Fottorino. La mémoire de l'eau. Une vérité hautement diluée. *Le Monde*, January 23rd, 1997.)

[3] Lotka AJ. 1925. Elements of physical biology. Baltimore: *Williams & Wilkins Co.* ; Volterra V. 1926. Variazioni e fluttuazioni del numero d'individui in specie animali conviventi. *Mem R. Accad Naz dei Lincei*. Ser. VI, vol. 2.

[4] The number of Avogadro is the number of elementary entities (atoms, ions, molecules, etc) contained in a mole of matter. It is usual to consider this number equal to 6.023×10^{23} even if is 6.022×10^{23} seems to be a better approximation. This number is a relation between the amount of matter of a mass m with the molecular mass of the elementary entity. Let us take the example of a molecule of anti-IgE. It is an immunoglobulin of molecular mass 150 000 (that is 150 000 g for a mole). Consequently, a solution of 1 mg/mL (or 1 g/L) of anti-IgE contains 1/150 000 moles of anti-IgE by liter (that is 6.67×10^{-6} moles/L or 4.0×10^{18} molecules). In the basophil degranulation test, the volume of anti-IgE solution added to the assay is 10 µL (that is 4.0×10^{13} molecules for the initial solution); we calculate easily that the 14th ten-fold dilution contains less than 1 molecule.

[5] Michel Schiff. Un cas de censure dans la science. L'affaire de la mémoire de l'eau, p. 47.

[6] *ibid.* p. 52.

Crossed portrait #3

By Eric Fottorino

"The memory of water was his joker"

"Son of a general practitioner, completing "baccalaureate" at fifteen years, hospital resident, brilliant, bragging, a little bit of a show-off, Jacques Benveniste took a different direction for research in 1969, the year of his departure for San Diego (California). During three years, he works in the laboratory that will isolate the famous PAF-Acether. For this breakthrough he wins the silver medal of the CNRS.

Committed to the left-wings politics, he was also the "Mr. Medicine" of Jean-Pierre Chevènement, between 1981 and 1983, when this one was Minister of Research. He is finally a scientific member of Inserm council. What he says has clout. The retort will be accordingly. Behind the knowledge hides the issue of power.

In 1982, an American team received the Nobel Prize for work nearby that of Doctor Benveniste. His close relationships assert that he felt bitterness, that the "memory of water" was his joker to pick up the supreme reward. He denies, a little irritated. At the age of twenty, Jacques Benveniste saw himself as a racing driver. He competed for races at Montlhéry (Essonne). He was offered to become a rally pilot. He chose another way, as risky."

(*Le Monde,* January 21st, 1997)

"To meet Jacques Benveniste was to be immediately exposed to this mark of the meeting. The mark of the intelligence in the raw, fast, in perpetual movement. An embodied intelligence, capable of speeding and skids, but very generous, opener of horizons, of unknown worlds and infinite hopes."

(*Le Monde*, October 6th, 2004)

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 *Lung-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 research 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*, and 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 occurred 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 occurred with the choice to speak only of histamine, to avoid the word "homeopathy" and to focus on "high dilutions". The second shift occurred 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 believe"

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 occurred 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 sulfoxide (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 disappeared. By introducing water gradually (10, 50 and 90%), the degranulating effect of the high dilutions of anti-IgE progressively appeared again.

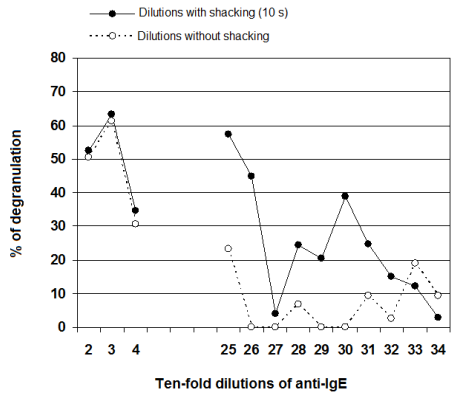

Figure 4.1. This experiment shows the role of 10 seconds-shaking using a rotating shaker to obtain active high dilutions. As expected, the first peak of degranulation (dilutions of anti-IgE $1/10^2$ to $1/10^4$) is obtained with or without shaking between each dilution. In contrast, high dilutions of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

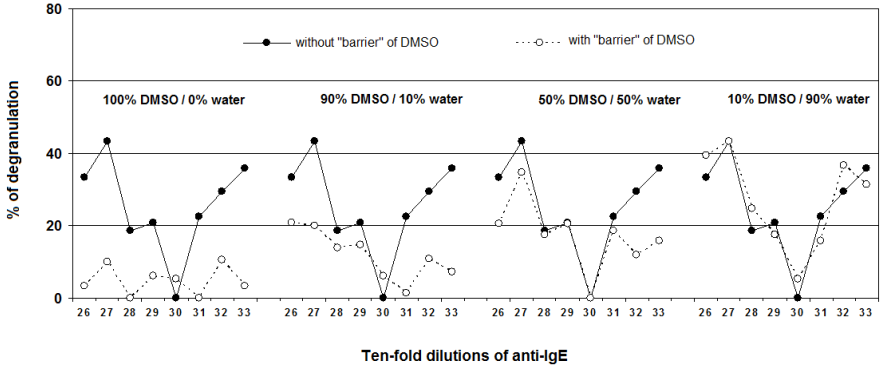

Figure 4.2. For these experiments, the dilutions of anti-IgE were performed up to $1/10^{33}$ but a "barrier" was inserted from $1/10^{15}$ to $1/10^{22}$ with dimethyl sulfoxide (DMSO); the next dilutions up to $1/10^{33}$ were performed again in the usual medium (buffered saline solution). The aim 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, state councilor, 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* April 1990)[1].

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

Chapter 5. Reproduction in Israel of the experiments of Clamart

"Either your are a crook or this is a new area for biology"

We have seen that in his mail to P. Newmark of January 13th, 1987, J. Benveniste announced that the experiments were going to be reproduced in other laboratories. The scientists involved in these experiments were mainly Israeli researchers. Their first contacts with the laboratory of J. Benveniste dated back to the end of May 1985 in Lyon at the Congress of the *Liga Medicorum Homoeopathica Internationalis* (LMHI) where B. Poitevin reported his results on high dilutions. Among the participants at the congress were Judith Amara and Menachem Oberbaum of the Kaplan Hospital in Rehovot near Tel Aviv. M. Oberbaum was a homeopathic physician and J. Amara was a pharmacist and a biologist. They expressed to B. Poitevin and J. Benveniste their great interest for their studies. On returning to Rehovot, M. Oberbaum transmitted to Uriel Zor – a researcher who worked at the Weizmann Institute on "classic" themes close to those of Inserm U200 – the text of the communications of Inserm U200 at the congress. Uriel Zor wrote then to J. Benveniste to ask him for advice to undertake experiments with high dilutions in cell systems that he routinely used.[1] One year later, in June 1986, M. Oberbaum proposed to J. Benveniste to attend a congress in Israel on alternative medicines and, at the initiative of U. Zor, J. Benveniste gave a conference on high dilutions at Weizmann Institute. Professor Meir Shinitzky – who will play an important role later – attended this conference.

J. Benveniste liked telling that, at the end of this conference, he had been shouted out in these terms:

> "I was invited last June at the Weizmann Institute to give a talk on the high dilutions. A very renowned colleague put it out this way: "J. Benveniste, either you are a crook or this is a new area for biology"." [2]

During the autumn, first results were obtained at Rehovot with basophils. On December 3rd, 1986, J. Benveniste wrote to U. Zor:

> "[Judith] told me that she has seen some degranulation by highly diluted anti-IgE but that did not make enough experiments to yield a proper statistical analysis. You must know that the Nature Editorial Board has practically accepted the paper provided that these results are verified in another laboratory."[3]

Then, J. Benveniste indicated that he also sent several tubes under a code that contained histamine at high dilutions and their controls. He added:

> "Since the paper in Nature bears upon the role of highly diluted histamine in inhibiting anti-IgE-induced basophil degranulation, I would propose you to check the latter results as soon as Judith can have the anti-IgE degranulation working on a regular basis. […] Then, if you (and obviously Judith) are willing to be associated to the Nature paper, I will glad to include your results in it."

We can see here the beginning of a change of strategy: the reproduction of the results in other laboratories not with high dilutions of histamine, but with high dilutions of anti-IgE. [4]

Thus, on February 3rd, 1987, J. Benveniste wrote to Professor Z. Bentwich, director of the laboratory where Judith Amara performed the experiments, as well as to Professor M. Shinitzky, from the Weizmann Institute. He asked them to supervise the experiments of Judith and suggested associating their names to the article:

> "The answer of Nature is very encouraging since they practically accepted the paper to the one and only condition that our results be reproduced in another independent laboratory. […] Judith Amara told me by phone that her experiments were recently validated by a statistical analysis. She is in the process of reproducing these experiments in your presence. […] Thus, as soon as you are convinced of the reality of this phenomenon, I will be glad to get this information from you in the form of a letter describing the results. I will then happy to associate you to the Nature paper in the form as you will decide: as authors, obviously including Judith Amara and, in this case, the institution will have to be quoted. I can also simply acknowledge your participation in the experimental process. However, the Nature paper deals with the inhibitory effect of high dilutions of histamine and they might ask that this part of the work be also reproduced." [5]

And on February 12th, 1987, J. Benveniste could triumphantly announce to P. Newmark:

> "Let me give you the latest news. The effect of the high dilutions of anti-IgE antibodies on basophil degranulation has been totally confirmed by the lab working on the system which is, to be fully open with you, the Weizmann Institute. They called me yesterday to say that around 1×10^{-30} M (theoretical) highly significant

> results have been obtained as determined by "very demanding statistical tests". They will perform another experiment in the presence of the two professors involved, next Sunday. If this works, they intend to write me a full report on these results and I will probably include them as authors in the paper." [6]

In this letter, J. Benveniste talked about the Weizmann Institute, of course more prestigious than Kaplan Hospital (whatever the last one is worth). Therefore, when M. Shinitzky withdrew from this collaboration, information that "the experiments were reproduced at the Weizmann Institute" continued to spread. [7]

But, for the moment, the machinery seemed well oiled. J. Benveniste went forward as a steamroller, looking for alliances and supports. The suggestion of P. Newmark to reproduce the experiments by another laboratory seemed on track and it seemed that it would be completed within a reasonable time. Without judging someone on mere intent, it was probably a delaying tactic from *Nature*. But J. Benveniste did not allow any loophole to *Nature*: if he filled the requirements, then the results had to be published. Otherwise, he was decided to make it be known. A small grain of sand however came to block the machine. Indeed, a few days after the letter to P. Newmark, J. Amara reported to J. Benveniste technical problems with basophils and she asked for assistance. E. Davenas said:

> "Judith had learnt the technique at Clamart. In autumn 1986, she began to experiment with Oberbaum, at Kaplan Hospital in the laboratory of Professor Bentwich who welcomed them. Boaz Robinzon, a researcher of the faculty of Rehovot, also participated in the experiments. At the beginning, they had results, then it did not work anymore. At this moment, they called on me." [8]

"Needless to say, these results puzzle us enormously"

It was then quickly decided that E. Davenas would go to Israel from February 21st to March 2nd so as to put the biological system back on the rails. A few days after her arrival, everything worked again regularly in the laboratory of Z. Bentwich at the Kaplan Hospital of Rehovot. And, what initially was not planned, it was asked to E. Davenas to perform blind experiments. However, the atmosphere was very tense and very passionate. According to E. Davenas:

> "All this happened in a painful atmosphere, with many discussions […]. The Israelis were very passionate. Some were in favor and others against. It was difficult for me, because I did not expect such an atmosphere. The only reason why I came was to show

> them the procedure. I did not intend to make neither blind trials, nor anything of this kind. I was in a spiral system, I could not withdraw any more". [9]

This slightly hysteric atmosphere was confirmed by J. Amara, M. Oberbaum and B. Robinzon for the last experiment of March 2nd, of which we will talk later. In response to the "nervousness" that E. Davenas would have shown during the experiments – according to words of M. Shinitzky reported afterward in the press – they wrote:

> "[…] the alledged "nervousness" of Dr. Davenas was rather less than would be expected given the importance of the challenge, the work overload that was asked to her in several successive days, and the nervous tension provoked by the constant monitoring under which she was working in a foreign environment. In this regard, we want to emphasis that apart from the preparation of the dilutions on that morning, Prof. Shinitzky was not present until the time the codes were broken. On the other hand, a lady from his laboratory came in shouting that she came to catch the "witch" cheating! and to save the face of her boss. The person that Prof. Shinitzky had sent and Dr. Deckmann demanded suddenly to change the experimental regimen and shouted a lot when they were denied. Thus, the whole climate was not the calm and quite environment one would expect for any experiment to be conducted under. We more than wonder, how a person who was not present at the place during most of that particular day, and whose representatives where very nervous, noisy and hostile, can give a testimony as to the behavior of Dr. Davenas." [10]

In spite of the pressure and of the hostility of some participants, all blind experiments were a success. First, a series of 4 very similar experiments were performed from February 23rd to March 1st. [11] The first experiment was coded by B. Robinzon and the next three experiments received a double code: first from M. Shinitzky and then from B. Robinzon, so that nobody could know the "active" tubes and the "inactive" tubes before the final unblinding. The results that were obtained were completely clear cut and spectacular (Figure 5.1).

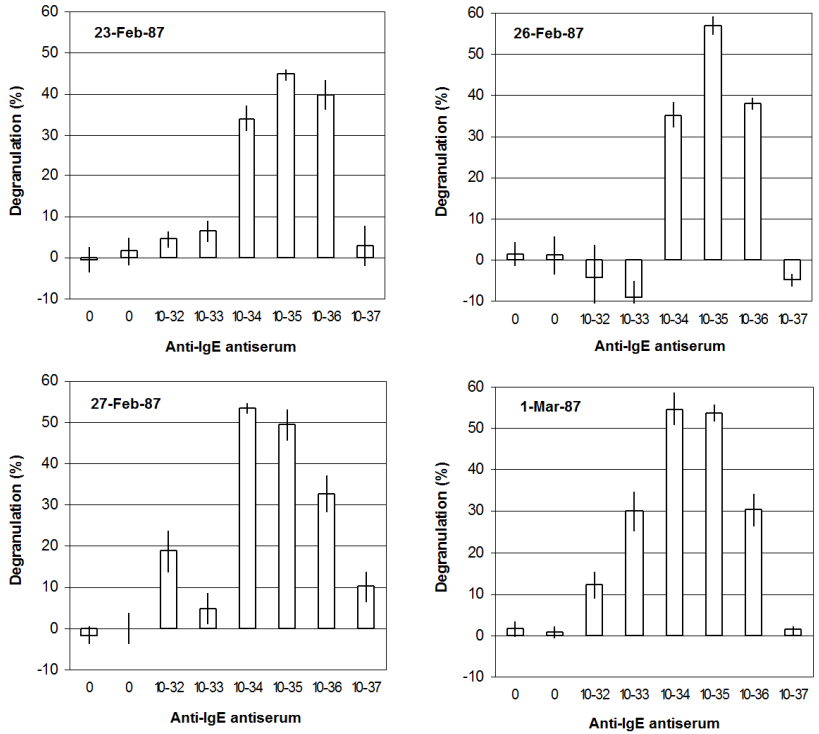

Figure 5.1. These graphs summarize the first four experiments performed in Israel by E. Davenas. Every bar represents the mean with its standard deviation of 3 repetitions within the same experiment. The tubes of dilutions were coded; the code of the experiment of February 23rd was a unique code and the 3 other experiments benefited from two successive codes. The low statistical dispersion (small standard deviations) was very much talked about. This point is discussed in Chapters 10 and 11. The raw counts of basophils of these experiments are given in Appendix 2 and the table of results as presented in the *Nature* article is reproduced Chapter 8 Figure 8.2.

After these 4 successful experiments, a last experiment was decided on March 2nd. The aim was to "find" three "active" tubes among ten tubes under a double code. Here is described in detail by J. Amara, M. Oberbaum and B. Robinzon this famous experiment of March 2nd, which was the last one of the series in Israel:

> "The last experiment that was performed at the end of the stay of Dr. Davenas at Rehovot was a critical one. That morning a sealed package sterile tubes was given to Dr. Davenas in the presence of the witnesses among whom Prof. Shinitsky, Dr. Deckmann and

ourselves, J. Amara, Dr. Oberbaum and Dr. Robinzon. Then Dr Davenas, while under close and constant supervision, prepared the dilutions in the usual fashion from 1×10^{-2} to 1×10^{-40}, starting from a concentrated solution of anti-IgE antibodies, that was immediately removed after she had sampled the aliquot. Following the preparation of the dilutions, Dr. Davenas conducted the first part of the experiment which was done in the open so that she could determine the active dilution between 1×10^{-30} and 1×10^{-40}. Dr. Davenas was supervised constantly and the dilutions were removed following sampling and stored at the cold room, to where Dr. Davenas had no access. […]

Dr. Davenas carried out experiment until, after having read the samples on the microscope, according the usual method, she found the solution of 1×10^{-34} of anti-IgE as that given a maximal effect on basophil achromasia. The second part of the experiment was aimed to study the reproducibility of the observation in a double-blind regimen. The active anti-IgE dilution (1×10^{-34}) and the control-buffer fluid, were each divided in 10 replicates by Dr. Deckmann, in the presence of Dr. Robinzon, Dr Oberbaum and another person from Prof. Shinitsky's laboratory and in the absence of Dr. Davenas. Then all participants vacated the laboratory except Dr. Robinzon and the person of Prof. Shinitsky's lab who had chosen at random, 7 control and 3 "active" (1×10^{-34} anti-IgE) tube and randomly coded them from 1 to 10. Then they had vacated the room and Dr. Oberbaum and Dr. Deckmann moved in and recoded the tubes by changing the numbers into letters at a random order.

Once the tubes were coded twice so that nobody could know what they mean, the tubes were given to Dr. Davenas who did another test in blood, identical to that of the first experiment. The time length of the whole experiment was from 9 a.m. to 9 p.m.

The code was broken in the presence of Prof. Shinitsky, Dr. Deckmann, Dr. Oberbaum, J. Amara, Dr. Davenas and Dr. Robinzon. Results were positive in the sense that Dr. Davenas found the 3 active tubes among the 10. It was that time that Prof. Shinitzky and Dr. Deckmann told the assistance that among the 10 uncoded remaining tubes, 1 control and 1 anti-IgE tube, had been taken by the person from Prof. Shinitzky laboratory in order to eventually proceed to all control possible analysis. We agreed on the principle of controlling the samples." [12]

Again, the results of the experiment perfectly fitted the code. The numbers of basophils counted decreased (58, 60 and 57) in the wells that corresponded to high dilutions of anti-IgE (Table 5.1). The results were all the more remarkable that the number of active tubes had not been indicated.

Open-label			*Number of basophils*
Control			105
Anti-IgE 10^{-2}			46
Blind	*code 1*	*code 2*	*Number of basophils*
Control	1	F	101
Control	2	D	94
$1/10^{34}$	**3**	**E**	**58**
Control	4	I	103
Control	5	A	94
$1/10^{34}$	**6**	**J**	**57**
Control	7	C	99
$1/10^{34}$	**8**	**G**	**60**
Control	9	H	92
Control	10	B	93

Table 5.1. The results of the last experiment performed in Israel by E. Davenas on March 2nd, 1987 during her stay in Israel are given in this table. The aim of the experiment was to "guess" the position of the active tubes among 10 tubes (the experimenter did not know the number of tubes) at the dilution $1/10^{34}$. The 10 tubes received two successive codes by two teams each including two people: first by B. Robinzon and a collaborator of M. Shinitzky (code 1) and then by M. Oberbaum and M. Deckmann (code 2). Three active tubes (E, J, G) were "guessed" without error.

On March 6th, a report of the experiments written by M. Shinitzky was sent to J. Benveniste. It was signed by Z. Bentwich, M. Shinitzky, M. Oberbaum, B. Robinzon and J. Amara. The results of experiments and statistical tests were described:

> "The experiments were carried out single or double blind under close inspection of Prof. Z. Bentwich, myself and the undersigned. In all experiments, without any exception, clear cut results were obtained where a typical bell-shape profile of degranulation was obtained at the range of anti-IgE concentrations of 10-32 to 10-37 mg/ml. Furthermore, the replicates in most tests were very close, in most cases even better than what we generally experience in similar conventional in vitro experiments. […]. If you wish, you

> could use this letter (but not part of it) as an official verification of your findings." [13]

In their report, M. Shinitzky and the other signatories mentioned the ultimate control of the solutions that must be performed:

> "Needless to say, these results puzzle us enormously and we have no logical clue or interpretation for them. In order to reduce the suspicion of improper conduct, we are now in the process of chemical analysis of the positive highly diluted anti-IgE taken from the last experiment, in comparison with the buffer. The results of this analysis will be in hand in a few days."

As soon as he received the letter of the Israeli researchers, J. Benveniste – of course – transmitted a copy to P. Newmark.[14]

"Needless to say there must be an error somewhere"

But, at the end of March, several weeks after the departure of E. Davenas, a phone call of M. Shinitzky on the 26th, followed by a letter of B. Robinzon on the 29th, caused consternation within the team of J. Benveniste. According to M. Shinitzky, there would be "anti-IgE activity" in the tube "$1/10^{34}$" supposed to contain anti-IgE at high dilution, undetectable by definition. For M. Shinitzky the validity of the results was questioned. The letter of B. Robinzon explained:

> "Enclosed please find a photocopy of the gel electrophoresis which were carried out with the active peak […]. Based on these, Prof. Shinitzky claims that the active peak contains immunoglobulin. Since I am not an expert in the field of protein identification I had consulted with 3 independent experts in this field. All the three of them could not agree with that conclusion. However, Prof. Shinitzky is not ready to accept their opinion. My advice is to consult with an expert in this field."[15]

J. Benveniste then wrote to M. Shinitzky:

> "Dr. Robinzon has communicated us the results of the electrophoresis that was performed on the samples. Needless to say there must be an error somewhere. It must be clearly established between us that the purpose of our collaboration and the coming of Elisabeth Davenas to Israel was certainly not to detect any improper conduct. It was to verify that the experiments could, indeed, be performed and, possibly, detect any methodological or theoretical error. You realize, I am sure, that for anybody from this laboratory starting from me, it would be totally

> foolish and scientifically suicidal to ask you to supervise experiments including any cheating process. […]. Thus, if I can always admit a scientific error, my honorability and that of my collaborators cannot be a matter of discussion for even a nanosecond." [16]

Then, the issue of electrophoresis was addressed:

> "The only question: where was the error done and how some antiserum or protein was confused with diluted solution? By contrast with the experiment done by Elisabeth Davenas, no control of this part was done. In particular, were the electrophoresis done blind? Another point: did you check for an anti-IgE activity of the protein you detected? We have now to solve this riddle and here is our proposal […]"

J. Benveniste suggested quickly about redoing the entire experiment with a double code – including for the electrophoresis – under the control of a bailiff and of the dean of the Faculty of Medicine, Pr. Jean Dormont, in order to clear up all doubts.

In their already quoted letter of November 1990, J. Amara, M. Oberbaum and B. Robinzon confirmed that the analysis of the incriminated tube had been unilaterally performed:

> "However, everything in this experiment was coded under the supervision of participants. Yet, no control was exerted on the choice and the fate of these tubes of which the results of the analysis were known only a month later. On the basis of this electrophoresis of which we have never seen the original gel, it was declared that an anti-IgE was present in the active tube where the dilution was theoretically so high that it should not be possible to detect trace of an antibody molecule. This implies that somebody added secretly anti-IgE antibody to this tube, modifying the whole high dilution effect." [17]

Concerning the idea of the content analysis of the tubes, the same signatories gave two slightly different versions. In 1988, they wrote:

> "The origin of the so-called "contamination" is our opinion no other than the albumin in the buffer. We would like to point that the proposal to examine the dilution was put to Prof. Shinitzky by us. Needless to say the examination was carried out in negligent manner, is that all that can be done is hypothesize."[18]

In 1990, as we have seen above, they seem to imply that M. Shinitzky took the initiative to put aside tubes and informed the other participants at the time of the unblinding. In any event, it seems nevertheless taken for granted that the analysis of the electrophoresis was complicated by the fact that large amounts of albumin were present in the solution. In a letter to J. Benveniste, B. Robinzon explained:

> "Not being an expert in electrophoresis, I consulted Pr Eli Cnani and Dr Ora Cnani at the Institute Weizmann, as well as Dr Aharon Friedman of our department, to ask them for their interpretation of this electrophoresis. They all independently confirmed that the system was overloaded in proteins, that they could find no proof of the presence of anti-IgE, or any immunoglobulin, and that bands could be formed by an overload of albumin." [19]

According to the experts, one of the reasons why the present proteins in the solution could not be anti-IgE immunoglobulins was given on the basis of the profile of the electrophoresis:

> "The experts that we consulted at that time with the photographs of the gels (see letter of July 1988) expressed the opinion that there were heavy protein contamination, probably a product of degradation of the BSA [= *bovine serum albumin*] that was added to the solution and that the presence of this overload could not allow any correct interpretation of these gels. Therefore an "anti-IgE" nature of this contaminant could not be affirmed especially that following reduction no 25K or 50K band had been found." [20]

The addition of bovine or human albumin aims at increasing the viscosity of the environment where cells are suspended to protect them during the various manipulations such as centrifugations. When their concentration is high, the molecules of albumin tend to "stick" together and a wide spot is obtained with the electrophoresis and not a narrow band. The journalist M. de Pracontal questioned M. Deckmann, the student of M. Shinitzky to whom the latter asked to perform the electrophoresis:

> "The atmosphere was "hot", very passionate […]. There were the believers and the skeptics. There was an atmosphere of mistrust, which deteriorated because, only Elisabeth Davenas was apparently able to succeed the experiment. It was difficult to explain. Moreover, she did not want anyone to stay next to her, as it made her nervous. She wanted to be alone.

> If the experiment would have been repeated, by somebody else, Shinitzky would have immediately stopped all other researches to work on high dilutions. He was favorable to these experiments. He would have supported them.
>
> At the end, there was a big mess. The Weizmann Institute decided to stay out of the affair. According to me, the Israeli results are certainly not a confirmation of the thesis of J. Benveniste." [21]

The words of M. Deckmann are interesting. Actually, the Weizmann Institute is one of the most prestigious research institutes in the world and it was likely that some people did not wish that M. Shinitzky committed for homeopathy with the reputation of Weizmann. Besides, M. Deckmann recognized himself that: "the electrophoresis does not prove the presence of anti-IgE." [22]

Quis custodiet ipsos custodes?

In this affair, another aspect has never been mentioned. Every reader of a detective novel knows indeed that it is always necessary to look "who benefits from the crime". If somebody had wanted to favor fate by putting a "degranulating" agent in some tubes (let us repeat once again that all the preparation procedure for the dilutions was permanently watched), anti-IgE was the last substance to envisage because – obviously – one would think about it at first in case of suspicions. It would have been much more wise (with nevertheless the skill of Randi) to add a product, which was not anti-IgE, able of degranulating basophils and if possible not a protein in order to pass the electrophoresis test without being detected. For example, calcium ionophore or any degranulating peptide. Furthermore, we must not forget that these blind experiments were improvised during the stay of E. Davenas in Israel.

On the contrary, if somebody wanted to cast doubt on the validity of the experiments, contaminating the dilutions with anti-IgE antiserum suited perfectly. Without being particularly gifted for conjuring, it was very simple, out of sight, to add "something" susceptible to be visible in the electrophoresis.

Naturally, this does not mean that somebody voluntarily added "something" in the tube. But the aim of this demonstration is simply to show – and during this episode, it was caricatural – that the burden of proof is always asymmetric. The one who calls into question – or seems to call into question – the established order must always appear with humility in front of his judges, the head through the noose. If an anomaly is noticed, suspicions go immediately towards him. Rights devolved to the skeptics are immense. In the present case one attended in a kind of role play where each – in a surprising way – stepped

accommodatingly into the role which was assigned to him/her. But, what happens when the judges do not have interest – whatever the reasons are – that the experiment succeeds?

To end on this animated episode, most likely each one was honest (for lack of having shown oneself as totally objective, honest and having keep a cool head). Nevertheless, one can only point out that the ambiguous result of the electrophoresis, due to the protein overload, was exploited with a biased key for reading, namely the supposed impossibility of the experiment; as a consequence, "something" must be present in the tube. Incidentally, it was possible to directly measure (or with the help of a specialized laboratory) the presence of anti-IgE in the tube without using electrophoresis, even in the presence of albumin. This has not been undertaken.

As regards the presence of E. Davenas that was necessary for the success of the experiment in Israel, B. Robinzon, J. Amara and M. Oberbaum answered by a letter where they described 11 experiments including a blind one that were performed without the presence of E. Davenas. [23] On the same subject, B. Robinzon answered at the same time to M. de Pracontal:

> "We made our own experiments, according to a standard procedure with 6 repetitions for every dilution, before and after Elisabeth Davenas' visit, with essentially the same results. […]
>
> I committed to this study so that a friend [Oberbaum] does not publish what seemed then to me a pure sham, but because I learnt to place the experimental data over any theory or faith, once convinced of the existence of this phenomenon, I had to sign the article, whatever the cost." [24]

Notes of end of chapter

[1] Letter of U. Zor to J. Benveniste of June 10th, 1985.

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

[3] Letter of J. Benveniste to U. Zor of December 3rd 1986.

[4] The effect of anti-IgE at high dilution was technically simpler to evidence and consequently easier to make reproduce by other laboratories than the effect of histamine at high dilutions. Indeed, in this last case, it was necessary to determine first the dilution giving the optimal "second peak" (preparation step), then to add histamine at high dilutions to cells (inhibition step) and finally to add the dilution of anti-IgE corresponding to the second peak (activation step). Evidencing the effect of anti-IgE at high dilution needs only the activation step.

[5] Letter of J. Benveniste to Z. Bentwich of February 3rd, 1987 (a similar letter was sent to M. Shinitzky).

[6] Letter of J. Benveniste to P. Newmark of February 12th, 1987.

[7] See in particular *Le Monde*, May 30th, 1988.

[8] M. de Pracontal. Les mystères de la mémoire de l'eau, p. 70.

[9] *Ibid.*, p. 71.

[10] Letter of B. Robinzon, J. Amara and M. Oberbaum to J. Benveniste of November 1990.

[11] On February 25th an experiment coded by Z. Bentwich had been performed, similar to that of February 23rd, but the effect of anti-IgE at the usual doses (1/1000) was low (both for open-label and blind samples) and all wells were not counted.

[12] Letter of B. Robinzon, J. Amara and M. Oberbaum to J. Benveniste of November 1990.

[13] Letter of M. Shinitzky and other signatories to J. Benveniste of March 6th, 1987.

[14] Letter of J. Benveniste to P. Newmark of March 9th, 1987.

[15] Letter of B. Robinzon to E. Davenas of March 29th, 1987.

[16] Letter of J. Benveniste to M. Shinitzky of April 17th, 1987.

[17] Letter of B. Robinzon, J. Amara, M. Oberbaum to J. Benveniste (November 1990).

[18] Letter of J. Amara and M. Oberbaum to J. Maddox of December 11th, 1988.

[19] M. de Pracontal. Les mystères de la mémoire de l'eau, p. 73.

[20] Letter of B. Robinzon, J. Amara and M. Oberbaum to J. Benveniste of November 1990.

[21] M. de Pracontal. Les mystères de la mémoire de l'eau, p. 74.

[22] *Ibid.*, p. 72.

[23] Letter of B. Robinzon, M. Oberbaum and J. Amara to J. Benveniste of July 30th, 1987.

[24] M. de Pracontal. Les mystères de la mémoire de l'eau. p. 76.

Chapter 6. Reproduction at Clamart… of the Israeli experiments

The bailiff, the dean and the basophils

In spite of the success of the Israeli experiments – which, we must remember, had not been initially scheduled – the question of the "contamination" could cause damage to the credibility of the whole research program on high dilutions. Consequently, in order to escape to the trap of useless controversies, J. Benveniste took again the initiative by organizing what he proposed to M. Shinitzky, namely the repetition of an identical experiment intended to remove the doubt on the electrophoresis. This situation was rather paradoxical. The Israeli experiments were intended to reproduce those of Clamart; now, it was necessary to reproduce them in Clamart!

J. Benveniste was all the more determined not to stay on what could be interpreted as a failure that he had just received a letter of *Nature*. It was the answer concerning the manuscript, which had been sent on March 9th with documents describing the results obtained in Israel:

> "The Editor and I […] are not persuaded in favour of publication. We have decided to seek more external advice before making any decision."[1]

J. Benveniste answered then to *Nature* that new experiments were going to consolidate the article:

> "I must say that I understand your reservation in accepting the results presented in our manuscript. However, I am afraid that more external advice will not solve this problem, since it is more a matter of personal belief and there is in fact no way for a reviewer to check the reality of the phenomenon. You have seen that these experiments were perfectly reproduced in Israel. However, they failed to properly control the lack of any contaminating compound in the diluted solutions."[2]

It may be noted in passing how J. Benveniste diplomatically "manages" the issue of the "contamination": the experiments were not designed to control a possible contamination.[3] Then he could move on to the description of the protocol intended to verify – now in blind conditions – that the solutions with high dilutions were not possibly contaminated with anti-IgE immunoglobulins.

He ended: "We do not expect these experiments before a month or so. Therefore, we are not in such a hurry to get a final decision". Thus, he skillfully returned the situation and he now imposed his timetable to *Nature* for the final decision.

The detailed protocols of the experiments were sent at the same moment to Z. Bentwich, M. Shinitzky, B. Robinzon, M. Oberbaum and J. Amara. Tubes would be coded at Clamart by Professor J. Dormont, dean of the Medicine Faculty and by Maître Simart, bailiff in Clamart.

The samples of the experiment were coded on April 22nd, 1987. The experiment consisted in testing blind the contents of 12 tubes: 4 control tubes, 2 tubes containing low dilutions of anti-IgE (1/100 and 1/1000) and 6 tubes containing high dilutions of anti-IgE (from $1/10^{32}$ to $1/10^{37}$). The results after unblinding (June 11th) are described in Figure 6.1.

But – the same causes leading generally to the same effects – the presence of albumin made difficult the interpretation of the electrophoresis! [4] This was therefore the same situation when the experiment was performed in Israel. The photograph of the electrophoresis could not be published because it was not "clean" and thus did not achieve the objective of the experiment: to show that there was no anti-IgE in the tubes where nevertheless a degranulating "activity" was present. Nevertheless the dosage of anti-IgE performed in a laboratory at Marseilles was convincing. Anti-IgE was detected in the dilutions 1/100 and 1/1000 but not in the high dilutions.

A new blind experiment was thus performed on May 12th, but now without adding albumin in cell medium. The experiment included less experimental data because it was especially intended "to make an image". Only Maître Simart and J. Benveniste performed the double blinding. Electrophoresis was not overloaded by albumin and its results fitted the measure of anti-IgE antibodies. The results for basophil degranulation are presented in Table 6.1.

Before unblinding, the results seemed clear cut again. If results should be predicted, one would say that *a* and *c* were controls, *h* and *m* were "classical" dilutions of anti-IgE and *e* and *p* were high dilutions of anti-IgE. Before even the unblinding of the experiments, J. Benveniste wrote to P. Newmark:

> "You will receive within a week a detailed report on the blind experiments that were conducted in cooperation with the Israel laboratories. The code is not yet broken but they appear quite successful." [5]

By doing so, J. Benveniste took an important risk: to be contradicted after unblinding; but transparency was a guarantee for credibility.

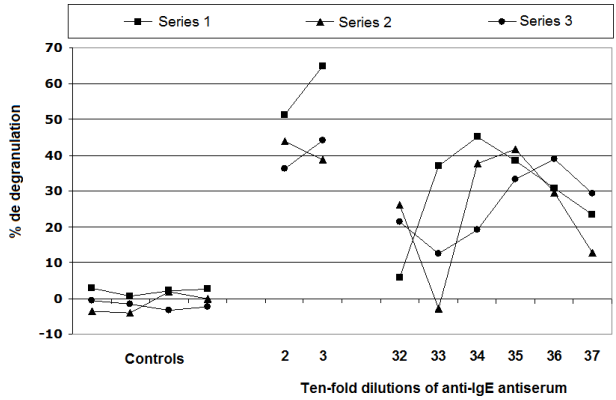

Figure 6.1. Blind experiment of April 22nd, 1987. Twelve tubes were tested in 3 sessions (series 1, 2 and 3) on basophil degranulation after a double blinding. Every series is assessed on the cells of different blood donors.
Experimental protocol: after dilution of anti-IgE up to 10^{-37} by E. Davenas, 8 tubes containing dilutions of anti-IgE (1/100, 1/1000, from $1/10^{32}$ to $1/10^{37}$) were coded together with 4 control tubes containing the medium of dilution alone. The first code was given by J. Benveniste and Maître Simart, bailiff, and the second code by Maître Simart and J. Dormont. Having put aside a part of the content for the test of basophil degranulation, the rest of each of 12 tubes was divided into 4 parts and then freeze-dried. Maître Simart sent a series of 12 samples chosen at random and sent them to two laboratories in Israel (M. Shinitzky and B. Robinzon) to perform an electrophoresis and a laboratory in Marseilles specialized in the production and the marketing of antibody to measure directly the presence of anti-IgE antibody. The scientist who performed this dosage preferred that no mention was given ("neither written, nor oral") of the name of his laboratory.
These results were published in the article of *Nature* of June 30th, 1988, which is reproduced Chapter 8 Figure 8.3.

	Donor 1		*Donor 2*	
Open-label	Number of basophils	% of degranulation	Number of basophils	% of degranulation
Control	54 ; 49	-	96 ; 102	-
Anti-IgE 1/100	9 ; 6	85%	53 ; 51	47%
Code	Number of basophils	% of degranulation	Number of basophils	% of degranulation
a	55 ; 51	– 3%	97 ; 99	1%
c	49 ; 53	1%	105 ; 98	1%
e	33 ; 30	39%	64 ; 65	35%
h	8 ; 12	81%	55 ; 50	47%
m	12 ; 15	74%	46 ; 48	53%
p	134 ; 135	33%	70 ; 68	30%

Table 6.1. Blind experiment of May 12th, 1987.

(Continued on next page).

(continued from previous page)

This experiment is a repetition of the experiment of April 22nd because the presence of albumin overloaded electrophoresis and made them difficult to analyze. Samples received codes by a bailiff and then by J. Benveniste. They were then tested with cells from two blood donors.
Two samples were inactive (*a* and *c*), two were active (*e* and *p*) and two were very active (*h* and *m*). This experiment was also a success after decoding, because *a* and *c* were controls, *e* and *p* were anti-IgE at high dilutions $1/10^{36}$ and $1/10^{35}$ whereas *a* and *m* were anti-IgE at "classic" dilutions, respectively at 1/100 and at 1/1000.
These results were published in Table 3 of the article of *Nature* of June 30th, 1988; this table is reproduced Chapter 8 Figure 8.3 and the corresponding electrophoresis made at Clamart is reproduced Chapter 8 Figure 8.4.

"I can understand the reservation of such a prestigious journal as Nature to publish these findings"

The unblinding of the experiments (those of April 22nd and May 12th) by the bailiff on June 11th in the presence of J. Dormont and J. Benveniste were again a total success.[6] The tubes *e* and *p* were anti-IgE at $1/10^{36}$ and $1/10^{35}$, respectively. The three tests (electrophoresis, dosage of anti-IgE, test of degranulation) were positive when anti-IgE at "classical" dilution was present. In contrast, only the test of basophil degranulation detected anti-IgE at high dilutions. The effect observed with high dilutions was thus not simply due to a contamination by anti-IgE.

On the same day, J. Benveniste wrote a long letter to P. Newmark with tables of results and copy of the electrophoresis reporting the experiments of April 22nd and May 12th. Large extracts of this letter deserve to be reproduced because they enlighten the future developments of the story. At first, J. Benveniste reconstituted the history of the facts that led to these experiments:

> "You must remember the letter from Israel that the involved scientists cosigned attesting the good results of the experiments. The only missing information was to eliminate the possibility of the antibody present at normal concentration in the active highly diluted tubes. About a month after the experiment, a report came from Dr. Shinitsky's laboratory that several bands were identified in the latter that could be immunoglobulins. However, a second group of scientists in Israel (Dr. Boaz Robinzon) affirmed that these could by no means be immunoglobulins. It was clear that we were bothered by the polymerized HAS [= *albumin*] present in all solutions. Moreover, by contrast with the rest of the experiment, the electrophoresis were not performed blind and no

attempt was done to measure anti-IgE activity. We therefore decided to launch to blind experiments." [7]

This passage of the letter to P. Newmark was then followed by the description of the experimental protocol of the experiments of April 22nd and May 12th. Then J. Benveniste got at the root of the affair:

"We feel that the main requirement expressed in your letter of 24 November 1986 that these results be confirmed in another laboratory has been adequately fulfilled. […] I must say that being myself bewildered by these findings, I can understand the reservation of such as prestigious journal as Nature to publish them. […] Thus, I would like to propose you to print the article preceded by a word of warning, or an editorial, where you express all the reservations that the editorial board can have towards such a heretic result. It could also be stated that I and the associated scientists have done all possible efforts to detect an error in methodology or interpretation, going well beyond what is usually done in similar experiments but that nevertheless we are fully ready to accept the challenge of any colleague that could detect some hidden flaw in them.

Thank you for your quick reply concerning your position on this difficult but fascinating problem."

The response of P. Newmark brought along a lot of information. He reported the written answer of an expert, the oral answer of another expert and he made a proposal:

"Thank you for your letter of 12 June, the content of which I have not fully absorbed yet. In the meantime, I think you should see the enclosed comment from a new referee of your paper;

These arrived before your latest letter but I had not sent them on to you because I had been hoping to receive written comments from another referee who, by telephone, had expressed concern at some "large unexplained differences between the data obtained in France and in Israel".

The comments that are enclosed reinforced our own view at the time that you had not provided us with evidence of a truly independent confirmation of your data.

We will need to consider carefully the new information in your 12 June letter and the suggestion that we publish your paper with an editorial. Could you, meanwhile, let us know both your

> reaction to the enclosed comments whether you could, in theory, incorporate any of the new information into your manuscript." [8]

In his comment of about twenty lines, the (American) expert – who did not know the results of the last experiments, but only the experiments performed by E. Davenas at Rehovot – insisted on the necessity of reproducing the experiments because, as he wrote:

> " […] The "independent" verification in Israel doesn't count. The material dated 3/6/87 is literally unintelligible as presented. The numbers are undefined, the protocol is presented in only a fragmentary manner and the experiment was analysed by one of the original team. That's not what I would call an independent verification."

And if the experiments were to be reproduced, he considered that it would anyway be necessary to perform a large number of experiments before publishing:

> "If the findings could really be reproduced, then there are a very large number of controls that need doing. To give a couple as an example: If the anti-IgE is effective at doses of less than 1 molecule per specimen, then its action would hardly be expected to exhibit species specificity; indeed plain old goat IgG should work just as well. "

This was an interesting point raised here. The expert basically said that if one admitted that the effect was real and was due to high dilutions of anti-IgE, he did not admit that this effect could possibly be specific. In other words, according to him this is not a key that opened only one lock which was generated during the dilution process, but rather a master key. We know now that this expert who examined the article of J. Benveniste was H. Metzger, eminent member of the NIH (*National Institute of Health*). We will see him appear on several occasions in this text.

Notes of end of chapter

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[1] Letter of P. Newmark to J. Benveniste of April 6th, 1987.

[2] Letter of J. Benveniste to P. Newmark of April 17th, 1987.

[3] The 5 experiment made in Israel by E. Davenas were nevertheless described in the article of *Nature* of June 30th, 1988 (Table 1 of the article for the 4 first ones and in the text for the 5th; see Chapter 8).

[4] It is surprising *a posteriori* that the experiment did not exclude albumin straightaway, as if the lesson of the experiment of March 2nd made in Rehovot had not been learned. An explanation could be that the idea that there was indeed a contamination was admitted by J. Benveniste and E. Davenas.

[5] Letter of J. Benveniste to P. Newmark of June 3rd, 1987.

[6] Certified report of the bailiff Me Simart of June 11th, 1987.

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

[8] Letter of P. Newmark to J. Benveniste (no date) as an answer to the letter of the latter of June12th, 1987.

Chapter 7. "I am sceptical for literary reasons"

"Please, help us to either detect the errors that we made or publish these data"

During the discussions with *Nature* concerning the first manuscript which – let us remember – concerned high dilutions of histamine, the second article was drafted with the results obtained with high dilutions of anti-IgE. J. Benveniste intended to submit this last article to *Science*, the other big international journal – but American – with a reputation and an influence comparable to *Nature*. Just after the acceptation of *Nature*'s article, J. Benveniste indented to submit this second article to *Science*, in order to take advantage of the breach that would then open. A phone call of P. Newmark however modified this strategy. This latter indeed explained to J. Benveniste that the design of the experiments reported in the article and the recent experiments of reproduction were too dissimilar. J. Benveniste recognized the rightfulness of the remark. He was however not disturbed because he knew that he could address this demand with the data from the article prepared for *Science*.

The debate on the "contamination" in Rehovot was thus at the origin of the new version of the manuscript that would be now submitted to *Nature*. One moves further away from the homeopathic products *Apes malefic* and *Lung-histamine*.

P Newmark being absent, J. Benveniste sent a long answer to J. Maddox at the beginning of July about the brief remarks expressed by the expert.

> "[…] the suggestion from Mr Newmark to "incorporate the new information into the manuscript" is perfectly well-taken. In fact, since a long time elapsed from the beginning of our discussion with Nature, much more work has been accumulated on the anti-IgE trigger itself than on its inhibition by histamine. Therefore it is logical to publish the former information first. A manuscript is now completely ready. It will be co-signed by the participating laboratory in Israel. After approval by them you should receive this new version within two weeks." [1]

Then he suggested to J. Maddox that – as an editor – he must now take the responsibility of a decision:

> "It is clear that all consulted referees don't want to see these disturbing data (you can trust me that they are disturbing for us too !) to be released, but they fail to find any flaw in these very stringent experimental conditions. I am afraid the responsibility of the publication must be taken at the level of the editors. I remind

> you my suggestion of an editorial from you (or if you wish from myself) along the line: "We don't understand how this works, nobody can detect any error or wrong doing, so we present the work for the scientific community to judge."

In his very long answer to the brief report of the expert, J. Benveniste reacted first to the question concerning the reproduction by the other laboratories: "[…] the usual procedure for publishing new, even controversial, results is to publish them first and then let the scientific community reproduce them." Then he explained that he nevertheless complied with the requirements of *Nature* and he described how he was successful in spite of the difficulties inherent to this sort of initiative to reproduce the experiments in Israel. About the so-called "unintelligible" results, one guesses the irritation of J. Benveniste in front of the obvious bad faith of the expert. He resumed the results point by point with a touch of irritation:

> "Here I do not understand why the numbers of basophils are "undefined" when they are under the heading "numbers of basophils"; I do not understand either why the referee find these data "literally unintelligible". He has had in hands the article itself which gives the methodology and everything is explained in these data sheets. […] Feb 27: 85, 82, 82 basophils in the control tubes (83.0 ± 1.0) vs 39, 37, 38 (38.0 ± 0.6) in the 1×10^{-34} anti-IgE dilution. What is unintelligible in these data ? Please look at these remarkably small variations of these counts, done completely blind. […] These conditions of experiments are particularly stringent and very seldom found in any biological experiment published in Nature or elsewhere. All these experiments were analysed by the scientists in Israel and not at all, as mentioned by the referee, by one of the original team."

Finally, he asked not to try to explain a phenomenon before admitting that he exists:

> "May I ask the referee (and the staff of the Journal) to consider these puzzling but indisputable data in cold blood ? We have the feeling that these experiments cannot be accepted in the first place and therefore must be declared unintelligible. I and the other scientists involved are "classical experimenters" with, in our respective field, strong international reputation. As the discoverer of the platelet-activating factor (paf-acether), now a fully-grown field of research, my results have never been contradicted. Thus it is not our interest to put ourselves in the middle of a controversy.

> But we are lead by these results that undoubtedly exist and will, sooner or later, be accepted. Please, help us to either detect the errors that we made (nobody until now has been able to detect them) or publish these data. But you cannot ask us to understand how things work before admitting that they exist. In this way each issue of Nature and other scientific publication would have 1 page and a half."

Then, at the end of August, J. Benveniste sent the new manuscript to J. Maddox. One more time, J. Benveniste pointed out that he complied with the requests of Nature: "As you will see, the submission of the new manuscript corresponds exactly to the demand of Dr. Newmark in his last letter to "incorporate… the new information into the manuscript" "[2]

"People who advance extraordinary claims must go to extraordinary lengths in their support"

The text of the manuscript that was then sent to *Nature* was very close to the one that was published in June 1988. Except for one figure, which illustrated the need of shaking between each dilution to obtain active high dilutions, the results of which were simply mentioned in the text, the rest of the manuscript underwent only minor changes. But almost one year have been nevertheless necessary before the publication. During this lapse of time, an epistolary (and phone) arm-wrestling took place. For the first months however, J. Maddox did not give news anymore.

At the end of September, good news arrived to Clamart. An Italian team had reproduced the experiment of degranulation with high dilutions and sent the results of 6 experiments. Of course, J. Maddox was informed: "These results from totally independent investigators will confirm you that the phenomenon is real and should be published." [3] These results had been obtained from Antonio Miadonna's Italian team to which Alberto Tedeschi belonged. The latter stayed in Clamart within the framework of a scientific collaboration (independently of high dilutions) and he maintained a friendly relationship with the team. But more importantly, he wrote several publications in the field of basophils and histamine release. He had already used the test of degranulation of basophils and therefore did not have to learn the technique. The weight of his results was thus important: he was an expert in this field and he performed experiments with total independence.

At the end of October, J. Benveniste telephoned and sent faxes asking to J. Maddox when he would take his decision concerning the article. J. Maddox finally answered:

> "Thank you for having been so patient with us. As you will have notice, I have not been able to come to grips with your manuscript as quickly as I had hoped when you telephoned.
>
> Bus now, alas, I have decided that we cannot publish your manuscript. The simple explanation would be to say that people who advance extraordinary claims must go to extraordinary lengths in their support. I would, on this occasion, be fairer to say that I am sceptical for literary reasons.
>
> You claim an astonishing set of observations, but then do almost nothing to discuss the possible explanations. We know, of course, that Galileo was more than anything excited by the implications of his surprising observations.
>
> I am sorry to send you these disappointing news." [4]

Thus, J. Benveniste was back to square one. Obviously, J. Maddox did not even consider necessary to submit the new version of the manuscript to the experts. Why did he ask for so many additional experiments since only "literary" reasons prevented him to publish the manuscript? With the intent of making fall J. Benveniste? With the intent that J. Benveniste would be finally get tired? For J. Benveniste, it was too much. On November 13th, he wrote to J. Maddox. There was no more room for kindnesses:

> "I must be a matter of langage but I do not understand your letter of November 4. After a first review of our paper you asked us to verify these results in an independent laboratory. This was done with our cooperation in one set of experiments in Israel and without any intervention from our part in another set in Israel, Milano and in Marseille. The latter result is remarkable since this experiment was specifically aimed at showing that we were wrong. Thus we have fulfilled your demand and now you refuse the paper for "literary reasons". There we are in foreign country since I cannot discuss scientific results on a literary basis. […].
>
> I am certain that Galileo would be proud to be compared to me. He was, just as I am, excited by the implications of his surprising observations but he did not solve the problem. Newton and Einstein did when they got the means for it. Would Nature have accepted a paper from Galileo? […] I expected you to wish to meet the people who did the experiments, see the lab books, in other words to examine (or send an expert to examine) the facts to help us bring them to the judgment of the scientific community or detect the bug. Instead of this, you dismiss the important effort on the basis of "skepticism for literary reasons"." [5]

J. Maddox replied to this letter only on January 21st. A negotiation gradually set up between both protagonists – on the initiative of J. Maddox – about mechanisms involved in the claimed phenomena. In the mind of J. Benveniste, it was necessary to first publish and then only an international cooperation with biologists and physicists alerted by the publication would allow casting some light on the described phenomena. For J. Maddox on the contrary, the publication had sense only if one explained what was observed. This suggestion to progress in the clarification of the phenomenon before publishing could be obviously interpreted as a new delaying operation of *Nature*:

> "I do honestly appreciate the puzzlement you must feel that we should first have asked for independent verification of your results and then that I should have written a frankly discouraging and sceptical letter. I do think, however, that this sequence of events is explicable by the conversation we had on the telephone in which I asked that you should speculate about possible explanations.
>
> At that stage, you said, if I understood correctly, that it might be something to do with the way in which macromolecules might leave their imprint on the structure of liquid water long after they themselves had been made to vanish by dilution, which is so much at odds with what we all believe (perhaps wrongly) to be the properties of liquid water that I could not help wondering why you appeared not to regard that as an issue as central as the one with which your paper dealt.
>
> Generally, we are for the publication of observations, however surprising, but when they are both surprising and inexplicable, I think it is fair that we should ask not merely for verification but also for an attempt at explanation or alternatively an acknowledgement of defeat in that direction." [6]

This idea that molecules would leave an "imprint" in water – what was popularized under the term of "memory of water" – was in fact not new. The reading of the letter of J. Maddox gives the feeling that he heard this "interpretation" for the first time during a phone conversation with J. Benveniste. In fact, this concept, which was far from being a highly-developed theory as one sometimes suggests, was already mentioned in the first versions of the article submitted to *Nature*.

Always faithful to his line of conduct, which consisted in not leaving the slightest chance of wrong footing him to *Nature*, J. Benveniste suggested integrating some experiments that began to explore the physical properties of the high dilutions into the future version of the article, what should allow

establishing the mechanism of the observed effects (or at least should allow drawing some avenues of research):

> "[…] we have started the job and I will briefly give you an outline of what we have obtained. By four physical means, we have, I believe, definitely answered to the criticism (that was as awkward as the results themselves) that after the first dilutions there was no more dilution thus still leaving molecules in the suspension. Heating, ultrasonication, freeze-thawing and filtration show that the activities at low vs high dilution, although identical in their biological effect, are different in their physical behaviour. The most impressive experiment is the following: a 150 kD IgG molecule does not, as expected, sneak its way through a 10kD filter whereas its ghost counterpart is, just a good honest ghost, found in the filtrate, demonstrating that these ghost molecules have no real structural presence in space but are most probably "composed" of a rearrangement of water molecules. Also quite impressive are the results of the heating experiment: whereas regular molecules react according to their thermal sensitivity all ghost molecules disappear at 80°C. […]" [7]

Finally, he asked to J. Maddox to take a clear position on a possible acceptance of the manuscript if these new results were to be integrated into the last version:

> "We believe that we have gone another step forward in the explanation of the phenomena. You cannot, in the present stage of knowledge and technology, ask us to go much forward since finding the whole answer to these data might take 20, 50 years or more. We do have now to present these results to interested scientists, in order to start the cooperative process.
>
> Be kind enough to drop a short note to indicate me if on this basis you are willing to reconsider the acceptability of the paper. It should now reach the volume of a full article. In this way, we will not waste time if you are definitively opposed – whatever our new evidence – to publish the paper. It will have to find its way somewhere. Many people believe that these experiments will change our vision of the world, with immense consequence. Nature is the vehicle for such an endeavour. I maintain my proposal of an introductory editorial from your staff or from myself. […]"

A proposition of J. Maddox

On March 14th, J. Benveniste and J. Maddox had a phone conversation, which led to the sending of the new manuscript to *Nature* on March 19th integrating the results mentioned by J. Benveniste in his last letter. These results were however only briefly described. Their complete description would indeed have weighed down the article. J. Benveniste renewed his proposal once more to accompany the article with an explanation by the editorial staff of *Nature*:

> "I would like to remind you my proposal of having this paper preceded by an editorial that would absorb the shock that any scientist will feel when reading these results (I can assure you that we feel this shock every day when looking at them). It should in my opinion explain why we are showing these data to the scientific community that is mainly to trigger experiments on other biological systems and international cooperation between chemists, physicists and biologists. It could also indicate that the editorial staff has seen the experiments mentioned in the text "to be published", that could not possibly be presented in a single article. […] As you will certainly agree, the challenge is enormous since the results might be among the most fascinating in recent times. Please answer as fast as possible." [8]

One month later, in his inimitable British style where understatement competed with litotes, J. Maddox answered to J. Benveniste by expressing once more time his skepticism. The last version of the article again had been not reviewed by experts. But J. Maddox made a proposal of publication – admittedly an amended publication – but a publication nevertheless!:

> "Many thanks for your revised manuscript, but I am afraid that my colleagues and I are still rather sceptical of it. For example, I am not convinced that the dilution procedure fully guards against the possibility of contamination.
>
> But I do have this proposal to make. We would send your article to Dr Walter Stewart, who acted as a referee for an earlier version. I believe you may not have seen his comments of 15 July, so they are enclosed. Obviously, some of his criticisms are outdated, but they will give a flavour of how he is likely to approach any new manuscript. We would show you his report on this occasion and then discuss with you the question whether we should publish an amended version of your manuscript together with a no-doubt amended version of Stewart's report.

> If that attracts you, I suggest that we have a word on the telephone. Otherwise, I fear that we are not able to publish your manuscript." [9]

J. Benveniste was thus invited to answer to a comment dating almost one year. Contrary to the previous comments, the expertise report had several pages and obviously W. Stewart had carefully read the text. The tone of the report was not aggressive, even if W. Stewart expressed his skepticism very clearly. Having in hand the report of the experiments made in Israel by E. Davenas, W. Stewart also commented about them. Thus, the low variability of the counts of basophils in these experiments amazed him:

> "The low variability of the three repetitions on each page of the data supplied with the supporting letter strikes me as quite extraordinary from a biological point of view. The authors of the letter, however presumably know the characteristics of their system. How do they explain the extraordinarily low variability? Does this cause them to question the validity of the data."

Then, comparing the results of the manuscript and those of Israel, W. Stewart wrote:

> "The results obtained in Israel, however, appear to be of outstanding statistical significance. […] How do the authors explain the difference."

J. Benveniste thus must react to a report that was irrelevant at this time and must answer to numerous groundless questions. However, concerning the question of low variability, J. Benveniste answered with pragmatic arguments to statistical ones. We notice in the comment of W. Stewart what will constitute the main criticism of the future report of *Nature*, namely "too good" results:

> "??? are our results too good ? May we remind the referee that all counts were performed "blind" (if I may say so). Dr. Davenas did not know what she was counting. She had been in a foreign laboratory, under an extraordinary pressure, with a lot of people accusing her for cheating (for what purpose ?). She kept her calm, giving repeatedly the same results even when tricks were used (announcing 5 control tubes when there were 7). This shows that: 1) the method for counting is simple and reliable, 2) Dr. Davenas is one of the best experimenters seen in ages. Her extraordinary log books, the photocopies of which were sent to Dr. Maddox, are there to witness this. You are free, as repeatedly offered by us to

> Dr. Maddox, to come and examine them at length, at our expenses […]"[10]

This debate which became central a few months later – with all its insinuations – is thus only sketched here but each of the protagonists is already in his future posture. On one side, W. Stewart for whom two plus two will always equal four. On the other side, J. Benveniste, more pragmatic, who did not understand how he could be blamed for having a too precise measuring instrument. We will return in detail during Chapters 10 to 12 on the arguments from both sides. Indeed, under the appearance of simplicity, this question deserves developments and detailed explanations.

"These results could well be the event of the century"

J. Benveniste dictated his answers to the expert report from Bermuda where he was invited to present his results to a conference from 15th to 21st April 1988 which was attended by many Nobel prize winners and also the philosopher of the sciences Karl Popper. The theme of the conference concerned the relationships of quantum physics and biology. With a limited number of participants, presentations took place in a rather informal and friendly atmosphere, often followed by passionate discussions on the beach. Naturally, J. Benveniste announced in his letter to J. Maddox his participation at this conference and the warm welcome that his presentation received among the elite of the science:

> " I was last week in Bermuda attending the conference "Overlap and Union of Quantum Theory and Biology". Here were some of the most prominent theoricians, physicists and biophysicists who invited me to present my results. A few names are Sir John Eccles, David Bohm, Finkelstein, Bryan (*sic*) D. Josephson, Cyril Smith. Something quite remarkable happened which is that, instead of my 1-hr presentation, I was asked to present and discuss these results 4 times for a total of 6–8 hrs. Most of the participants agreed that 1) they could not find any flaw in the experimental design (they were especially impressed by the filtration experiment showing the absence of "classical molecules"); 2) they could well be the event of the century and some of these men stated that they were the most important they had seen in all their life; a theory seemed to fit best that was put forward by Emilio del Guidice from Milano : the organisation of water dipoles, creating an electromagnetic field that could mimic the one originated by the original molecule." [11]

Then, J. Benveniste confronted J. Maddox with his responsibilities:

> "You will certainly think that I am putting pressure on you and try to influence you. This is certainly the case. Through more and more contact with colleagues, especially of this high level, I am gradually realizing the enormous possible impact not only on biology but on physics of water and transmission of specific informations. Since you are now on the process of reaching a decision I thought useful to bring these informations to you. […] Finkelstein offered me to publish these data in the "Journal of Theoretical Biology" but there is no doubt in my mind that – besides its scientific level – Nature is the ideal place to trigger a multidisciplinary debate."

At the beginning of this text, we reported different reasons that could have decided J. Maddox to finally publish the controversial manuscript. It is possible that this conference in Bermuda is also an element to consider. Indeed, it is likely that the director of *Nature* who continued to be skeptical (it is a euphemism) about the results about high dilutions could have been anxious to be accused of preventing the diffusion of results supposed (rightly or wrongly) to be important. Moreover, this accusation would originate not only from J. Benveniste – who after all was known only amongst biologists – but also from Nobel prize laureates and great names in physics. Indeed, one must not forget that J. Maddox, via his numerous contacts related to his position, had probably heard of this conference. This is only a hypothesis, but the possible anticipation of charge of scientific obstruction should also be probably taken into account in order to understand his subsequent attitude.

Notes of end of chapter

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[1] Letter of J. Benveniste to J. Maddox of July 6, 1987.
[2] Letter of J. Benveniste to J. Maddox of August 20, 1987.
[3] Letter of J. Benveniste to J. Maddox of September 27, 1987.
[4] Letter of J. Maddox to J. Benveniste of November 4, 1987.
[5] Letter of J. Benveniste to J. Maddox of November 13, 1987.
[6] Letter of J. Maddox to J. Benveniste of January 21, 1988.
[7] Letter of J. Benveniste to J. Maddox of February 2, 1988.
[8] Letter of J. Benveniste to J. Maddox of March 19, 1988.
[9] Letter of J. Maddox to J. Benveniste of April 21, 1988.
[10] Letter of J. Benveniste to J. Maddox of April 29, 1987.
[11] Letter of J. Benveniste to J. Maddox of April 26, 1987.

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! [5] "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.

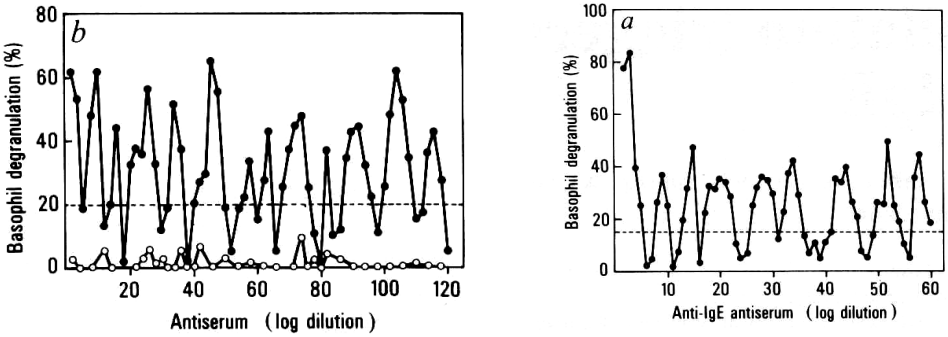


Figure 8.1. Reproduction of Figure 1 of the article of *Nature* of June 30th, 1988, p. 817. The black circles correspond to anti-IgE and white circles to anti-IgG (inactive control).

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 1×10^{-1}*	35.5±1.8 (56)‡	42.3±4.8 (53)	27.7±0.7 (66)	40.0±1.5 (62)
aIgE 2×10^{-2}	77.6±0.8 (4)	87.3±1.2 (3)	66.3±2.3 (18)	93.7±1.9 (12)
aIgE 1×10^{-3}	76.0±1.1 (6)	88.7±1.8 (1)	77.7±1.8 (4)	74.7±2.8 (30)
aIgE 1×10^{-4}	53.6±1.4 (33)	52.7±1.4 (41)	38.0±0.6 (53)	48.3±2.4 (55)
aIgE 1×10^{-5}	45.0±0.5 (44)	35.0±1.0 (61)	41.3±1.8 (49)	49.3±1.2 (54)
aIgE 1×10^{-6}	49.0±1.7 (40)	50.3±0.7 (44)	55.0±2.1 (32)	74.3±2.3 (31)
aIgE 1×10^{-7}	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^{-3}) 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*	μ ml^{-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	I	*A*	*B*	
Tyrode's	0	0	—	—	$< 1 \times 10^{-3}$
Tyrode's	0	0	—	—	$< 1 \times 10^{-3}$
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	3	—	—	$< 1 \times 10^{-3}$
aIgE 1×10^{-36}	40	35	—	—	$< 1 \times 10^{-3}$

* 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.

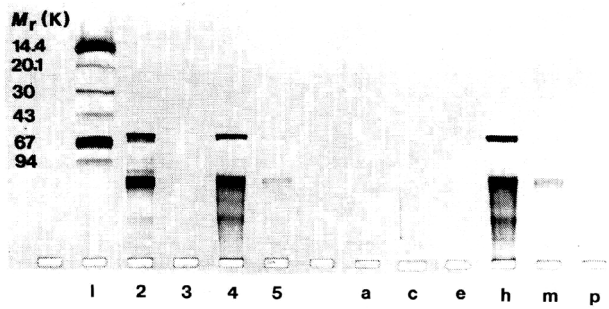


Fig. 2 Electrophoresis (polyacrylamide 7–15%, bands revealed by silver staining): samples numbered 1 to 5 are standards for the blind experiments *a*, *c*, *e*, *h*, *m*, *p*. Lane 1, Molecular weight standards for electrophoresis; lane 2, monoclonal IgG added with human serum albumin; lane 3, Tyrode's 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^{36} anti-IgE dilution; *h*, 1×10^7 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 heat-sensitive or heat-resistant 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.[6] 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: Weizmann 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.[7] 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] The reason of this new section which was created on this occasion has been given by a former editor of *Nature*: "Significantly, the Benveniste paper ran under the special heading of 'Scientific Paper'. According to Charles Wenz, then the Coordinating Editor of Nature, none of Maddox's subeditors would accept responsibility for printing the paper in their own sections." (Melinda Baldwin. Credibility, peer review, and *Nature*, 1945–1990. *Notes and Records. The Royal Society journal of the history of science. doi:10.1098/rsnr.2015.0029).*

This quotation confirms that J. Maddox decided to pubmish the manuscript against the opinion of his collaborators.

[6] A former assistant of B. Pomeranz, Norman Allan, told the visit of E. Davenas in these terms:

"Bruce Pomeranz lab was one of three labs that replicated the Beneveniste degranulation protocol. I have read on-line a critic/skeptic claiming that all replications were made by Davenas and only by Davenas. I was working in Pomeranz laboratory throughout this time period. As I remember, originally Pomeranz and Fortner went to Paris for two weeks to learn the protocol. Then, to begin with in our lab, the assay/anomaly/phenomena worked, manifested clearly perhaps 20-25% of the time. And therefore at some point Davenas came over to Toronto for two weeks to supervise and help us work out the kinks. While she was with us, supervising, the assay worked consistently (I believe the manifestation of the phenomenon during that time approached 100%). However, after Davenas left, over a period of about three weeks, our efficacy slowly then degrading back to the 20% we had previously seen" (http://www.normanallan.com).

[7] 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).

Chapter 9. "A report whose conclusion would be: magic is true"

The trio enters the track

As soon as the article was published, it was necessary to get ready for the arrival of the investigators. But, as we have already said, there was no particular anxiety about this visit. Yet, to say the least, the composition of the trio was not neutral.

At the time of the survey, John Royden Maddox was 62-year-old. Of Welsh origin, he was a physicist and a chemist. He taught theoretical physics at the University of Manchester during six years from 1949 to 1955. Then he left the university to manage the science column of *Manchester Guardian* from 1955 to 1964. He became Director of *Nature* from 1966 to 1973. He then delegated the direction to manage the Nuffield foundation which financed research projects intended to promote education. He resumed his director's position of *Nature* from 1980 and onwards. However, when he got his former functions back, the writers of *Nature* distrusted him and transmitted a petition to the direction of the journal so that J. Maddox would not be involved in the management of the scientific manuscripts. The latter explained this attitude in the following manner: "They were extraordinarily on their guard to see me come back […] because I had acquired, not without any reason, the reputation of being stubborn, somebody who was determined, but also unpredictable." [1]

For his part, J. Randi, born Randall Zwinge in Toronto, was 60 years old in 1988. He was a very well-known stage magician in the Anglo-American world. Since the 50s, he participated in very popular television programs in the United States. He acquired an international fame in the 1970s when he accused Uri Geller to use conjurer's tricks "to twist teaspoons". Especially, J. Randi was a founder member of the CSICOP (*Committee for Scientific Investigation of Claims of the Paranormal*). It is an association of "skeptics", which is dedicated to demystifying and denouncing individuals who claim to be endowed with paranormal powers. J. Randi wrote in particular several books to fight popular beliefs concerning paranormal. One of his favorite targets was parapsychology, especially when performed in universities because one of his favorite theses was that scientists were very easy to fool. What he considered as one of his most great success was the "project alpha". This project consisted in introducing two of his magician stooges within a university team which experimented in the field of parapsychology. This team had received an important legacy in 1979 to evidence paranormal effects (such as psychokinesis and telepathy). The team thus recruited individuals claiming to have unusual capacities. During several years,

both stooges of Randi who had succeeded to be selected were themselves particularly "competent" and the studies focused on them. Therefore, they made people believe they had "powers" although they used methods of conjurers and stage magicians. The mystification was revealed in 1983.

As for W. Stewart, then 43-year-old, he owed his celebrity for his investigations in several affairs of scientific misconduct. Chemist and physicist by training, researcher at the NIH, he had nevertheless no doctorate. With his boss Ned Feder, he specialized in revealing frauds of other scientists: "on the campus of the NIH at Bethesda, in Maryland, where he shares a tiny office with his friend Ned Feder, his name arouses disgusted or negative reactions: he is the "informer", "the one who bites the hand that feeds him", "a bastard who strikes a blow at the credibility of science" and "tarnishes the scientific community." [2]

The first affair which made W. Stewart famous was the case of the scotophobine in 1972. This biological factor was supposed to transmit learning from a rat to another one, namely the fear of darkness. W. Stewart reported that the way of selecting data (among other criticisms) was responsible for this "discovery". The article and its refutation by W. Stewart were simultaneously published in *Nature*. Another famous affair in which W. Stewart and N. Feder were involved was the case Darsee, named after a cardiologist of Boston who produced an impressive amount of experimental data with which he drafted articles, some being published in scientific first-level journals. The affair burst in 1981 and was the occasion, beyond this case of obvious fraud, to question the system of "peer review" which had missed numerous discordant results and obvious errors. In 1988, at the time of the present story, W. Stewart struggled with the Baltimore case, an extremely complex history in which the Nobel prize laureate D. Baltimore was accused of having covered made-up data. The affair gained considerable importance with hearings organized by a member of parliament, Senator John Dingell. Several committees of inquiry later, D. Baltimore as well as the researcher in cause were finally acquitted in 1996.

As the three musketeers of Alexandre Dumas, the investigators were actually four. A young man named José Alvarez accompanied J. Randi. His arrival in the laboratory of J. Benveniste had not been announced by J. Maddox who nevertheless managed the survey. The exact role of J. Alvarez during the survey remained obscure. J. Randi presented him as an assistant to whom he "taught the job". We must recognize that he did not disturb the team. Apparently in no hurry to perfect his apprenticeship, he spent the early stages of the survey sleeping in a corner of the laboratory, probably as a consequence of jet lag. Afterward, we saw him only occasionally.

In fact, José Alvarez, 19-year-old, was a friend of J. Randi and was an artist performance in Plantation in Florida, the city where J. Randi resided. With the help of this latter, J. Alvarez became famous the same year in 1988 in Australia. Indeed, at the request of an Australian television channel, J. Randi trained J. Alvarez to play the role of a "medium" named Carlos supposed to be in communication with a spirit having lived several thousand years before. The purpose was to estimate the degree of credulity of media and public. A press kit was made including numerous indications which should have put on the track of the trickery if a simple investigation had been made on the so-called medium. This one was the subject of numerous articles in press, radio and Australian television. The trickery peaked with the gathering of numerous "believers" in a room of the Opera of Sydney on February 21st, 1988. One week later, the mystification was revealed during the television program which had sponsored this "performance".

If the coming of a "real false medium" in the laboratory of Clamart had been known at that time, it would probably have been the occasion of numerous jokes in the press which already ridiculed the presence of a "magician". Especially, it would certainly have dealt with a severe blow to the seriousness of the "performance" organized by *Nature*. The impression of a "circus" atmosphere, which will be reproached after the visit, would have been considerably strengthened. In spite of this risk, it is surprising that J. Maddox authorized J. Randi to come accompanied with his friend. But maybe J. Maddox too did not know the recent exploits of the latter.[3]

The team of Clamart, even though they understood the profiles of the investigators a little bit better, was however not conscious that the curriculum vitae of the latter were so "heavy". Naively, thinking that it participated in a scientific controversy where each participant was supposed to be honest and open to the opposite arguments, the researchers of Inserm U200 understood only afterward that the investigators could not return empty-handed from their trip to Clamart. Their honor was at stake. They must return from their expedition with a new trophy to add to their collection.

The last details concerning the arrival of the investigators were quickly set at the end of June. Christian Boiron himself as CEO of Boiron Laboratories sent a fax to the investigators to announce them his invitation "to study the scientific results on high dilutions carried out at the Inserm Unit 200 in Clamart." [4] The fact that Boiron Laboratories – first world manufacturer of homeopathic products – financed their stay did not apparently disturb the investigators. In the investigation report, J. Maddox recognized that hotel expenses had been actually paid by these laboratories. In his defense, we must acknowledge – as the

developments of this text will show – that the financing of their stay by manufacturers of homeopathy did not influence their conclusions in a direction favorable to homeopathy! However, in the investigation report, they pretended to have discovered during their stay at Clamart that homeopathic laboratories had participated in the financing of the research of J. Benveniste.[5]

The narrative of the week

Large extracts of the internal report of Inserm U200 that Elisabeth Davenas drafted immediately after the departure of the "guests" will serve us as common thread. Sometimes transcribed in telegraphic style, this document gives nevertheless an idea of the atmosphere during this week and especially allows understanding the sequence of the experiments. Finally, in order to allow the reader to understand the various experiments performed during the week, Table 9.1 summarizes the characteristics of each experiment that was commented in the investigation report of *Nature*. The reader can refer to it in the course of reading.

Although he was not present during the famous week (he nevertheless interviewed the various protagonists afterward), the journalist M. de Pracontal described well the general atmosphere of this week:

> "One imagines the atmosphere: Stewart with the finesse of a big hamburger and approximately so quiet as an aviary of parakeets, overexcited at the idea of letting a clue escape; Randi who for understandable reasons has the right to touch nothing, but who watches everything with an eye of lynx; Maddox, very phlegmatic, very British, observing the advancement of the operations as if he was a simple spectator; and Benveniste, furious of seeing that he is not at home any more in his own laboratory." [6]

Let us therefore begin the chronological narrative of this week. We remind that the protagonist belonging to the laboratory of Clamart and named "Francis" by E. Davenas is the author of the present book. We will comment the investigation in Chapters 10 to 13.

N° exp	Blood donor	Series of anti-IgE at high dilutions	Day of preparation of experiment	Day of basophil counting	Counting by :	Comments
A	Hospital	Series n°1 of Monday	Monday (open-label)	Tuesday afternoon (open-label)	ED	Coagulation issue
B	Hospital	Series n°1 of Monday	Monday (open-label)	Tuesday afternoon (open-label)	ED	
C	Lab (BP)	Series n°2 of Tuesday	Tuesday (open-label)	Tuesday evening (open-label)	ED	
D	Lab (K)	Series n°2 of Tuesday	Tuesday (open-label)	Wednesday afternoon (blind)	ED	
E	Hospital	Series n°3 of Wednesday	Wednesday (blind)	Thursday morning (blind)	ED + FB	
F	Hospital	Series n°3 of Wednesday	Wednesday (blind)	Thursday afternoon and evening (blind)	ED + FB	Serious problem: number of cells (leucocytes) very different from one count to the other.
G	Lab (BP)	Series n°3 of Wednesday	Wednesday (blind)	Friday morning (blind)	ED + FB	

Table 9.1. Summary of the characteristics of the 7 experiments (from A to G) that were performed from July 4th to 8th during the investigation of *Nature*. The reader can refer to it in the course of reading.

Monday 4th, July

"In the morning: explanation of the experimental process to W. Stewart.
Afternoon: realization of two experiments, under control of W. Stewart.
[E. Davenas describes the preparation of high dilutions and cells from two different donors as well as the experiment itself]
6) Stop of the reaction […] Refusal of the experts to seal both plates or to sign on the adhesive tape.
7) Counting on the next afternoon, open-label, Stewart neglecting the possibility of blind counting in spite of our request." [7]

Tuesday 5th, July

> "In the morning: realization of two new anti-IgE experiments with 2 bloods and new series of anti-IgE dilutions.
> 1) Blood n°1: 20 ml of blood (Bernard Poitevin) collected on 4/7/88 in the evening by Corinne […]
> 2) Blood n°2: 20 ml of blood (Karine, trainee) collected on 5/7/88 in the morning by Corinne. Allergic to some drugs. […]
> 3) Realization of a new series of anti-IgE dilutions, under the control of J. Maddox and, from time to time, J. Randi. […].
> 5) Counting: blood n°1 (Bernard), open-label, on the evening; blood n°2 (Karine), blind, on the next evening. […].
> Comments:
> - During these 2 experiments performed on Tuesday morning, Stewart made statistical analyses on the results obtained previously. J. Maddox controlled the process of the experiment. […]
> - Stewart asks me to count all the experiments performed between Monday and Tuesday but does not want that I count them blind → I count 2 experiments performed on Monday and the experiment n°1 (Bernard) performed on the morning.
> The experiment n°2 (Karine) will be counted blind the next day (on Wednesday, July 6th): J. Maddox and W. Stewart did not want to seal the plate which stayed one night at 4°C; it is Stewart who put down the content under the slides of Fuchs [=*hemocytometer*] after I showed him how to do, namely to shake several times (but slowly) to re-suspend and not put down several times from the same well at the risk of obtaining erratic counts (no more twice). One must also pay attention to wash the Fuchs slides between each count.
> Afternoon of Tuesday, July 5th, 88 (→ 10 p.m.): counting of 2 experiments performed on Monday, July 4th, 88. Counting of the experiment n°3 (Bernard) performed on Tuesday morning, July 5th, 88."

Basophils of three experiments were counted on Tuesday (until very late in the evening). The results are shown in Figure 9.1. E. Davenas noted about the first experiment: "blood with rather low degranulation even with strong concentrations. Blood n°1 was the one with micro agglutination during cell wash". Indeed, for the first experiment, the profile of degranulation was rather chaotic and the first peak reached not very high degranulation percentages. The second and third experiments (experiments B and C) on the other hand were more satisfactory and corresponded to quite typical effects with high dilutions (Figure 9.2).

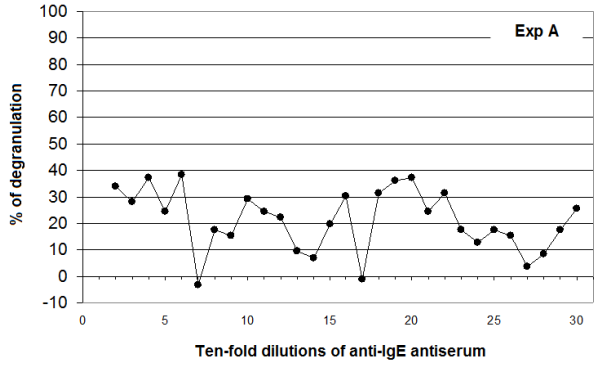


Figure 9.1. The first experiment (experiment A) performed open-label was not a complete success. There were both weak degranulation of basophils with low dilutions of anti-IgE and an unusual profile with high dilutions, probably due to "micro agglutination" of cells. This problem generally occurred when the anticoagulant, which was added to blood to prevent coagulation, was inefficient (for example, because the tube had not been returned after blood sampling to favor the mixture of the anticoagulant with blood).

"On Tuesday evening, while I am counting the second experiment, Jacques tells me that the next day Stewart wants that I make 3 whole experiments with dilutions of anti-IgE from 1×10^2 to 1×10^{30} (3 different bloods). With anti-IgE completely coded. The reading will also be coded.
I protest because it is far too much. What is the point of counting, alone, the first 4 experiments: why they do not want that I count blind as we ask them?! Then, they will not want to take into account the results.
At the time, I refuse to count the 3rd experiment. Finally, I do it, Jacques tells me that we cannot refuse what the experts want at the risk of appearing "to hide" something.
I thus count but I propose that the next day I count the 4th experiment (at least!) blind and that the 3 experiments be performed not on the entire anti-IgE range, either only on a part (for example: from 10^{20}à 10^{30}) or 2 duplicate experiments on a part of the range. But not three on the entire range!
But Stewart refuses. He has said. We have to do the way he wants to. He also always refused to make an experiment where we test an anti-IgG range versus anti-IgE".

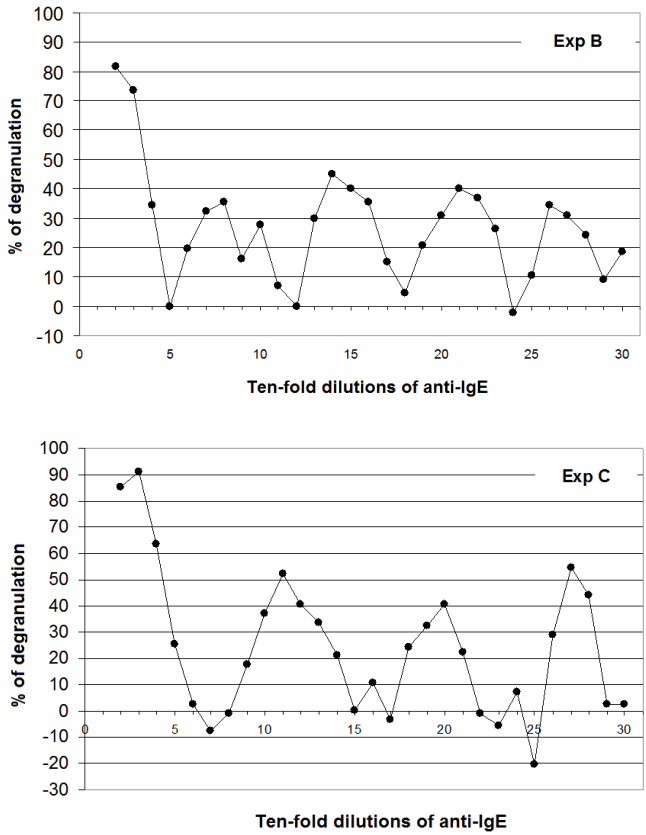


Figure 9.2. The experiments B and C were completely in accordance with the expected results. An effect of anti-IgE with high dilutions was obtained with "waves" of degranulation after the first classic peak.

Wednesday 6th, July

"Realization of 3 experiments under constant control. […]
1) Blood.
Given the good result obtained with Bernard's blood (3rd experiment), W. Stewart asks to take again his blood. […] Two bloods come from Béclère *[hospital]* […].
2) Realization of dilution range and coding.
While Randi and his partner prepare a randomization of 5 ml plastic tubes + green corks in Francis' office in the new building, I perform the anti-IgE range in my lab, under the control and with the help of Stewart. I brought new 5 ml tubes, new corks, new tips … I do not have the right to touch tubes, tips, etc.
Stewart places and numbers himself tubes from 2 to 30 on a sample rack. For each dilution, he gives me the tube and takes back the previous tube and plug it.

> I do 10-fold dilutions of anti-IgE with […] duration of rotating mixer = 15 sec. Tubes are plugged with orange corks.
> At the end of the dilutions (from 1×10^2 to 1×10^{30}), I point out that it is necessary to add controls […]. Thus, Stewart adds 5 tubes numbered from 31 to 35 corresponding to controls.
> When the dilutions are done, I take them and go down the stairs with Stewart and Bernard Poitevin in Francis' office where J. Randi, his partner and J. Maddox are.
> The tubes in which the dilutions will be transferred are on a sample rack hidden by a sheet under the eye of a camera which recorded the previous randomization and which will record the coding.
> I sign, with W. Stewart, the sheet where the code will be noted and I leave the room having left the dilutions – under the eye of the camera and the only experts. Jacques does not have the right to approach this door (to see if everything is according to the rules…). Only the experts know the code.
> It is Ruth (in my absence → lunch) who brings back the dilutions in my lab with Stewart, again under the eye of the camera. The tubes have now green corks.
> The code, placed in a scotch-taped and signed envelope is stuck on the ceiling of the lab by Stewart so that nobody touches it!
> 3) Realization of the experiments
> Stewart stays permanently in my lab to watch the dilutions when I go away to centrifuge the bloods […]. After 30 min of incubation (Stewart stayed in the lab permanently), one stops the reaction by adding 90 µl of staining agent with the multichannel pipette.
> Three plates are blocked with adhesive tape, numbered from 1 to 3 and placed in a white polystyrene box with a lid.
> This box is closed by Randi with an English newspaper and with adhesive tape; under the eye of the camera, one records the "result" of the operation from every angle. The box is put in cold room until the next day […]." [8]

The blind counting of basophils for experiment n°4 was then performed. About this experiment E. Davenas noted:

> "This experiment was counted in blind conditions: W. Stewart put down [samples] in chambers. He forgot the dilution 1×10^5. Some wells were counted as duplicates. However, if one compares with my own worksheet, one notices that 3 counts did not match with any dilution (C; D; CC; cf. photocopy). There are wells for which he was not sure: does it correspond to these counts? One will not know because Stewart left with the counts, the code, the calculations…! […] "

The relationship between the 39 blind counts of E. Davenas and their report by W. Stewart after unblinding deserves to be described in detail (several counts can correspond to the same dilution). These data are described in Table 9.2. One notices that three accounts are missing. Indeed, W. Stewart became muddled with the codes and the lists of counts. He was unable to say to which dilutions corresponded these three accounts. Relatively to the 39 counts, it was considerable coming from an "expert" who was supposed to control the quality of the work of researchers.

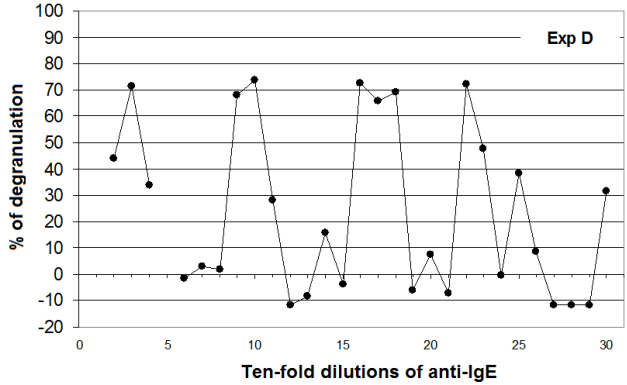


Figure 9.3. These results (experiment D) played a central role in the investigation report published one month after the inquiry. The investigators criticized the high percentages of degranulation (70%) and the fact that this positive result was obtained after a blind counting of basophils whereas the preparation of the experience was open-label (even if this preparation had been made under constant surveillance). But, W. Stewart made errors when preparing the counting chambers and for 3 counts of basophiles, he was unable to associate the corresponding well.

On the evening of July 6th, in spite of the errors due to the inattentiveness of W. Stewart, a discussion took place after the unblinding of the 4th experiment. Indeed, in spite of the errors of the latter, the success of the experiment annoyed the three investigators very much:

> "Following the results obtained for the 4th experiment, there was a rather "hard" discussion with J. Maddox, J. Randi, W. Stewart, Jacques and me on Wednesday, July 6th in the evening.
> - The experts recognize that they are amazed by the reproducibility of the counts in duplicate.
> - They are amazed (with us) by a so high degranulation with high dilutions (may be due to the fact that Karine is allergic to some drugs: basophil hypersensitivity).
> - Rather vigorous discussion about "sampling error". After reading my laboratory notebooks they do not see any note about this "sampling error" which we can expect: variability of test counts. Is the presentation of results correct? Should "negative" degranulation be reported? What is the limit of significance? Is each count not associated with the same 20% of error? They admit that it does fit with the 4th blind experiment but they do not want to take it into account because only the counting was done blind – they forget that J. Maddox watched me experimenting – they thus wait for the results of experiments done on Wednesday with all the possible and conceivable rigor […]
> - They also blame for the "too good" results of Israel and overall the "too beautiful" results reported in my lab books […]"

N° of counting	Number of basophils	Corresponding dilution	N° of counting	Number of basophils	Corresponding dilution
A	30	10^{-17}	U	97	Control
B	58	10^{-4}	V	49	10^{-2}
C	84	**UNKNOWN**	W	98	10^{-29}
D	17	**UNKNOWN**	X	23	10^{-10}
E	21	10^{-22}	Y	Not counted	
F	85	10^{-7}	Z	91	10^{-15}
G	63	10^{-11}	AA	81	10^{-20}
H	88	Control	BB	98	10^{-28}
I	63	10^{-11}	CC	27	**UNKNOWN**
J	93	10^{-19}	DD	60	10^{-30}
K	94	10^{-21}	EE	84	10^{-6}
L	78	Control	FF	76	10^{-26}
M	94	10^{-6}	GG	27	10^{-18}
N	46	10^{-23}	HH	98	10^{-27}
O	84	10^{-26}	II	95	10^{-13}
P	98	10^{-12}	JJ	24	10^{-16}
Q	25	10^{-3}	KK	54	10^{-25}
R	28	10^{-22}	LL	88	10^{-24}
S	86	10^{-8}	MM	29	10^{-9}
T	74	10^{-14}	NN	27	10^{-9}

Table 9.2. This table presents raw data for experiment D shown in Figure 9.3. We note the absence of identification of 3 counts C, D and DC due to errors of W. Stewart.

Thursday 7th, July

"Counting of the two experiments performed on 6/7/88.
Protocol established by Stewart:
1) We will be two for the counting: Francis and me. Each one with a series of chambers (that implies 2, 3 even 4 pipettings in wells when these latter are counted in duplicate… It is too much for a well and can entail an erratic count … (I had said it to Stewart, he does not want to take it into account).
Francis and I must not speak and nobody can see us or speak to us. Even – especially – Jacques.
2) It is Stewart who puts down the contents of wells in the chambers of Fuchs, under Corinne's eye, in the lab room near this one where we count. W. Stewart shakes with a 100-µl pipette and puts down exactly 15 µl under slides with another pipette […]. He brings us chambers while we are counting → No pause. We are sometimes obliged to tell him to slow down because chambers dry or blush by waiting for such a long time.
From 10 a.m. to 2 p.m.: 56 counts corresponding to plate X […] There were overall 35 wells → Most of them were counted in duplicate (56 counts).
From 4 p.m. to 10 p.m.: 72 counts corresponding to plate Y. [..] Counting very difficult, pale basophils, poor preparation, different cell densities (up to 2:1 ratio) according to chambers (we have pointed out it and showed to Stewart and Maddox). All wells were nevertheless counted in duplicate.

> The counting was too long and too painful. The plate stayed all afternoon and all evening long outside. We should have stopped counting, Francis and me. It was useless and tiring. Furthermore, given the cell preparation, it was obvious that we could say nothing, conclude nothing with this experiment."

At the risk of laboring the point, I add that I actually disturbed J. Maddox who, posted in the entrance of the room, killed time by darkening sheets with mathematical calculations of integrals. I had then made him notice the huge differences of cell densities from one well to the other one, what invalidated the experiment. He had then pointed out the fact to W. Stewart who did not deny the problem. They told me to record my comment on the counting worksheet so that it would be taken into account at the time of the analysis. Why should we then continue in these poor experimental conditions? I was told that these results would be nevertheless "useful for statistics".[9] We will see how these remarks have been taken into account.

Friday 8th, July

> "Counting of the 3rd experiment prepared on Wednesday, July 6th.
> Given the time spent (and lost) counting the experiment n°2, the last experiment is counted on Friday morning.
> In agreement with Jacques and J. Maddox, we refuse to count more than 40 wells (the experiment has 32 wells).
> The same protocol is thus set up. For us the silence, for the others, the magic tricks of Randi. As for the previous evening.
> For this experiment: 40 counts corresponding to the plate Z (= plate n°3 = Bernard). At the end of counting, as we count faster [..], W. Stewart suggests us counting the other wells so that there would be more duplicates. We refuse. […].
>
> Unblinding - Discussion - Results
> When the countings were finished, W. Stewart makes us sign our worksheet of counts, Francis and me. Corinne also signs the worksheet which records the numbering of the wells during the blind counting. W. Stewart and J. Randi also sign.
> We go downstairs in meeting room for a first assessment of the results before the opening of the code. In other words, to try and guess where controls, low and high dilutions could be […]. We come back to get the code stuck on the ceiling with great ceremony. W. Stewart climbs on the ladder to unstick the envelope. He is the only one who is authorized to make it. All this is filmed by Jacques and Randi. It is me who bring back the envelope downstairs (duly accompanied).
> Then the great process of envelope opening with Randi, the Grand Master on the subject. It lasts 20 min overall (perhaps more). At first inspection, the brown adhesive tape which stuck the code on the ceiling is not completely as one would expect, what makes thinking that, suggests that … Finally, we move on to the next stage: inspection of the transparent adhesive tape signed by the 3 experts, apparently everything is well. Randi wants to open the envelope without unsticking or tearing it but by cutting it with scissors → I go back up to the 2nd floor to take my scissors. After my return, Randi cuts the envelope in its right extremity, extracts delicately the content, which is the code folded in a aluminum

> sheet which is neither wrinkled nor torn → finally, nobody touched the code. Randi extracts finally the worksheet of code… We are lastly about to decode… He is going to open the worksheet (folded in 4)… No! we read before a series of notes (that I had written to Jacques) concerning what I considered improper in these experiments. I have no more this sheet. The experts took it. From what I remember, there were remarks on the repeated pipetting in wells that induced errors […] I pointed out that we could not take into account the experiment counted on the previous evening because, with cell densities so different from a chamber to the other one, it was impossible and even erroneous to make an interpretation of these results.
> When we realize that W. Stewart filled not only my Fuchs but also those of Francis, and that Randi made his magic tricks during all this time… This leads dreaming… One wonders moreover with what right Randi signed the sheet of transcription of the code of the counts that have been filled by Corinne and W. Stewart…
> I agree for coding the tubes of dilutions, but not again the counting. Otherwise it would have been necessary that Corinne put down the contents of wells in the chambers of Fuchs. Indeed, finally, W. Stewart knew not only the code of the dilutions but also the code of the counts… And I would not be amazed if he knew the codes given his extraordinary capacity of mental calculation and to remember numbers…
> It seems that they decided to code the counting when, on Thursday morning they found – dixit Randi – that the code in the ceiling maybe had been touched. It is not true because the previous evening – in the hotel of the experts during the cocktail – it had already been decided that Stewart would fill the chambers with the help of Corinne. Moreover Jacques called Corinne to prevent her.
> On the other hand what was decided at the last moment was the participation of Francis for counting. We learnt that only on Thursday morning.
> We learnt later also that, finally, they did not transfer my dilutions in new tubes as they had said but that they had only changed the orange corks with green corks and had erased the *[numbers of]* dilutions with alcohol and stuck labels with the code number (they filmed this episode). This was done so that we cannot, in case of negative results, impute the failure to the transfer […].
> We arrive finally at the unblinding. While Jacques reads, Stewart transcribes. There are so many numbers – counts of Francis and mine – that it is really difficult to analyze everything at first glance but what appears immediately is:
> 1) Very heterogeneous controls […]
> 2) Very poor duplicate counts, while those of Wednesday evening for my 4th experiment, open-label for preparation but blind for counting were perfect.
> 3) Some discordance for some wells between my counts and those of Francis.
> During the heated discussion between the various interlocutors (J. Maddox, W. Stewart, J. Randi, Jacques, Bernard, Francis and me), Randi and Stewart photocopy the codes, but extraordinarily when they leave (finally) late in the afternoon at top speed, we have no document! Jacques must retrieve the results to the hotel, at midnight, when Stewart is still there.
> (My last 2 laboratory notebooks n°4 and n°5 will be got back the next day after departure of Stewart who wanted to study them again during the night although he took all photocopies – with the photocopy of the first laboratory notebooks)."

During the discussion, the main reproaches of the investigators concerned mainly the lack of statistical studies, the reproducibility of the experiments and the lack of objectivity of the experimenter that counted basophils ("does Jacques trust his collaborators?", asked J. Maddox). According to them, odd

results obtained in a single system did not allow claiming such conclusions. Furthermore, the investigators questioned the results obtained in Israel by E. Davenas. Indeed, as recorded by E. Davenas, the investigators asked about the experiments performed in the Israeli laboratories:

> "Who made them? How was made the blinding? If there is no blind counting, it is possible to recognize tubes if they were marked said Randi! That takes the cake! I made dilutions in sterile conditions, from new tubes, unwrapped, under the supervision of several persons. On the other hand, in Israel, there was a double coding of tubes by 2 groups of 2 persons, therefore nobody knew. Furthermore we worked only on a part of the range and every dilution was tested in triplicate (3 wells for every tube). There were thus true triplicate counts. Here there was only a simple code that the experts were the only to know […]. On the other hand there were no true duplicate counts but a double counting of the same well".

The issue of the multiple countings in the same well is an important point. Indeed, we knew from our own experience that they could lead to erratic counts because there were small volumes of cell suspension in each well.

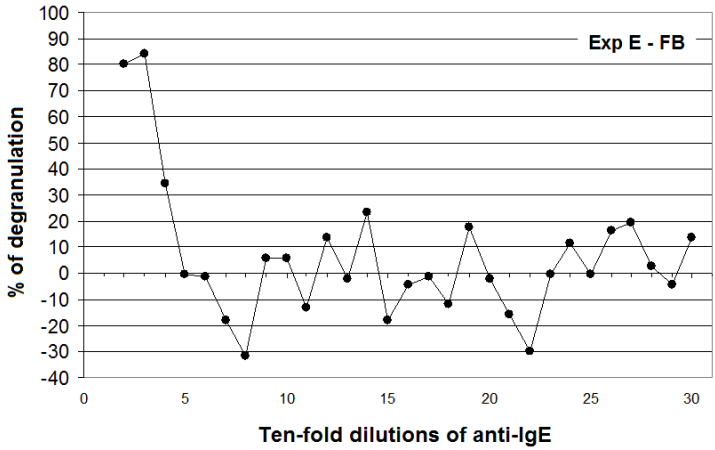


Figure 9.4. In experiment E, both preparation and counting of basophils were done blind in contrast with experiments B and C. Two experimenters – ED and FB – counted basophils. The experiment was not conclusive.

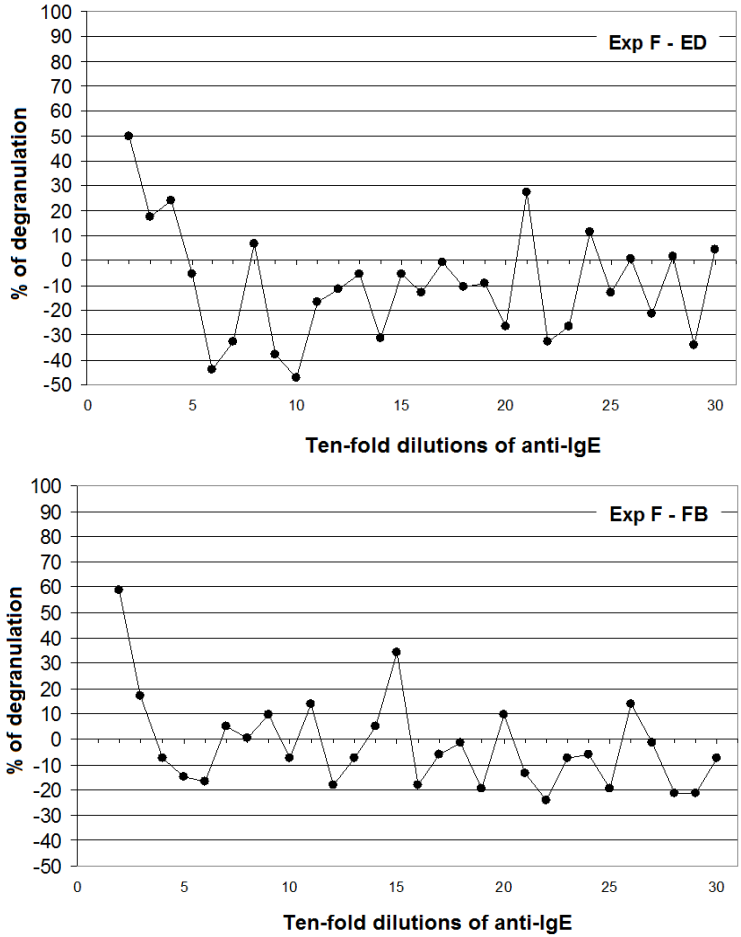


Figure 9.5. The experiment F played (as experiment D) an important role in the investigation report of the investigators. Indeed, each of the experimental points was counted in duplicate. Moreover, the same experiment was counted by both experimenters. We will see in the text how this failed experiment was exploited by the investigators. They ignored an issue despite repeated remarks during counting (and recorded in writing): the cell density varied in an unusual way from one count to the other one. Note on this matter the high negative percentages of degranulation what is completely extravagant. Several reasons could explain these poor results: repeated pipetting in the same well, poor technique for putting down the cell suspension into counting chambers (let us remind that this stage was performed by W. Stewart). A detailed analysis of this experiment is performed in Chapters 11 and 12.

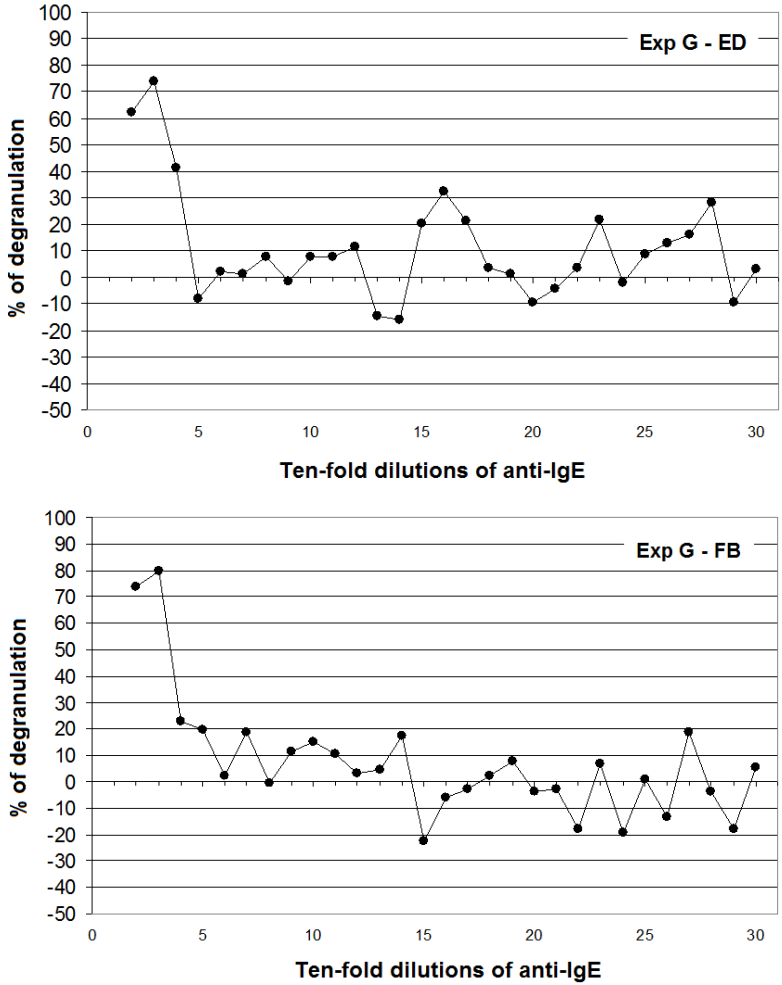


Figure 9.6. Experiment G was done blind and was a failure. Note that all blind experiments (experiments E, F and G) were performed with the same series of anti-IgE at high dilutions. An important control would have consisted in verifying that this series of high dilutions of anti-IgE was effectively effective in *open-label* experiments. This control has not been performed.

The debate with Maddox's team went on. J. Benveniste explained that "if such an experiment, performed in these conditions might cancel five continuous working years and a whole set of convergent successive experiments, then it was necessary to abandon any reasoning and any scientific approach." [10]

The extremely fast English language of the three investigators made sometimes the understanding difficult. The loud and high-pitched voice of J. Stewart, his poorly mastered excitement did not facilitate concentration. J. Randi learnedly explained to J. Benveniste that if he claimed holding a unicorn in his garden, it was normal that one checked this more carefully than for a simple goat. In a totally surrealist moment, the secretary of the laboratory stuck the head through the door and asked what she had to tell to Japanese television which waited for an interview of J. Benveniste.

Then, J. Maddox wrote on several paper sheets three telephone numbers which he distributed to the members of the team. It was his telephone numbers at office, at home and… in weekend. It was – he told us – in case we would have forgotten to say something. Maybe he hoped that somebody was going to admit that she/he was the one who manipulated all the experiments in the back of J. Benveniste.

Quickly, the three hunters of unicorns gathered their belongings, switched off the tape recorder which recorded the discussion and got back the numerous photocopies which they made. They left the laboratory in a few minutes to go to wait for a taxi. Along the way towards the exit of the building, they passed in front of a table stocked with bottles and surrounded with some people looking distraught. They will interpret later this scene as the anticipation of a victory. It was simply a student celebrating the end of her internship.

A few moments later, a press photographer seeking news about the inquiry saw a group of three individuals standing near the building, looking as conspirators and examining with perplexity a document, a plane ticket probably. In a professional reflex, the photographer took remote shots. Only a few moments later, he understood that he was lucky enough to hold at the end of his objective J. Maddox and his two stooges in a funny group portrait. [11] The idea that they were the investigators of *Nature* did not cross his mind. He had indeed wondered who these "three gangsters" (*sic*) were. The anecdote succeeded in making J. Benveniste smile, but the team was knocked out and, in meeting in the office of the latter, tried to get a grip on oneself and to review the situation which was suddenly very uncomfortable.

"I understood that we had been scammed"

This is the story of this week at the Unit 200 of Inserm. These few days were the peak of "Benveniste's affair" after what nothing will ever be as before. J. Maddox had succeeded. He was going to make "explode in mid-flight" the theme of research on high dilutions. Nevertheless, he had been just about to fail. Later, he "innocently" admitted, clearly recognizing that the fate of the laboratory of Clamart was sealed even before the first basophil had been counted:

> "The experiments worked well. I was very worried that they obtained experiments so perfect from their point of view. I wondered what we were going to do if, after all, all that we had to say was that Benveniste was right. I had committed to publish the investigation report. I risked being in the situation to draft a report whose conclusion would be: magic is true." [12]

Thanks to the authority and the leading position of *Nature* in the scientific world, J. Maddox was successful thanks to an uneven balance of power to make the events coincide – even if it meant inducing them – and his vision of "true science". As J. Benveniste told:

> "I had in my lab one of the men with the highest position in science, John Maddox. I was in the position of a man who meets the Pope and the Pope asks for his wallet; what was I to do? It is not easy to say no." [13]

Both stooges of J. Maddox – who in fact had been instrumented by the latter – left the scenery and, with the authority of *Nature*, J. Maddox could now draft a report where nothing would be spared to J. Benveniste and to his collaborators. He had nevertheless offered to them to come to repentance, but because of their refusal, there would be no mercy. Indeed, before the episode of the telephone numbers intended for those who would have had possible faults confessing, he had proposed to J. Benveniste to back-pedal:

> "When Maddox, as soon as the code was unblinded, turned towards me by asking immediately: "you remove your paper?", I understood that we had been scammed" [14]

Of course, as we will see, J. Benveniste answered the criticisms and he did not hesitate in turn to attack the rough methods of the investigators. Even if *Nature*'s team came back from Clamart with few objective facts in their shoulder bag, the dominant message was that the experiments were an "illusion". It was difficult in front of a truth so clearly and brutally expressed – with furthermore the authority conferred by *Nature* – to answer by explaining some

methodological subtleties. Only some clichés circulated with efficiency: the magician, the envelope stuck on the ceiling and the jokes on the water which lost the memory. The rumor made the rest and J. Benveniste was even more marginalized.

Already, on Tuesday, July 5th, 1988 in the evening, the latter participated in a meeting between scientists:

> "One evening of this week, I went to a dinner at the invitation of Minister of Research Hubert Curien, together with John Maddox, with about fifteen French scientists of the highest level, with the managing director of the Inserm P. Lazar, and of ephemeral Minister for Health Léon Schwarzenberg.
>
> By going to this dinner, I hoped to find the support of the French scientific community, which was until then sorely lacking to me. I would indeed have wished that the Minister or the politico-scientific authorities appoint a team of recognized experts in charge of advising me, determining which controls I must do and which hypotheses for the interpretation of the results I could consider. During the meal, I understood very quickly that I could expect no support, and that I had been invited to my own public execution. At one moment, I was quite simply accused by a professor of the "*Collège de France*" (who has an illustrious name but does not seem to have made discoveries justifying his position in the scientific Establishment, nor his arrogance) "to dishonor the French scientific community". This must be understood as: to deprive some of my fellow countrymen, who were potential Nobel prize laureates, of their possible distinction." [15, 16]

Notes of end of chapter

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

[2] P. Alfonsi. Au nom de la Science, p. 84.

[3] In 2011, Alvarez was arrested and jailed because he was accused of identity theft. In 1987, he had stolen the identity of a man from New York together with his date of birth and Social Security number in order to obtain a U.S. passport. This passport allowed him travelling with J. Randi in different countries. Therefore, the true identity of the man who accompagnied J. Randi in July 1988 in France was in fact Deyvi Pena who came from Venezuela in the mid-80s on a student visa. J. Randi and Deyvi Pena married in 2013 (https://en.wikipedia.org/wiki/James_Randi).

[4] Note that the initial invitation was from July 2nd to 7th.

[5] "[…] we were stunned to learn that the salaries of two of the co-authors of the article of Dr Benveniste were paid through a contract between INSERM U200 and French Boiron firm, a manufacturer of pharmaceutical and homeopathic products, as our notes of hotel." (*Nature*, July 28th, 1988, p. 287).

[6] M. de Pracontal. Les mystères de la mémoire de l'eau, p. 41.

[7] Internal report of E. Davenas, July 1988.

[8] Randi said in these terms how the coding was performed: "All the operations took place under the control of a video camera. Elisabeth Davenas brought numbered tubes containing the dilutions in a separate room, put them on the table, then left the room. Stewart, Maddox and myself stayed in the room, windows of which we had masked with some opaque paper so that one cannot see what took place there. We also made sure that there were no microphones. Then, always in front of the camera, we erased the numbers registered on tubes, and replaced them by labels numbered according to an unpredictable code. This code was transcribed on a paper, which we put in a big envelope closed with a special adhesive: if somebody tried to open the envelope, visible tracks would be left. One could not either read the data through the envelope, because I had wrapped the envelope in a sheet of aluminum.

We then returned the tubes to Elisabeth Davenas. At this stage, none of the experimenters could know which tube to contaminate. Then, the coded dilutions were put in touch with basophils, the colouring agent was added and the preparation was placed in a cold room." (P. Alfonsi. Au nom de la Science, p. 46).

[9] This important point is not reported in the investigation report of *Nature*. We had already reported this issue to M. de Pracontal when he collected our testimony in 1988 (cf. Les mystères de la mémoire de l'eau, p. 49).

[10] P. Alfonsi. Au nom de la science. p. 34.

[11] This picture allowed illustrating in particular an article of *Liberation* of July 23-24th, 1988 ("La mémoire de l'eau au microscope magique" *[The memory of water under magic microscope]* as well as an article in *Le Monde* of January 21st, 1997 of E. Fottorino (« La mémoire de l'eau. Du rêve au soupçon »).

[12] M. de Pracontal. Les mystères de la mémoire de l'eau, p. 42.

[13] Martin J. Walker. Dirty Medicine. *Slingshot Publications*, London (1993).

[14] P. Alfonsi. Au nom de la science, p. 33.

[15] The same episode is told in nearby terms by E. Fottorino (*Le Monde*, January 21st, 1997): "One evening of this hard week of examinations, Minister of Research, Hubert Curien, invited Doctor Benveniste to a dinner. John Maddox also participated in the party, together with about fifteen scientists. Jacques Benveniste is relieved at first. He hopes that a real committee of researchers appointed by public authorities will exercise a control more serious than the pantomimes of an illusionist. It will not be the case. Professor Pierre Joliot, of the "*Collège de France*", deeply blames doctor Benveniste for dishonoring the research: "I understood this evening that I was not their man. They implicitly told Maddox: make what you want with him. (...) One left me to the dogs." "

[16] J. Benveniste. Ma vérité sur la mémoire de l'eau, p. 70.

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 immunoglobulins 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 Israel – 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 consequently 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 the electrophoresis. 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 October 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-theorist" and "Benveniste-the-pragmatic" seems to tilt widely in favor of the first one.

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

Notes of end of chapter

[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.

Chapter 11. Law of small numbers… big consequences

"Statistics is indeed an eminently cheerful science, which requires no mental overwork".

Alphonse Allais. *Ne nous frappons pas* (1901).

Despite the optimistic quotation of the French humorist Alphonse Allais, the two chapters that follow are the most technical ones of this book. Their reading requires a minimum knowledge in statistics. I nevertheless invite the readers who are not fond of mathematics (they are not however of a high level; they are only mathematics for biologists…) to read them, even if he/she jumps the too difficult passages. These chapters are indeed important because they undermine the central argument of the investigation report which is, let us remember, that the variability of the repeated counts of basophils were too low according to chance. A summary of the main conclusions is placed at the end of the next chapter.

Reminder on the law of small numbers

The law of small numbers is a statistical law which derives from the binomial law. It governs the counting of objects of any kind. Thus, the counts by unit of time of a radioactivity counter which records the radioactive decay of a substance behaves according to the law of small numbers. If the number of "tops" by unit of time is small enough, then their distribution (number of intervals of time with 0, 1, 2, 3 "tops", etc.) conform to the distribution of Poisson. One of the remarkable consequences of the distribution of Poisson is that the variance s^2 of a series of counts is equal to the mean of these counts: $m = s^2$.

In the case of cell counts, the law of small numbers also applies with some conditions. One considers in this case that the surface of counting is constituted by a large number of elementary surfaces (condition 1: n is a large number) and that the probability of presence of a cell on each of these elementary surfaces is low (condition 2: p is small). The third condition is that the counts must be independent from each other. Thanks to the relation $m = s^2$, the comparison of the variance and the mean allows estimating the homogeneity and the "correctness" of the counts.

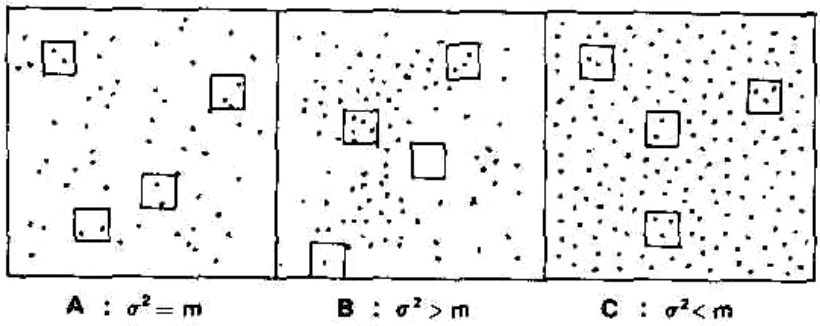


Figure 11.1. This figure illustrates the relationships between the variance and the mean according to the law of small numbers. This law governs the counts of particles such as blood cells, bacteria, etc. In the case of an enumeration, the law of small numbers applies when the probability of an event (presence of a cell) is low and when the number of possible locations (elementary surfaces) for this event is high (*p* small, *n* high). Finally, the various counts must be independent. In this case it can be demonstrated that the variance is equal to the mean as in the situation *A* (see text for the situations *B* and *C*).

(Reproduced from S. Frontier, Méthode statistique, Masson, 1980)

In the "real" life, these conditions are not always satisfied. Three cases can appear which are depicted in Figure 11.1. On the left of this figure (case A), the law of small numbers is verified and the scattering of the counts fits $m = s^2$. In case B, the scattering of the counts is more important than predicted by the law of small numbers. In this case the law is not verified because the "particles" that are counted tend to attract each other and to form aggregates ($s^2 > m$).

In the case C, on the contrary, the particles that are counted tend to arrange in a more regular way than chance would allow and consequently the variance of samples is lower than the mean $s^2 < m$). This arrangement is met for example when particles tend to repel each other and to consequently equalize the distances separating them.

What criticized the investigators?

The demonstration of the investigators is summarized by the figure below. It represents the "standardized" distribution of the mean difference of the counts made in duplicate from the results in the notebooks of E. Davenas. According to the investigators the scattering of the counts is narrower than the scattering which one would expect according to the law of small numbers. In other words, the profile of skyscraper ("pooled data") should be closer to the profile of a tumulus ("theoretical best").

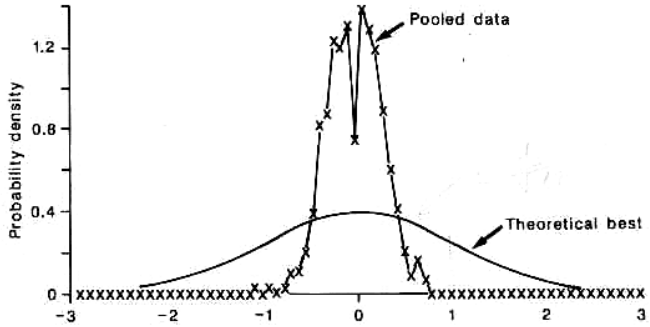


Fig. 4 ***Comparison of measured departures of duplicate normalized readings from their means with the gaussian distribution expected.***

(*Nature* 1988, 334:289)

Figure 11.2. The aim of this figure, which was repeatedly reproduced, was to demonstrate that the counts of basophils of the experiments reported in the laboratory notebooks were biased. But, as described in the text, on one hand, the normalized variable was calculated in an erroneous manner leading to "dramatize" the narrowness of the distribution and, on the other hand, experimental data published in 1981 showed that when the density of basophils increased, the modeling by the law of small numbers did not fit the counts in "real life".

This figure had once again the honor to appear in the issue of *Nature* of October 27th, 1988 when J. Maddox published a text of 4 pages intended to put an end to the debate. He commented the figure in these terms:

> "[*The figure*] is compiled from all multiple measurements of the same samples recorded in the notebooks. Its striking feature is that the distribution of the discrepancies of measurement is, for whatever reason, narrower than the Gaussian distribution expected for sampling errors." [1]

On the other hand, according to the reasoning of the investigators, if one proceeds in the same way with the blind counts performed during their expertise, one notices that the law of small numbers is respected with a variance almost equal to one (Figure 11.3).

The conclusion of the authors of the report was simple: the data were biased, consciously or unconsciously. As we will demonstrate, the reality is far from being such an obvious fact. First of all, the investigators made an error – a mathematical error – by applying without precaution a formula of statistics.

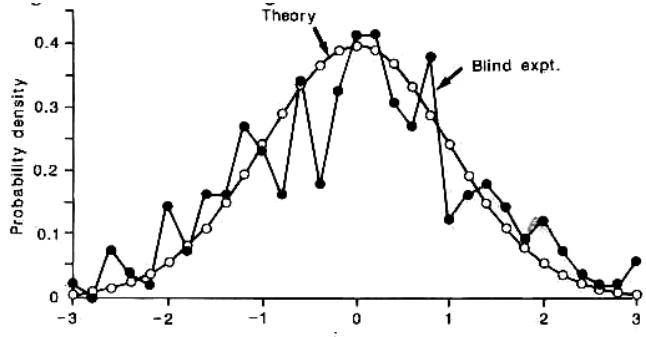


Fig. 5 ***Same as Fig. 4 except that data derive from duplicated readings within the blind experiments only.***

(*Nature* 1988, 334:289)

Figure 11.3. This Figure in the investigation report was the counterpart of Figure 11.2. The variations within every pair of counts of basophils in blind experiments were shown. A distribution with a standard deviation close to 1 (unit) was obtained (abscissa at half-peak) thus indicating, according to the investigators, that in the blind conditions of the investigation the counts of basophils fitted, as expected for cell counts, the law of small numbers. Put into perspective with Figure 11.2, this figure would be thus the proof of an experimental bias for the results of Figure 11.2. However, a distribution of according to the law of small numbers (Poisson's law) with a variance close to 1 (unit) should be obtained only in ideal conditions, without added statistical noise. Furthermore, the formula for the "reduced variable" used for this figure was calculated with an wrong "expected standard deviation" (see text).

What was the expected sampling error?

Contrary to what one would be entitled to demand from a scientific investigation report, the report of *Nature* gave very few explanations on the methods and did not present tables of the data included in the analysis. Let us remind that this analysis was not peer-reviewed. Nevertheless, it was clearly indicated that the calculation of the distribution of both curves described above was performed in the following way:

> "The recorded values have been normalized by subtracting the mean and dividing by the square root of the mean (the expected sampling error). If the only source of error were sampling error, the standard deviation of the plotted curve should be unit (1)." [2]

Actually this method of calculation – with the results obtained during the investigation – gives a distribution with a standard deviation close to 1, which is compatible with the law of small numbers (if we suppose that there are no disturbances other than the statistical fluctuations). From W. Stewart's original data, we selected all the counts which were performed in duplicate through

blind experiments during the investigation. These counts are in fact from experiment F (cf. chapter 9), each experimental point having been counted twice by each of the two experimenters. These 134 counts of basophils (67 pairs of counts) are reproduced in the appendix so that the interested readers can make their own analysis.

By using the method described in the report, we obtain the distribution in Figure 11.4.

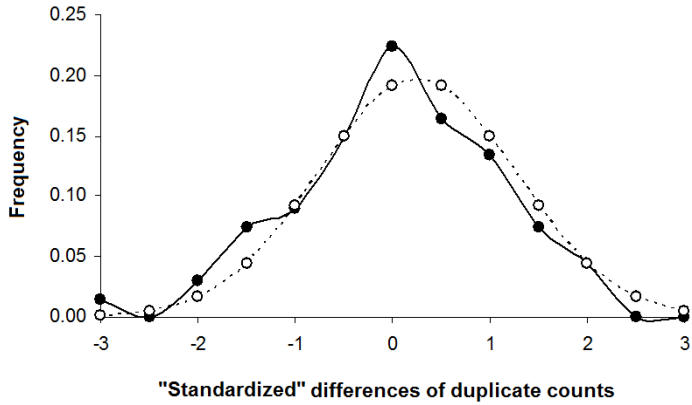


Figure 11.4. With the counts of basophils of experiment F (Figure 11.3) made in duplicate during the investigation of *Nature* (cf. Chapter 8), we calculate, as W. Stewart did, the standardized difference of the couples of counts using the method of the latter. We find the result presented in the investigation report of *Nature* (reproduced in Figure 11.3). The curve in dotted line represents the theoretical distribution of the reduced centered variable (that is with mean = 0 and standard deviation = 1). The abscissa of every point is the upper margin of the considered interval.

In accordance with what the investigators noticed, the standard deviation of the distribution is thus close to 1 (by calculation we find exactly 1.09) what would be actually compatible with a distribution in compliance with the law of small numbers (we can estimate it graphically as the abscissa corresponds to half of the height of the peak).

Moreover, it is rather surprising to find a standard deviation close to 1 because we saw that the cell counts of experiment F were very erratic and that the counting of basophils had been completed only due to J. Maddox and W. Stewart's insistence, precisely for "statistical analysis". It would not be surprising – on the contrary – to obtain an observed variance wider than the

expected variance because of a disturbance due to the addition of "statistical noise". Paradoxically, knowing the experimental conditions of experiment F, one can now consider that the results of W. Stewart were "too beautiful" to be true! But, since these results fitted the conclusion that the investigators had predefined, they did not push the analysis farther.

In fact, the formula used to calculate the standardized variable was *false*!

It seems that in their haste, the investigators forgot some rules of statistics.

What formula was it necessary to use?

The formula applied by W. Stewart as indicated in the text of the report (see above) on every pair of counts of basophils (x, y) to calculate the "standardized" variable is the following one:

$$\frac{x-(\frac{x+y}{2})}{\sqrt{\frac{x+y}{2}}} \qquad (1)$$

One subtracts from every count x the mean of the two values x and y and one divides by "the expected sampling error", that is, always according to W. Stewart, the square root of the mean.

However – contrary to the statement of the investigators – the expected sampling error (standard deviation) *is not the square root of the mean of the two counts*. Indeed x, on one hand, and the mean of x and y, on the other hand, are two random variables which are *not independent*. It seems that the investigators applied without precaution the classic formula:

$$\frac{x-\mu}{\sigma_x}$$

This formula allows standardizing the distribution of the values of a random variable X of theoretical mean μ and of theoretical standard deviation σ_x. In the present case, we have to deal with the *difference of two random variables*. Let us resume the formula (1). The numerator can be simplified as follows:

$$x-(\frac{x+y}{2}) = 1/2x - 1/2y$$

Because x and y are two independent random variables, we can now estimate the expected standard deviation from this linear combination. Indeed, the variance of the linear combination $aX + bY$ of two independent random variables X and Y is:

$$\sigma^2{}_{(aX+bY)} = a^2\sigma^2{}_X + b^2\sigma^2{}_Y$$

The expected standard-deviation is therefore:

$$\sigma = \sqrt{1/4\sigma^2{}_X + 1/4\sigma^2{}_Y}$$

Indeed in this case a = 1/2 and b = -1/2 and since with the law of small numbers the expected variance is equal to the mean:

$$\sigma = \sqrt{1/4x + 1/4y}$$

We obtain thus the value of the normalized variable:

$$\frac{x-y}{\sqrt{x+y}} \qquad (2)$$

In fact, the correct approach consisted in studying the distribution of the differences of the couples (x, y) with an expected variance equal to $x + y$ (because in this case $a = 1$ and $b = 1$). The formula (2) is then immediately obtained.

Moreover, one easily calculates that the method used by W. Stewart underestimates the standard deviations of the standardized variable. Indeed, the formula (1) used by W. Stewart can be simplified as:

$$\frac{x-y}{\sqrt{2(x+y)}}$$

With the correct method, the variance of the standardized variable is *twofold higher*; in other words, the standard deviation is 1.4 times higher than the correct value. If one needs to be convinced of the reality of this error, one can redo the same calculations of the standardized variable on a series of pairs randomly obtained according to the law of small counts. Thus, the results obtained with 1000 pairs randomly generated are the following ones:

1) Method of W. Stewart: variance = 0.50 (i.e. standard deviation = 0.71)

2) Correct method: variance = 1.01 (i.e. standard deviation = 1.00)

We notice that, as expected by the calculation above, the calculation done by W. Stewart gives a variance half of the variance calculated with the correct method (and thus a standard deviation 0.71 fold the correct value).

The first consequence is that the standard deviation of the duplicate counts in notebooks of E. Davenas is not too narrow as J. Maddox and W. Stewart hammered over and over again (it is 1.4 times wider). The second consequence is that the value of the standard deviation of the figure supposed to show the

conformity of the distribution to the law of small numbers for blind experiments is not close to 1 but to 1.4 (the exact calculation gives 1.48; this calculation can be verified from the results of the experiment F given in appendix). Nevertheless, thanks to their "results", the investigators asserted in their report:

> "The duplicate measurements in our strictly blinded experiments were especially important. First, they show that sampling errors do indeed exist, and are not "theoretical objections". Second, they show that the two observers were counting as accurately as could be expected, which gives the lie to the later complaint that the results of the double-blind experiments might be unreliable because the observers had been exhausted by our demands." [3]

One remembers that the "counters of basophils" had drawn the attention of W. Stewart and J. Maddox on the very large differences of cell densities from one chamber of the hemocytometer to another one (cf. chapter 9). This was not surprising given the "method" that W. Stewart had imposed to achieve his goals. The latter indeed pipetted and pipetted again on numerous occasions the low volumes of cell suspensions in spite of our warnings in front of these modifications of the technique. W. Stewart had decided to proceed in this way to get enough duplicate samples for the two experimenters. The investigators carefully avoided reporting this crucial problem for the credibility of their demonstration.

Consequently, thanks to a false formula which minimized the standard deviation (it multiplied it by 0.71) and thanks to poor experimental conditions which increased the dispersal of the measures (standard deviation = 1.48), one compensating the other, the investigators were lucky enough to get a standard deviation close to 1! (exactly equal to $1.53 \times 0.71 = 1.09$) [4]. This visible good "modeling" of the results with the law of small counts strengthened the character of uninfringeable mathematical law which could not be challenged. The investigators could assert thanks to this "result": "the two observers were counting as accurately as could be expected"!

A few years after the investigation, in 1992, M. Schiff (already met in Chapter 3) studied the laboratory notebooks of E. Davenas to redo the same calculations as W. Stewart. He noticed this:

> "From the laboratory notebooks, I made what Stewart should have made: to analyze the dispersion of blind counts in controls. The dispersion rarely reached values as high as those produced during the investigation of Maddox or were seldom as small as the values exhibited by Stewart." [5]

Furthermore, there is another aspect concerning the dispersion of the counts, but not a mathematical argument, that the investigators did not take into account.

The article of Nancy of 1981

In 1981, well before the affair, an article of H. Gérard *et al* was published concerning technical improvements of the test of basophil degranulation. [6] This article proposed a simple method using centrifugation to obtain basophil-rich blood cells. The researchers of Nancy made the following observation: the law of small counts was verified when the number of basophiles was low, but *was not verified when the cell concentration increased*. Indeed, they noticed that the standard deviation of the measure decreased compared with the expected value when the number of basophils increased thanks to the enrichment in cells. The relationship between cell density and standard deviation is shown in Figure 11.5. Thus, with a mean count of basophils at 75, the standard deviation was only 4.5, which is a standard deviation approximately *half* the value calculated with the law of small counts.

This article was well known of J. Benveniste and his collaborators and these results confirmed their own observations. Therefore the fact that the law of low counts was not respected in all cases for basophil counts did not shock them and this notion had been incorporated in their daily practice.

It is probably why J. Benveniste considered the arguments on dispersion as "theoretical" and did not attach to them – wrongly – so much importance as the investigators. It is moreover surprising to see *a posteriori* that in his answers, J. Benveniste evaded this question. To theoretical arguments, he answered by pragmatic arguments:

> "The central argument of the report bears on sampling errors and statistics of which we are so aware that we performed numerous control experiments. They show similar standard deviations and variances in 24/28 comparisons of blind (4 series, 90 samples, without the Israeli experiments) versus open (7 series, 183 samples) control wells.
>
> Did the "experts" understand that the real controls are water or anti-IgG most often paired with anti-IgE? […] Other allergy tests correlate with degranulation (reference in article), so why is it that our statistics fit for 40 to 70 per cent degranulation at regular ligand concentration and not for the same high dilution." [7]

The empirical results of H. Gérard *et al*, which were obtained not in the ideal world of the mathematics but in "real life" are obviously very interesting for our

demonstration. They confirm the idea that the law of small counts is not adequate to model the dispersion of basophils when they are counted in a hemocytometer under a microscope.

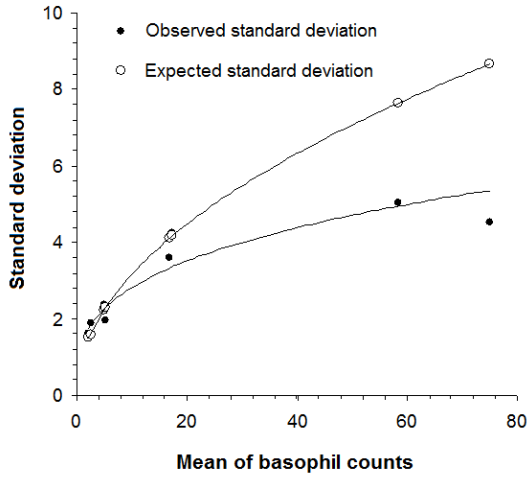


Figure 11.5. This figure, performed with the results of the article of H. Gérard *et al* (1981), indicates how vary – in real experimental conditions – the standard deviation according to the number of basophils counted in samples (black circles). Twenty samples were counted to determine each mean with its standard deviation. This result is thus described in the article: "In reality, multiple counts made on various bands of the hemocytometer with samples variously enriched with basophils show that the distribution is Gaussian with a standard deviation lower than the square root of the mean, especially for high enrichments". Indeed, if the standard deviation of the counts was in accordance with the law of small numbers, it should be approximately equal to the square root of the mean number of basophils counted on the various samples (white circles).

From the Massif Central to the Alps

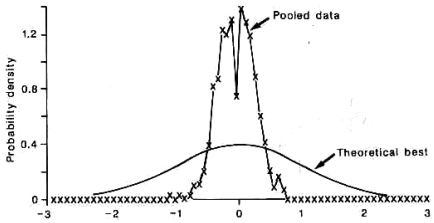
Let us examine again the figure of the investigation report of *Nature* that was supposed to demonstrate a bias due to the experimenter because the distribution of mean difference concerning the duplicate counts was too narrow. Using a software we can generate virtual "counts of basophils" by taking into account both the results of the article of H. Gérard *et al* and the calculation error of W. Stewart evidenced in the previous chapter. We suppose that we "count" in duplicate 1000 wells containing basophils with a mean of 75 and a standard deviation of 4.5 (these values are obtained from the article of H. Gérard et al; see Figure 11.5). We apply the formula that had been used in the report to calculate the "standardized" distribution of the duplicate counts.

As depicted in Figure 11.6, the distribution obtained by taking into account both the dispersion of basophils in the reality of the laboratory and the erroneous calculation of W. Stewart has an aspect which is very similar to the figure in the report of *Nature*. Therefore, the thin aspect of the distribution has nothing surprising and is thus not related to any data "manipulation". If somebody is to blame, it is rather among the investigators.

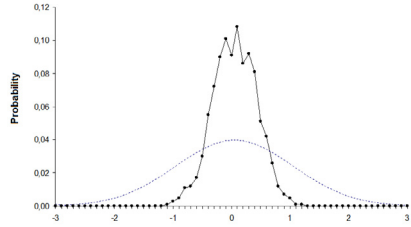
We thus notice that the "central argument" of the sampling error was an idol with feet of clay. Having apparently the solidity of a theorem of mathematics, it nevertheless suffered from two crippling defects. On one hand, an error in the use of the statistics led to more "dramatic" results, supporting the expectations of the investigators. On the other hand, being new to this sector of research, the investigators had not taken into account the pragmatic knowledge of the researchers who considered this "anomaly", which the investigators have blown up out of proportion, as unexceptional. *A posteriori*, the description by W. Stewart telling how he sketched the "narrow" curve by analyzing the results from the laboratory notebooks of E. Davenas is particularly interesting:

> "From the evening, I analyzed with the computer the data of the laboratory notebooks. I introduced data, and I made arrangements to draw a graphic curve to compare them with the optimal results which we could achieve, according to a mathematical modeling. At the end of the second day, it was obvious that the agreement of the data was far too precise. It was not possible that the data fit so well." [8]

We see perfectly how the key for reading of W. Stewart worked: the results "must" fit a predefined mathematical model. At no time, the doubt crossed the mind of W. Stewart as for the legitimacy of the model, its accuracy and its limits.[9]



The graph in the report of *Nature* 1988 (334:289 et 335:762).



Modeling taking into account both the results of the article of Gérard *et al* (1981) and the erroneous calculation of the investigators.

Figure 11.6. The left figure was twice published in *Nature* and was frequently reproduced in the press. Calculated by W. Stewart from the laboratory notebooks of E. Davenas, this figure was supposed to be the demonstration that repeated counts (duplicate counts) were submitted to a bias of the experimenter. The flattened curve (*theoretical best*) corresponds to the standardized distribution that one should observe if the counts fitted the Poisson distribution (law of small numbers) which classically governs this type of enumeration. The result reported by W. Stewart (*pooled data*) was narrower. According to him, this was the proof that there was a bias related to the experimenter. In other words, the results were too good to be true. The reality was not however so simple. On one hand, W. Stewart used an erroneous formula (see text). On the other hand, he did not take into account the knowledge of the researchers who practiced this technique and had noticed and published that the variance of the counts of basophils was lower than expected according to the law of small numbers. By taking into account these results (and with the incorrect formula), the modeling of a series of "counts of basophils" generated by a computer (right figure) gives a result that is very close to the result obtained by W. Stewart (left figure). Therefore the counts of basophils extracted from the laboratory notebooks of E. Davenas had nothing exceptional and they could not be suspected of a bias (either unconscious or voluntary). These calculations and this modeling can be easily done again by the reader (see text).

Notes of end of chapter

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

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

[3] *Ibid.* p. 289.

[4] It is possible that W. Stewart included in his calculations some counts made in duplicate in the experiments D, E and G. If we include these counts the conclusions are the same and we find $1.50 \times 0.71 = 1.06$ for standard deviation.

[5] M. Schiff. Un cas de censure dans la science. L'affaire de la mémoire de l'eau, p. 238 (translation of the French text). The same idea can be found p. 143 of the English version of the book [*Schiff, M. (1998). The Memory of Water: Homoeopathy and the Battle of Ideas in the New Science, London, Thorsons Publishers.*]

[6] H. Gérard, B. Legras, D.A. Moneret-Vautrin. Le test de dégranulation des basophiles humains (TDBH). Intérêt d'un leucoconcentration et du calcul statistique appliqué au taux de dégranulation [*The human basophils degranulation test (HBDT). Leucoconcentration and statistical calculation applied to the degranulation rate*]. *Pathologie Biologie* 1981 ; 29 : 137-142.

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

[8] P. Alfonsi. Au nom de la science, p. 92.

[9] On October 8th, 2014, there was a symposium at the Unesco in Paris entitled "*Biology in the Light of Theoretical Physics: New Frontiers in Medicine"*. On this occasion, the mathematician Cédric Villani, who received the Fields Medal in 2010, did a talk entitled "*Memory, oblivion and reproducibility: an outside view on a never solved controversy"* in which he reported some thoughts on the case of the "memory of water". Having read the present book as a source of documentation, he stated about the statistical approach of *Nature*'s investigators: "Stewart forgets experimental data according to which basophils at high concentration are not scattered according to the law of small numbers, so that usual statistical calculations should be modified. To top it off, it appears that Stewart did an elementary error in his calculation of the variance. More than 15 years later after the disputed article, Francis Beauvais recalculates by taking into account these two effects and shows that statistics that were considered by *Nature* as a mathematical proof of error are in fact fully compatible with successful experiments. It is finally a fascinating textbook case about poor use of statistics that could be analysed for lessons of epistemology or statitics".

Chapter 12. Much ado about nothing?

Having demonstrated the flimsiness of the main argument concerning the investigation report, let us nevertheless resume the affair from the beginning. What amazed the investigators, as they expressed on numerous occasions, was the small sampling error of the duplicate or triplicate counts of basophils that were recorded in the laboratory notebooks of E. Davenas – they were "*made up*" said W. Stewart. The same criticism was made about the results of the article of *Nature* (corresponding to the experiments performed in Israel). Why – regardless of any calculation – did the results often seemed "too good"? Here again, some mathematical considerations could help to consider this issue in a different way.

The misleading consequences of asymmetry

First of all, what does "too good" counts mean? Let us suppose that we perform three successive counts from a tube that contains (with certainty) 100 basophils (per volume unit). It is, according to the statistical terminology, like a box from which we obtain random samples. We take three successive samples: we find 99, 101 and 113. We can calculate the mean, the variance and the standard deviation (it is the famous sampling error that is the square root of the variance). The calculation gives a mean of 104.3 with a standard deviation of 7.6 and a variance of 57.3. Generally we express this result in the following manner: mean ± standard deviation = 104.3 ± 7.6 (n=3).

What we try to assess is the number of basophils in the tube. We have here an approximation of this. We conceive that the more the number of samples is the higher, the higher our confidence in this result. The standard deviation (sampling error) gives us an evaluation of the variability between the various counts. As regards an enumeration we know that, with some conditions (see previous chapter), the law which *a priori* applies is the law of small counts. As we have seen, variables distributed according to the law of small numbers have a variance which is equal to the mean.

Let us resume the calculation obtained above from three samples. Its variance (57.3) is lower than its mean (104.3). Was it therefore "made up"? Not necessarily, because this variance itself fluctuates at random. But within what limits? It is what we are going to evaluate. We will suppose that we are in ideal conditions and that only random is responsible for the results. In other words, we suppose that there is no statistical noise added to the law of small counts.

We use the following procedure: we take 3 samples and then we calculate the mean and the variance of these 3 counts. We reproduce the same operation until we obtain 1000 means of 3 values and their respective 1000 variances.

Among the 1000 means and the respective 1000 variances, what is the percentage of variances (s^2) which will be superior to the mean (m) and what will be the percentage of the variances lower than the mean, that is:

(1) Percentage of triplicate counts with $m > s^2$ (equivalent to $s^2/m < 1$)?

(2) Percentage of triplicate counts with $m < s^2$ (equivalent to $s^2/m > 1$)?

The first answer that comes to mind is: 50% for (1) and 50% for (2). Our intuition suggests us that, due to the law of large numbers, we shall be able to obtain approximately as many values on one side as on the other one.

Are we so sure of this result? Let us perform a computer simulation with random numbers generated according to the law of small numbers. We thus obtain 1000 counts in triplicate (generated with a mean equal to 100 and consequently with an overall variance equal also to 100). We then calculate the ratio s^2/m.

	Count 1	Count 2	Count 3	s^2/m
Series 1	93	90	117	2.19
Series 2	97	108	112	0.571
Series 3	104	107	108	0.041
Series 4	112	115	110	0.056
Series 5	99	84	105	1.219
Series 6	129	95	97	3.402
Series 7	110	76	97	3.12
.....				
Series 1000	99	99	94	0.086

We can now graphically show as a cloud of points these 1000 values of s^2/m and study class distribution:

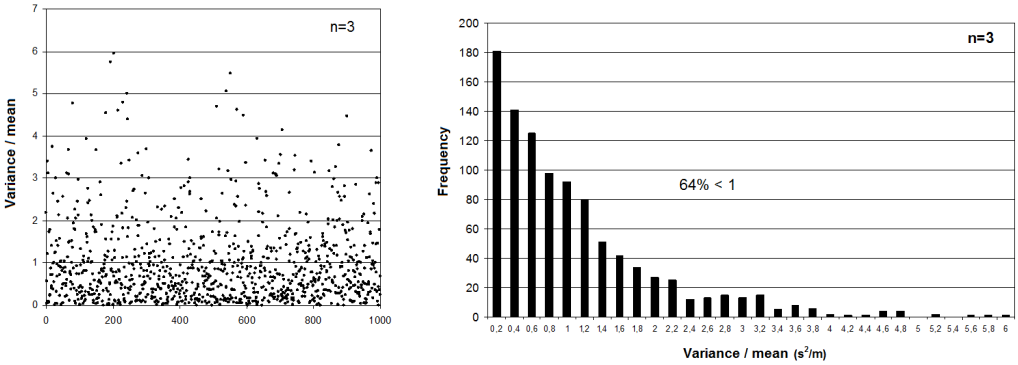


Figure 12.1 Distribution of the ratio variance/mean of small samples (n=3).
NB. For this histogram and the next ones, each value of x-axis corresponds to the upper limit of the interval.

Our intuition was thus completely wrong since we observe that the law of distribution of s^2/m is asymmetric. We find that the distribution on each side of the mean is not 50/50 but 64/36. Furthermore, the most likely values are smaller values of s^2/m! *The mean of the 1000 ratios s^2/m is nevertheless close to 1* according to the law of small counts.

Our intuition (and our poor knowledge of the statistical laws) first led us to confuse the *mean* of a variable and its *mode* (that is the value which is the most frequent). The mean corresponds to the mode only in the case of symmetric laws of probability. The paradoxical conclusion (often poorly understood because not intuitive) is that – due to the asymmetry of the ratio variance/mean for the small samples – *the variance is more frequently lower than the mean.* It is a fundamental result. No doubt that it will make statisticians and mathematicians smile because it is probably an obvious fact for them. I am not certain that this "obvious fact" was shared within the team of the investigators and – let us be honest – among the members of the team of Clamart.

Let us pursue our exploration and see what happens in the case of duplicate counts:

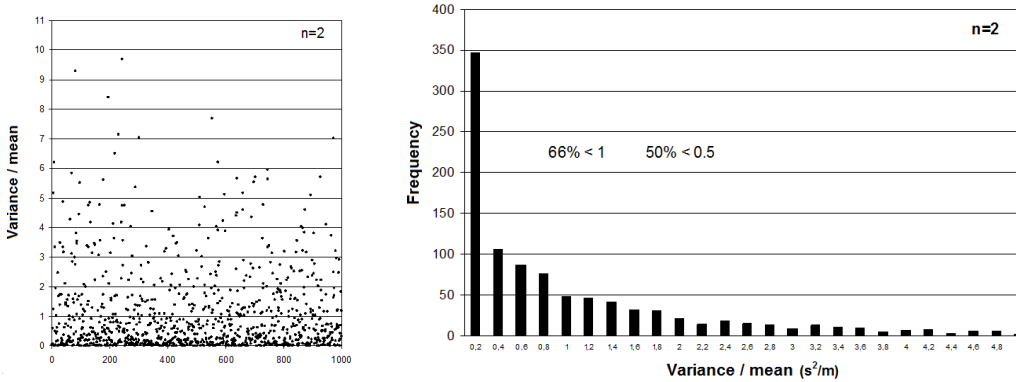


Figure 12.2. Distribution of the ratio variance/mean of small samples (n=2)

The difference is even higher: in 66 % of the cases, the variances are lower than the average. And in half of the cases the ratio variance/mean is lower than 0.5. We end now our exploration with n = 10 (Figure 12.3).

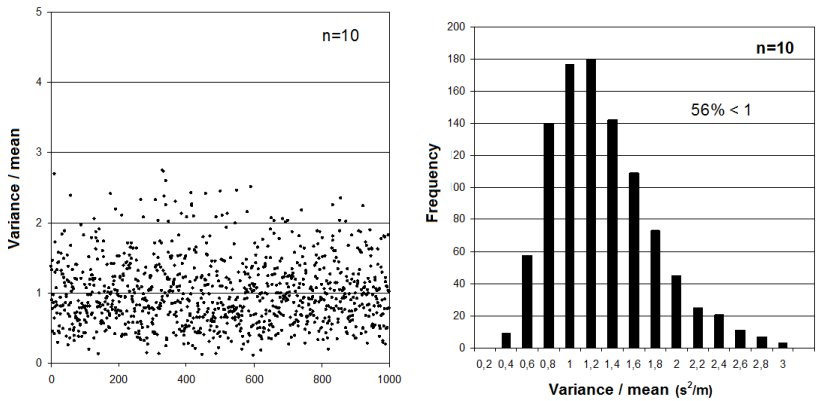


Figure 12.3. Distribution of the ratio variance/mean of small samples (n=10).

With samples of 10 values, there is a trend for a more symmetric distribution (but we have still 56% of values lower than 1). For samples above 30, the distribution is symmetric (Gaussian).

To sum up, one can notice that the distribution of the variances of small samples (n=2 or 3) is strongly asymmetric (here we used a Poisson's distribution, but a Gaussian distribution would give similar results). The consequence is that if we try to verify the fairness of counts using the variances of small samples (as it is often the case), we risk to conclude that the results are "too good". Here is for example a computer simulation of 10 counts of basophils corresponding to the law of small counts:

These wells are supposed to contain the same number of basophils (100). Every result is given as mean ± standard deviation.

Well 1 :	117 ± 6	Well 6 :	99 ± 3
Well 2 :	92 ± 2	Well 7 :	110 ± 8
Well 3 :	101 ± 13	Well 8 :	106 ± 16
Well 4 :	95 ± 6	Well 9 :	96 ± 8
Well 5 :	94 ± 3	Well 10 :	93 ± 5

Mentally, we calculate the variances by taking the square of the standard deviation. We notice that except for wells 3 and 8, the variance is very often smaller than the mean and frequently very small. We begin to be suspicious. Indeed we learnt at school that with this kind of counts the variance must be equal to the mean and that it is precisely a method to verify that counts are without bias. Were the values "made-up"? For the variances superior to the mean, we could imagine that the volumes were not quite exact or any other explanation (statistical noise). But for the variances lower than the mean, the only explanation is that "order has been introduced". Let us remind that this reasoning is made with values obtained from a computer simulation (they have been not selected).

Application to the results of Israel of February-March, 1987 (case with n=3)

Armed with our updated knowledge, we now resume these controversial basophil counts and calculate the ratio s^2/m (variance/mean) of Table 1 of the article of *Nature* (namely the 4 experiments made in Israel by E. Davenas with theirs results in Appendix 2) and then we calculate the distribution of the values:

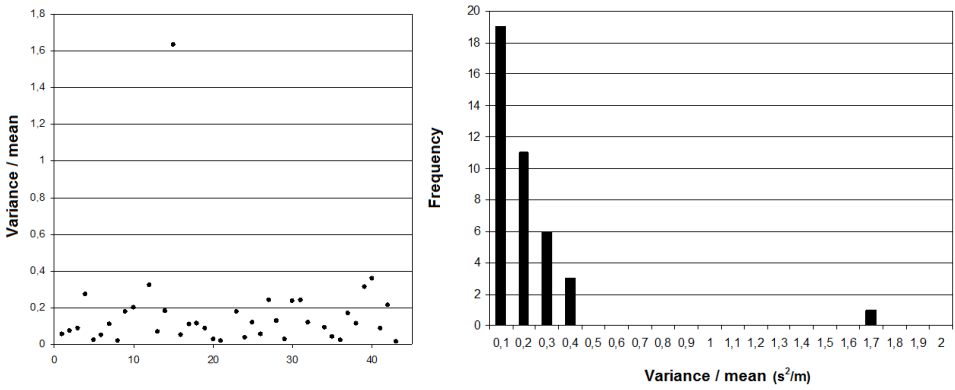


Figure 12.4. Distribution of the ratio variance/mean of the Israeli experiments of February-March 1987 (small samples with n=3).

One can observe once gain the same strong asymmetric distribution with the highest probability for the smallest values. It is difficult "to build up" such results. The reader can try to simulate results by inventing triplicate counts and he/she will notice that it is not easy to obtain such a distribution, especially if one does not think about the aspect of distribution that must be asymmetric. It is – for those who would have doubted – an argument in favor of the "sincerity" of the counts performed in Israel.

Playing the devil's advocate, we notice that the mean of the ratio variance/mean is not 1, but only 0.16. However, by taking into account the results of the article of H. Gérard *et al*, the ratio for approximately 80 basophils should be noticeably lower than 1, approximately 0.34, what is closer to 0.16 without achieving it nevertheless.

It is not impossible that some odd values were counted again, "by precaution", because they were too far from the two other counts. In other words, we cannot objectively rule out a conscious "experimenter effect" on the triplicate counts. On average, this procedure *changes nothing* to the result of the experience because values which are "too far" occur with an equal probability in a direction or in the other one. Given that the "label" of the tested sample which was not known (*blind* experiments), the results could not be biased in favor of an effect of high dilutions. Let us remind that the purpose of these experiments *was not to verify the validity of the law of small counts on repeated counts*, but to assess a possible difference between "active" samples and "inactive" samples with the most precise method.

Application to the results of investigation of Nature of July 1988 (case with n=2)

Let us study now the distribution of the ratio s^2/m for the experiment which had been counted in duplicate and in blind conditions (case where n=2), namely experiment F counted on July 7th (see Appendix).

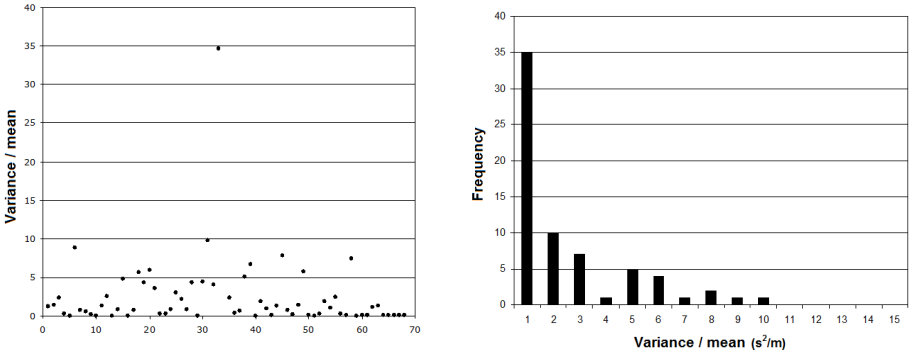


Figure 12.5. Distribution of the ratio variance/mean of the experiment F performed during the investigation of *Nature* in July 1988 (small samples with n=2).

We immediately notice the difference of abscissa of the ratio variance/mean in comparison with the experiments of Israel or with the experiments simulated by a computer for n=2. The problem here is not to explain too small variances (compared to the mean), but to explain *very high variances*! The additional statistical noise is obviously very high (the mean of the ratio variance/average is 2.4). This very high variance could result from errors in pipetting the sample volumes or from heterogeneity of the cell suspension.

Let us repeat, at the risk of annoying the reader, that: 1) these technical steps were managed by W. Stewart; 2) it was precisely this experiment that had been used for sketching the famous expected distribution when the counts were done in blind conditions.

Is there a physical phenomenon which could explain the too low variance of the counts of basophils?

We saw in the previous chapter that if the particles (cells, bacteria…) that are counted tend to repel each other, then their dispersion decreases and the variance of the counts is lower than the expected variance. By which mechanism, could basophils tend to remain at a distance from each other?

To explain this "anomaly", we must find a mechanism which concerns basophils and not the other cells (let us remind that only 1% of all white blood cells are basophils) and if possible only those basophils which are counted, i.e. colored basophils (not activated).

The explanation could be precisely related to the staining of basophils. Indeed, toluidine blue stains basophils in a particular manner: the staining agent is blue, but basophils are colored in red. The phenomenon is named metachromasia. Metachromasia is a property of some staining agents which color tissue structures with a color different from that of the initial staining solution. This property is observed only for some electropositive stains such as toluidine blue. The metachromatic reaction is the hallmark of polycationic structures on which binds the staining agent. Indeed, basophil granules are mostly composed of a matrix of acidic mucopolysaccharides which is very electronegative. The *high density of negative charges* is responsible for the shift of the emission wavelength of the staining agent (from blue towards red) because of "aggregation" of molecules of staining agent.

Toluidine blue could thus be seen as a marker of structures having an important density of negative charges; in this view, granules of unstained basophils have lost their electronegative charges (see Appendix 1). As we all know, charges with same sign repel each other. Consequently, during the few minutes when cells settle in the chamber of the hemocytometer, the *repulsive electrostatic forces* that originate from basophils would tend to slightly repel other basophils. The distances of one basophil with its closest neighbors would consequently be more regular than allowed by chance. And this would be especially the case as the concentration of basophils is high as reported in the article of H. Gérard *et al* because the intensity of the electrostatic force decreases with the distance.

Other mechanisms could be suggested to explain the observations of H. Gérard *et al.*[1] Although there is at present no certainty on the reasons of this deviation from the law of small counts, this allows nevertheless illustrating the idea that it is sometimes simplistic to apply a mathematical law on a complex physical or biological phenomenon without precaution.

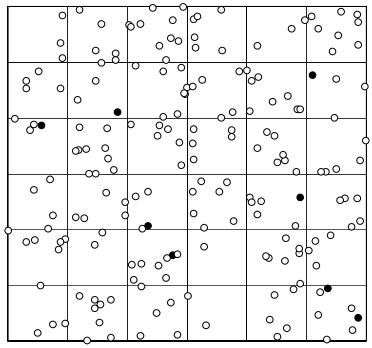


Figure 12.6. If the position of each basophil (black balls) is independent of the positions of the other basophils and white cells (white balls), then the law of small counts apply when one counts a series of samples taken from the same population. However, if a repulsion force (or a mechanism leading to an identical effect) is present, then the distances between basophils are more regular than expected according to the law of small numbers. The consequence is that the variance of the counts decreases because order has been introduced. This is what is suggested by empirical data obtained with basophil counts. It could involve an electrostatic force (force of Coulomb) taking its source from the sulphated glycoprotein matrix of the basophil granules which possess numerous electronegative charges. It is precisely because the density of electronegative charges of this matrix is high that the phenomenon of metachomasia occurs with toluidine blue when basophils are stained. Since such a repulsive force would decrease with the distance, this would explain why this phenomenon would be especially visible with high cell concentrations, as noticed by the authors of the article of H. Gérard *et al.*

Why an effect related to high dilutions was not highlighted in the last three blind experiments of the investigation?

First, let us be clear, it is possible that, even performed in better conditions, the experiments in the center of the debate would have been negative. Only someone totally uninvolved in experimental biology and medicine could be surprised by this fact. Of course, it sometimes happens that one tests "massive" hypotheses for which the use of statistical methods is not necessary. In general, a bench experiment is infrequently a long quiet river. And, as explained by J. Benveniste:

> "[…] All which seems to have interested *Nature*'s people, it is that the experiment could, once, not succeed. But we knew that already! We did not need them to know that! And I have the impression that their purpose was to push the system to its limit, to create problematic working and achievement conditions to obtain, finally, a failed experiment." [2]

To guard against various biases of interpretation, it is important to decide *a priori* (that is before knowing the result) what are acceptable experimental conditions. For example, in the case of high dilutions of anti-IgE, the experience accumulated during three working years, allowed defining – among other conditions – that it was necessary to get correct controls and first peak (i.e., included in predefined limits) even before considering the results with high dilutions. It is surprising to notice that the experts were flabbergasted when they found out (or pretended to find out) that in some experiments), no degranulation with antiserum anti-IgE was observed:

> "We were surprised to learn that the experiments do not always "work". […] It also appears that some bloods that "do not degranulate" are often encountered; we were informed that, in this event, data are recorded but not included in the analyses prepared for publication." [3]

Let us suppose that we test the effect of a medicine on a population of patients. It is quite possible – it is even the rule – that the medicine is ineffective in some patients. We are not surprised by this fact. It is for these reasons that statistics are used to analyze the results, not on an individual basis, but on the entire populations of patients. We are here in the same scenario. What is important is to know if, *overall,* on the whole set of experiments, a statistically significant effect is obtained in the presence of high dilutions. For J. Benveniste, the experience accumulated by his team during several years, including numerous blind experiments with an appropriate statistical analysis, had a weight that was far greater than these three negative experiments performed in poor experimental conditions and, furthermore, with a unique series of anti-IgE dilutions. The purpose here was not to demonstrate a mathematical theorem for which a unique counter-example is enough to invalidate it.

A last-minute correction

We remember that a sentence reporting the results of the 4th experiment had been deleted in the investigation report (it was present in the printer's proofs). This sentence said basically that the effects noticed with the high dilutions were nothing else than statistical fluctuations, but that this explanation did not apply to all results and particularly to the famous 4th experiment.

In fact, this sentence deleted at the last moment represented only a part of a paragraph interesting to reproduce in its totality because it concerned – again – the sampling issue:

> "The control values are used to normalize the readings obtained with reagents at high dilution. Despite the laboratory's convention

> of presenting data as the percentage of degranulation by diluted agents relative to the controls, it appears not to have been considered that the counting error is the statistical sum (square root of the sum of the square) of the sampling error in counting a single well and the estimated error of the mean of the control samples. In the particular case of the first experiment, for example, we estimate the expected sampling error to 14 per cent. It seems clear that many of the peaks reported as significant at Clamart 200 (*sic*) are well within two standard deviations of the line of null "achromasia", even when no account is taken of other sources of error (such as failure to record basophils).
>
> 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." [4]

This passage – even if it was not kept in the published version – confirms the real obsession of the investigators towards the error of sampling. Here, J. Maddox tried to create suspicion (by very technical arguments). Basically, he suggested that the researchers of Clamart selected some results that in fact had emerged from the statistical noise.

However, the approach for the calculation was correct in this case in contrast with the erroneous calculation above. This incoherence could perhaps give some explanation for the calculations with the inaccurate formula that were performed on site by W. Stewart who came to Clamart with a microcomputer – a Macintosh – and from the first day recorded data of the laboratory notebooks of E. Davenas.

J Maddox having finally decided not to publish this passage, we cannot accuse it in bad faith, however he was tempted once again to confirm his prejudice on an experiment which was of poor quality (experiment A; see chapter 9). If J. Maddox had followed the same reasoning on the experiments B and C (see chapter 9) – which he preferred not to show in the investigation report – he should have recognized that these results were not "artefacts of statistical noise". Maybe it is the reason why J. Maddox preferred to delete this passage.

On good usage of the irony

The investigators thus showed a rare insistence on the issue of the error of sampling. Not having discovered the supposed cheater during their investigation, it was the only objective fact that they brought back from their expedition. Furthermore, not explaining in detail their calculations and the

precise origin of their data and using the authority conferred by *Nature*, it was difficult for the reader of their report to question an argument presented as a theorem.

The "obviousness" of their calculation was apparently not enough for the investigators and they made a mockery of J. Benveniste. They thus noted in the report:

> "Ironically, he is himself one of the three authors of a paper published in 1981, in which such this issue had been addressed in a superficially similar situation (Petiot, J.F., Sainte-Laudy, J. and Benveniste, J. Ann. Biol. Clin. 39, 355 ; 1981) […]. That brief paper deals exclusively with the effect of sampling errors (not other kinds of errors) on the interpretation of measurements of intact basophils after white-cell suspensions had been allowed to react with allergens via their attached IgE molecules." [5]

Irony is sometimes a double-edged weapon. Indeed, it is a pity that the investigators did not read more attentively this "brief article" of Petiot *et al* that they quote with an undisguised pleasure. They would have found out the following information:

> "The experience of Gérard et al as well as our showed us that this estimator of the variance [*i.e., mean of counts of basophils*] is biased. The type-1 risk is thus reduced, certainly lower than the formulated risk, which is the risk of false positive results." [6]

The authors clearly formulated a notion which was already known in the "community" of the users of the test of degranulation, that should have alert the investigators: the variance observed for the counts of basophils is lower in practice than the value calculated with the law of small counts. This sentence did not seem to have aroused the interest of the investigators. They did not indeed hesitate to explain that "the data lack errors of the magnitude that would be expected" and that "repeat observations agree more closely than would be expected from the underlying distribution." [7].

The difference of appreciation about the importance of the sampling error according to the investigators or according to J. Benveniste is rather delicious. J. Benveniste who dismissed any "theoretical" consideration as soon as the facts contradicted it, is in the lineage of Claude Bernard for whom: "the experimental method […] is nothing else but a reasoning with which we submit methodically our ideas to the experience of the facts" or, according to another close sentence, "When we meet a fact which contradicts a prevailing theory, we must accept the fact and abandon the theory, even when the theory is supported by great names

and generally accepted".[8] We are thus in the presence of an approach, which we could define as pragmatic. Pragmatism is rather attributed to the Anglo-American researchers. Indeed, according to this cliché, the latter are not very disturbed about theories when "it works".

In contrast, the Cartesian mind, which requires a theoretical frame for any sort of observation, would be rather privilege of the French tradition. And when there is a contradiction between facts and theory – when "it works" while the theory fails to explain these facts – what makes the Cartesians? According to Descartes: "And the demonstrations are so certain that, even if experience seemed to show us the contrary, we would nevertheless be obliged to place more faith in our reason than in our senses". And, ironically, the investigators that came however across the Channel and across the Atlantic adopted an ultra-Cartesian attitude: as the facts did not fit with their expectations, then, in good Cartesians, they rejected the facts.

A sum up for Chapters 11 and 12

For the reader who skimmed through the previous two chapters, here is a summary of the scientific criticisms that could be directed to the investigators of *Nature*:

1) Poor methodological and scientific practices:

- The investigators made a *calculation error* that minimized the variance of the difference of the duplicate counts;

- Concerning these repeated measures, the investigators did not take into account the fact that the *variance of small statistical samples* (counts in duplicate or triplicate) have more often than not low values because the law of distribution of the variance is asymmetric (while respecting of course the law of small numbers on average). The consequence of this asymmetry is that the results of the counts of small series could seem "too good";

- The investigators systematically highlighted in their report the experiments that nevertheless did not achieve the *criteria of quality* and therefore must not be considered.

2) Knowledge of the research area not taken::

- It was a *well-known* (*and published*) *notion* among researchers who used the test of degranulation that the error of sampling was lower on average than calculated with the law of small numbers, in particular when the cell density was high;

- It is possible that this lower dispersion of the basophil counts could be *explained by a physical phenomenon* which would tend to make basophils repel one another due to, for example, electrostatic charges.

In conclusion, not having succeeded in exposing the one who "played a trick on J. Benveniste", *Nature*'s investigators have fallen back on technical arguments based on statistics because, according to them, the results were "too good". Nevertheless this central argument of the investigation report was also irrelevant.

Notes of end of chapter

[1] M. Schiff (Un cas de censure dans la science, p. 237) suggested that repulsive forces at long distance called forces of Frölich could play a role in the low variance of basophil counts. Such a long-distance force could indeed play a role in the interaction between red blood cells (Rowland et al. A Frölich interaction of human erythrocytes. *Physics Letters* 1981 ; 82A : 436). However, it does not seem that this type of force plays a role in the present case because as regards red blood cells, this strength is observed only if cells are alive. Indeed let us remind that the staining solution for basophils fixes cells by the ethanol.

[2] P. Alfonsi, Au nom de la science, p. 33.

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

[4] Printer's proofs of July 25th, 1988.

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

[6] J.F. Petiot, J. Sainte-Laudy, J. Benveniste. Interprétation du résultat d'un test de dégranulation des basophiles humains. *Ann Biol Clin* 1981:39:355–359.

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

[8] C. Bernard. Introduction à l'étude de la médecine expérimentale (1865).

Chapter 13. "If one wanted, one could look at fingerprints"

The sprinkler sprinkled

Because of the authority of *Nature*, the report that was published after the investigation struck a harmful blow to the credibility of the results reported by J. Benveniste. However, the journal of London faced numerous criticisms. Indeed, besides the scientific aspect of the affair, the attitude of *Nature* for its management was not comprehensible for numerous observers.

After the investigation, *Le Monde* published an article where J. Benveniste was backed quite evidently. The commitment of the journal appeared through titles and paragraph headings: "a strange anti-fraud squad", "sleight of hand in the laboratory", "a group strangely constituted"[1]. F. Nouchi, the *Le Monde*'s journalist, moved in the laboratory on Wednesday during the famous week and, with the agreement of J. Benveniste, he dressed in a lab coat to go unnoticed in the laboratory. He reported in an article the atmosphere which prevailed there, then adding: "we wondered how a researcher with the temperament of Benveniste could accept such machinations." [2]

At the time of the publication of the investigation report in *Nature*, the direction of Inserm issued a press release again:

> "The additional publication appearing in the issue of "Nature" dated July 28th, 1988 and the diverse comments which accompany it confirm the Institute in its principle of reserve, inspired by the respect for the freedom of research. In particular, the Inserm Administration judges that its role is not to take part in the debate that today brings into conflict Dr Benveniste and the editors of the journal concerning the processes used by "Nature". This debate enters, obviously, the field of the controversies announced by the previous communiqué of the Institute. [3]

In this press release, the direction of Inserm thus confirmed its desire not to interfere in what it considered as the normal process of the research, even if we guess a light criticism towards the "processes" of *Nature*". Then, in the same text, the Institute reminded that all the laboratories were submitted to an evaluation every four years by their "peers" and that it will be the case for the Unit 200 in spring 1989. The communiqué concluded that at this moment the passions "will have calmed down to leave room to the indispensable serenity of the long-term scientific judgments".

This press release allowed the direction of Inserm to remind the policy of the Institute based on the "freedom of the research", undeniably a noble task. When the work of the researchers at the Institute was threatened by outside elements, the direction of INSERM nevertheless considered that it should not intervene. It was thus a new version of the "fox in the free henhouse" applied to scientific research and its institutions.

We can summarize the criticisms towards *Nature* and its investigators through several main questions that we will be considering successively.

Critic n°1: "Why to publish these results if Nature considered that they were false?"

It was the most frequent criticism. As we saw, the – surprising – answer of J. Maddox was that J. Benveniste would have removed his article if an investigation had taken place before publishing the article. In a letter to *The New York Times* of September 26th, 1988, J. Maddox clarified his thought:

> "For the well-being of the scientific community as whole, there is an urgent need that practitioners know that second rate science exist, can be exposed, and should be more openly categorized as such." [4]

A posteriori, it is obvious that the investigators thought – even before entering the laboratory – that the results were false. However, after the investigation, their comments on the reasons of the "falseness" of the results were a bit discordant.

With their *a priori* ideas, it was absolutely impossible for the investigators to quit the laboratory with "positive" results (in the sense of J. Benveniste) or even with ambiguous results. We remember that J. Maddox had firmly expressed his obligation of result in these terms: "I had committed to publish the investigation report. The risk here was to end up in the situation where I would have a report whose conclusion would be: the magic is true." [5]

The whole investigation report thus took care to highlight an absence of results. This was the reason of the sentence deleted at the last moment, which risked contradicting the rest of the article because, according to the words of J. Maddox himself, simple statistical fluctuations could not explain the results of the 4th experiment. However, at the same time, W. Stewart and J. Randi made statements in the press that were full of allusions. It should be reminded that this report was nevertheless signed by the three investigators. Obviously, it was J. Maddox who held the pen and who took care of erasing everything which could be understood as a charge of deceit. J. Maddox was a director of a newspaper and he knew that he was not protected from the laws on the press concerning the defamation. As he had no proof of a fraud, he based the text

mainly on technical questions of a statistical nature. Without making an unfounded accusation, it is possible that J. Randi and W. Stewart felt left out during the elaboration of the report and that they wanted to bring their "personal touch" outside the "official" report of *Nature*. This last hypothesis is not extravagant since according to an editorial manager of *Nature* "it was a bit of caper to get this particular gang together and take them to Paris."[6]

In a letter which he sent to J. Benveniste during the summer 1988, J. Randi did not hesitate to say:

> "[…] in the set of experiments that were supervised, double-blind,[7] by the Nature team, we have positive proof that there was an (unsuccessful) attempt to cheat, and we know who did it." [8]

Not long after, in *Liberation* of October 3rd, 1988 (quoting the Portuguese weekly journal *The Espresso* of the same day), J. Randi stated:

> "We do not hesitate to assert that contrary to what was said or told, we possess the proof of fraud or more exactly deceit." [9, 10]

Interviewed by the journalist M. de Pracontal, he even stated about the famous envelope stuck on the ceiling:

> "If we wanted, we could look at fingerprints. I do not believe that it is necessary to make it, I do not want to destroy somebody." [11]

In another occasion, J. Randi again indicated:

> "If fingerprints other than mine appear there, it will prove something. A friend, who works in a laboratory of police in Washington, suggested analyzing these fingerprints. I did not consider this necessary."[12]

It was talking too much or not enough. It is really a pity that J. Randi did not accept the proposal of his police friend. We note that in August J. Randi knew the culprit and later he had only the means to know him. Afterward, J. Randi used more gentle words and spoke of "self-delusion".

W. Stewart played the same game of allusions. We remember that he had asserted with a finger snap that the results were "made-up". In *The New York Times* of July 27th, just after the publication of the report, he also adopted an off-the-wall position about the report:

> "Their report avoided any charge of fraud. But Dr. Stewart said in a telephone interview that bias was "not an adequate explanation" for some of the reported dilution results. He declined to say

> whether he thought there had been trickery, but he said that the uniformity of some test results was disturbing." [13]

Likewise, answering to M. de Pracontal about the "bias of the experimenter", W. Stewart affirmed:

> "Unfortunately, it does not take into account all the results. As you know, the experiments were reproduced in an Israeli laboratory. But it raises a problem because there were not true reproductions. Elisabeth Davenas indeed went to Israel. On this occasion, she performed experiments whose results are published in *Nature*. Yet, these results are "too perfect" and they cannot be attributed to an observation bias because the countings were done blind. In this case, I have no other explanation than the deceit." [14]

Contrary to what W. Stewart suggested about the experiments performed in Israel, we have seen that the repeated countings (in triplicate) were not blind; it was each dilution that received a code number. A bias of the experimenter cannot objectively be eliminated concerning the triplicate counts. However, the purpose of the experiment was to detect a difference between "active" tubes and controls. This point has been already discussed in Chapters 10 and 11 and we have seen that several explanations, not mutually exclusive, could explain these counts that W. Stewart considered as "too perfect".

During the same interview, M. de Pracontal pointed out to W. Stewart that he did not notice a deceit at Clamart. He answered:

> "No, except the fact that somebody touched the envelope containing coded data that we had stuck on the ceiling of the lab. But this attempt of fraud did not succeed. However, the precautions taken in the case of the Israeli experiment did not prevent a deceit. And there is another aspect than I do not want to discuss here."

We will never know this "other aspect", because when M. de Pracontal asked W. Stewart what he was referring to, the latter refused to say anything more because he explained: "I did not speak about that publicly before".

These sudden innocent maiden reserves of W. Stewart were rather surprising for anybody who knew the character and his doggedness in previous affairs where he investigated. No doubt that if he had discovered a substantial proof of deceit, he would not have hesitated to make it public.

These inconsistencies between, on one hand, J. Maddox who tried to show that the results did not exist[15] and, on the other hand, J. Randi and W. Stewart who insinuated that there was deceit enabled J. Benveniste to say:

> "Let us underline incidentally a delicious contradiction: on one hand, Maddox who goes everywhere claiming that "there is no result" and on the other hand, Randi who accuses us of having cheated!
>
> It would really be, for the first time ever, an absolutely extraordinary deceit: cheating to have no results!!! " [16]

He also summarized these inconsistencies with this sentence: "A fraud with five laboratories and no results!" [17]

Critic n°2: "Nature went out of its role of scientific journal"

The mainstream press as well as some medical and scientific journals – regardless of their appreciation for the works of J. Benveniste – criticized during summer 1988 the attitude of *Nature*, which went out of its role of scientific editor and had played the role of a "scientific thought police".

Thus, in *The Los Angeles Times* of August 7th, 1988, one could read:

> "Science editors should not dismiss results out of hand simply because they conflict with orthodox views. Throughout history, much progress in science has come from just such challenges. Every new idea starts out being unorthodox. At the same time, it is also true that most unorthodox ideas are wrong. The problem is to distinguish the right ones from the wrong ones beforehand.
>
> The editors of *Nature* probably acted correctly in publishing the paper despite their misgivings. It is better to err on the side of publishing too much than of suppressing a potentially worthwhile idea. Publication allows the results to be scrutinized and tested by others. Still, the magazine might have conducted its investigation before it published the paper rather than afterward." [18]

In *The Scientist*, E. Garfield summarized all arguments very clearly. More specifically, he suggested the use of a procedure which – contrary to the investigation of *Nature* – would at the same time evaluate the research while respecting scientific approach and ethics:

> "In sending its own team (including Maddox) to France to investigate the experiments, *Nature* showed poor judgment. Why the team did not include an immunologist is baffling. In broader terms, it is even more regrettable that the journal took upon itself

> this role of jury *after publishing the article*. Why not before? A better course, as many have noted, would have been to send an independent, fully expert group before a decision to publish had been reached – in effect, a more intensive process of peer review. If it had done so, and had still decided in favor of publication, it could have printed it and the independent investigators' report in the same issue." [19]

And after:

> "Furthermore, the investigators' report (July 28, pages 287-90), in tone and length amounting to a bludgeoning of Benveniste and company, only reinforces the question, "Why didn't they check this out before publishing it?" Moreover, Benveniste's seemingly sincere and wounded response (page 291) prompts real sympathy for the French investigator, despite what may be thought of his experiments and claims.
>
> Nature made a regrettable series of editorial decisions – sloppy at best, irresponsible at worst. Even Walter Stewart, one of the investigators and a reviewer of Benveniste's original paper, now says that its publication was "an imposition on the scientific community" (Wall Street Journal, July 27, page 30)." [20]

For other detractors of *Nature*, the journal was not sufficiently open to new ideas:

> "The fury of Nature's attack on Benveniste has prompted some scientists to suggest that the journal is not open enough to unorthodox ideas. "If journals try to suppress or discredit heterodoxy, they will suppress both good and bad," says Harry Collins. "Marie Curie and her work would have fared very badly if she'd been treated like Benveniste." " [21]

The most direct and the most explicit criticisms (but not necessarily the most disinterested) came from other directors of prestigious journals, in particular from Arnold Relman, editor of the *New England Journal of Medicine* – the equivalent of *Nature* for medicine – and from Daniel Koshland, editor of *Science* (and additionally direct competitor of *Nature*…).

Thus, for A. Relman:

> "What the journal should not have done [...] was publish the paper and then undertake an investigation itself. A journal should not be an investigative body, [...]. An editor's job is to see that material is rigorously and fairly reviewed [...] and when a journal acts as

> Nature did, the editor becomes the judge, the jury, the plaintiff and – in some sense – the accused. Such a fraud investigation by the editor is a conflict of interest. [...]" [22]

And A. Relman specified at another opportunity:

> "Truth squads and special investigative teams are not only unnecessary, but would also be destructive of the scientific spirit." [23]

One could quote also the point of view of D. Koshland:

> "D. E. Koshland Jr., editor of Science […] said he found the original report "more flimsy" than the editor of a journal would like. Dr. Koshland said the improbability of the test results had been established by many earlier experiments and the data published in this case did not seem to make sense. They were "internally peculiar", he said.
>
> The role of a general scientific journal, Dr. Koshland asserted, should be to "encourage heresy but discourage fantasy." While there is nothing wrong to publishing something that turns out to be wrong, he suggested, the situation is different when a proposition, such as perpetual motion or "memory" in water, is totally implausible." [24]

In France, the journal *La Recherche* also wondered about the strange chronology with publication initially and investigation over a second time:

> "The investigators came to the laboratory of J. Benveniste fortnight after the publication of the article, why did not they come before? The composition of the group obviously implies that J. Benveniste is a fraudster, so why publish him? Among all experiments that have been performed, it seems that only one was not convincing and it was enough for W. Stewart to denounce the fraud; what is the meaning of these checks which were made in the most total confusion?" [25]

But, curiously, the author of this article considers that "*Nature* probably underwent many pressures to comply with such a mock investigation". As we have seen, this hypothesis does make sense because the investigation accompanied the decision to publish and the least we can say is that the initiative of the investigation and the conditions of the latter were the personal decision of J. Maddox.

A large number of scientists who did not approve the work of J. Benveniste thought nevertheless that *Nature* assumed exaggerated rights by conducting an investigation which moreover was similar to a "circus". *Nature*, according to them, should not have published these results. So H. Metzger – who was one of the first experts of the article – and S. Dreskin in a *Correspondence* to *Nature* explained:

> "It is reasonable to ask whether the observations of Davenas *et al.*, should have been published in *Nature*. We think not. One of us (H.M.) reviewed this paper in April 1987, and urged that the findings be checked by one or more laboratories chosen by the editor. Instead, Dr Benveniste made his own choice, and Nature decided to publish the report and then to despatch an investigative team consisting of the editor, a magician and a scientist, none of whom has experience in the relevant field. Their report provided no support for the published claims and will dismay serious scientists: it adds to the circus atmosphere engendered by the publication of the original paper. […] We believe that the approach chosen by *Nature* is regrettable. We feel that all ideas no matter how revolutionary deserve to be heard. However, when new data are proffered that grossly conflict with vast amounts of earlier, well-documented and easily replicated data, a different editorial standard is required. Before the imprimatur inherent in publishing them in a leading scientific journal is granted, the new results must be reproducible by disinterested individuals familiar with the field." [26]

The use of the word *imprimatur* is rather unexpected about scientific publications because it seems to endorse the idea of an "official science". We could add that the implementation of special editorial requirements for results that question the scientific knowledge would certainly have slowed down the diffusion of discoveries in the past. The opinion of H. Metzger reflects however a very frequent view of science. This conception of the scientific approach is justified when a new domain has been opened after a significant progress. It is however a conservative attitude which certainly obstructs the progress of new ideas when the preceding paradigms are questioned.

J. Maddox answered then directly to H. Metzger and to the other critics in an editorial in the same issue of *Nature*. First, he addressed to his "colleague" D. Koshland – without naming him – who had thoroughly criticized the coverage of the affair:

> "Metzger goes on to echo a not disinterested toffee-nosed opinion recruited last week by the *New York Times* that journals such as this should not lend their reputation to spurious science by publishing it." [27]

Having settled a score with his competitor, J. Maddox then argued that journals as *Nature* received "a torrent of heterodox would-be literature offered for publication", while underscoring that "it is rare that some such claim should come from a government-supported laboratory, that its principal author should urge publication in the face of common sense – and should complain that failure to publish will be tantamount to the suppression of the truth."

But above all, according to J. Maddox, the non-specialized journals such as *Nature,* are also empowered with a role of information and education. Thus, he explained, "there is occasions when publication of spurious science may be a public service". Then he quoted the example of an article published 16 years before about scotophobin where W. Stewart has already played an important role:

> "Some readers may recall the case of scotophobin, a protein suppose to reside in the brains of trained rats which, when injected to naive rats, would transfer the first rat's learned capacity to run a maze, for example. Nature published a version of such a manuscript after several preliminary accounts had appeared elsewhere, but accompanied it with a devastating critique from Mr Walter Stewart […]. Nothing much has been heard of scotophobin since. Is not a little of the "circus atmosphere" inescapable on these occasions?
>
> Not that belief in the magical properties of attenuated solutions will be as quickly exorcised. Since the emergence of homeopathic medicine in the early nineteenth century […] the theory of biological activity at extreme dilution has been a theory in search of verification. It would be naive to expect that the hunt for verification will now be abandoned simply because Nature's opinion of Benveniste's experiments is unsatisfactory."

Here again one notices that it is undoubtedly homeopathy that J. Maddox had in line of sight. But the words "magical" and "exorcised" are strange under the pen of *Nature*'s director! We could also add that the silence following the prohibition of a research area did not prove *a posteriori* that there was nothing of interesting to explore.

Critic n°3: "The investigators were self-proclaimed experts"

Among the three investigators, the one who best exemplified the self-proclaimed expert of "scientific misconduct" was obviously W. Stewart. Taking his role of "Mister Clean" of science with utmost seriousness, he did not smile, he never laughed. As "hung-up" as J. Randi was extrovert, he was the exact opposite of the latter. J. Randi indeed was always ready to show one of his surprising magic tricks. In front of this professional clown, the absence of sense of humor of W. Stewart was even more obvious.

Thus, on the last day of the week of the investigation at Clamart, J. Benveniste joked and – tongue in cheek – proposed a position to J. Maddox when – the reality of high dilutions having finally been recognized – he would be at the head of a prestigious institute. W. Stewart – who attended the scene – took the proposal seriously. This is demonstrated in the report he spontaneously did to the journalist who interviewed him early 1989:

> "He even told Maddox that when this was over he'd be happy to offer him a job. He was apparently serious, but I was flabbergasted. Even the world's top scientists don't go around offering job to John Maddox, who, as editor of Nature, already has a distinguished job." [28]

J Maddox recognized himself that the special behavior of W. Stewart was a problem:

> "Stewart has no manners" [...], "He's a zealot". As the temperature rose, so did the pitch of Stewart's voice". Maddox explains, "He does have a high-pitched voice and when he's tense, his voice sounds like that of a Dalek [29]. We had to tell him to talk naturally." [30]

At the same time, pursuing his obsessional crusade for more "purity" in science, W. Stewart drifted during a colloquium over the ethics in scientific research. *Nature* distanced itself – once more – from W. Stewart and reported this revealing episode on the state of mind of this character:

> "Stewart has incurred researchers' wrath for his investigations of alleged scientific fraud, investigations that have been marked at times by an almost religious fervour. Indeed, at the Bansbury meeting, Stewart astounded participants by equating the moral taint of scientific fraud with that of Holocaust. Although his point was the responsibility for identifying and tackling problems falls on everyone's shoulders, the idea that an incorrect scientific paper, even one written with knowing deception, can be in any way

> compared with the slaughter of 6 million people suggests that his enthusiasm for his work has exceeded reasonable bounds; he may no longer be a credible force in these investigations." [31]

It is unfortunate that, six months before, W. Stewart was considered by *Nature* as a "credible force".

Critic n°4: "The experts have no scientific qualifications in the assessed area"

Concerning their lack of scientific qualifications, every investigator justified himself with his own arguments. In a letter that he sent to J. Benveniste during summer 1988, J. Randi explained that he nevertheless had some scientific past:

> "As a youth, I took summer employment with the Banting-Best Laboratory in Toronto, Canada, as a mere glassware washer. I hardly required a doctorate in Detergent Science to fill that position but my employer recognized that my dedication in performing that simple task indicated that I might step up to more important involvement in the zinc-protamine insulin assays that were the product of the laboratory. I learned proper pipetting procedures and a rather sensitive sugar titration process upon which the entire bio-assay depended. […] True, I have no academic background to support my claim; but I feel that I need not present my credentials and my passport before reporting a fire..." [32]

Indeed, a fireman in the Opera does not need to possess the qualifications of a tenor. One does not ask him however to appear on stage or to judge skills of the singers.

As for W. Stewart, he willingly recognized that he had no doctorate and only a few publications to his credit. To a journalist who asked him how it was possible that in twenty working years, he published less than a dozen articles, he answered: "I publish only when I have something I think is worth communicating to other scientists. This hasn't happened frequently." [33]

It is well intentioned not wanting to submerge his colleagues by useless readings, but apparently this rather short explanation was not enough for the NIH who employed W. Stewart. Indeed at that time, in an article of *New Scientist*, the Director of the NIH declared about W. Stewart and of his colleague N. Feder:

> "They are supposed to be working scientist, and their scientific productivity has been extraordinarily low. They hasn't been much originally for a while." [34]

And, according to *Science:*

> "Stewart and Feder may be self-appointed guardians of scientific accuracy, but they have managed to get NIH's approval to spend 20% of their time on investigations of published papers. In fact, they have been spending closer 100%, according to their supervisors." [35]

And after:

> "By Stewart and Feder's own admission, their research is somewhat on hold and misconduct studies occupy most of their time. They said it because NIH has so cut back their research resources that they can no longer do science.
> […] They accuse NIH officials of retribution. In off-the-record interviews with Science, NIH sources argue that when space is tight, as it is all over the campus, you do not assign large amounts of space to unproductive workers."

Then why did the NIH continued to employ researchers as W. Stewart? According to the same source of the journal *Science*:

> "[…] it would be political suicide to go after Stewart and Feder, whose public status as whistle-blowers has gained them the protection of powerful members of Congress [...].
> "It costs NIH perhaps a couple of hundred dollars to keep Stewart and Feder", [...]."The political costs of dumping them would too high"."

As regards J. Maddox, accused with his team-mates of amateurism by J. Benveniste, he answered with these arguments:

> "The short answer to the question is that if a group of mere amateurs can so quickly discover procedural errors of such importance, that is sufficient justification." [36]

The argument is somewhat circular. Indeed, according to J. Maddox, what a self-proclaimed expert names "error" proves *a posteriori* his skill in the domain. We have seen the limits of this rather strange conception of the expertise. And, if we fully extend this reasoning, we can wonder why scientific journals – such as *Nature* – keep up-to-date lists of (true) experts in all scientific domains for reviewing of manuscripts.

Critic n°5: "Why was a magician present in the team?"

The presence of a "magician" in the team was a recurring reproach. It participated in the atmosphere of "circus" which for some – as H. Metzger, one of the experts appointed by *Nature* to analyze the manuscript – was harmful to the image of science. Still, nobody knew at this moment that not only was a "magician" was present in the laboratory of Clamart, but also a real "false medium", namely J. Alvarez, the person who accompanied J. Randi! To further complicate the situation, we know now that J. Randi was aware that J. Alvarez was not the true name of his assistant and close friend. Indeed, this latter was travelling in France under a false identity that he had stolen some years ago… (See note 3 Chapter 9).

We have seen that the reason for the presence of J. Randi is now obvious. Indeed, J. Randi was not just any "magician" or conjurer. He was a founder member of the CSICOP (*Committee for the Scientific Investigation of Claims of Paranormal*). This association created in 1976 aims at pursuing and at denouncing what it considers as "false science". In 1996, J. Randi created his own foundation. Certainly, one can only agree with any effort tending to develop critical and scientific mind. The reading of the papers of the CSICOP reveals however a rather primary scientism accompanied with some arrogance. In the reports of the CSICOP meetings, science is in fact barely mentioned and seems secondary. It is not the scientific knowledge which seems to be the mainspring of the association, but rather the pleasure to pursue, to chase away and to denounce. After the exploit has been achieved, mocking appears to be the main mode of expression of the members of the CSICOP.

J. Randi was thus not a neutral observer. He was not only a conjurer specialist in "manipulations" as J. Maddox had initially presented him. As W. Stewart, he led his own fight as self-proclaimed expert. Every new "trophy" added to his fame of debunker. He could then hold interviews, conferences, articles and broadcast shows. It was his "small business" which appeared then to work well. It is true that the credulity is widespread and that the absence of scruples of the quacks ensure him an almost unlimited business. But were methods used by J. Randi to denounce false prophets or astrologers adapted to scientific expertise? Is any singular phenomenon observed within a laboratory inevitably a matter of embezzlement or deceit? Is not there some risk of derive towards a thought police organized by uncontrolled brigades in the name of "scientifically correctness" that they would have defined themselves?

In fact, the question of the participation of a magician in the investigation of *Nature* means wondering: "*Why a plan of experiments or a detailed program was not performed?*" The answer to these two questions is the same. Indeed, the absence

of a plan of experiments and the presence of J. Randi share the same logic, namely that the investigators were not inspired by a scientific approach, but hoped to quickly find the proof that the experiments were forged.

In the context of a scientific approach, a plan of experiments would have allowed defining what was acceptable for all parties concerned. Particularly the results could have been published in a peer-rewieved article describing the experiments in detail. In case of a disagreement on the interpretation of the results, two contradictory articles could have been drafted. It was then building a scientific controversy with sound arguments, always more useful than the hullabaloo which resulted. We have the feeling that the certainty of the investigators to hold the truth authorized them to assume rights on the team of J. Benveniste by not considering them as full partners, but as subjects who allowed them illustrating their thesis on "scientists who delude themselves".

In the logic of the investigators, a plan of experiments could only disturb them in their research of the "smoking gun". Considering the laboratory of Clamart as a field of experiments, it is obvious that they preferred to keep control. A plan of experiments would have retrained them. It was preferable for them to decide only according to the events. That is why the first three days, the investigators wished only to observe how experiments were done and to consult the experimental data recorded in the laboratory notebooks. They appeared to glean from right to left in a kind of Sunday walk, as told by J. Benveniste:

> "That lasted five days. When they arrived on Sundays, they did not even know how long they would stay! And every evening, we told them: "Well, that worked. Are you convinced? Is that enough?" – and they answered: "No, no! We want to do again tomorrow!" [37]

The only one of the investigators who really appeared "to work" was W. Stewart. J. Maddox let him do, just calming him down when he was warming up. For example, when someone approached a little too much for his taste in the room where E. Davenas counted basophils under a microscope:

> "Joking around, John Maddox pretended to be there only for lip service "Jacques, he told Benveniste, these experiments are really extraordinary. And you are so kind…" " [38]

Today, being aware of the frame of mind of the investigators at the onset of the survey, one understands better their behavior. They had to demonstrate during these few days that somebody cheated. Indeed, as clearly expressed by J. Maddox:

> "We thought it quite probable that there was someone in Benveniste's lab who was playing a trick on him." [39]

In other circumstances, J. Maddox declared:

> "We envisaged the possibility of a joke, a hoax performed by somebody else than Benveniste, or a member of his team. Obviously we thought of a swindle, but I must specify that we found no proof in this direction. But, in front of such strange experimental data as those that Benveniste sent us, was it not normal to suspect the worst?" [40]

And yet:

> "We thought we would find a "poltergeist" or more seriously, some obvious errors." [41]

During the same interview, J. Maddox specified:

> "But, before coming to Paris, one year ago, we suspected that somebody could play a trick on him. That is why we included a professional illusionist in our team, James Randi. The latter, well known to have discovered and reproduced the "tricks" of Uri Geller, declared from the second day that his presence was no longer justified."

This is the reason of the very open behavior of the trio, investigating in a very "naturalistic" way, observing the life of the laboratory, without particular constraints for anybody. In the casting, J. Randi had to unmask "the spirit-rapper". It was his specialty. However, he quickly declared – on Tuesdays, as said J. Maddox – that his mission was ended.

The investigators then had to face the facts, the explanation which motivated their action, namely the presence of a cheater in the laboratory, did not hold water any more. It was nevertheless difficult for them to stop and to go home empty-handed. It was thus necessary to use plan B.

The problem was that they had most probably no alternative plan. They must then improvise. We enter then the second part of the investigation where the observers became actors and got involved in the experiments. As seen at the end of Chapter 11, it was also on Tuesday evening that W. Stewart concluded – after an erroneous statistical calculation – that the results reported in the notebooks were "too beautiful". The tactics for the next days was then set up. The purpose was no longer of chasing away the presumed cheater, but of discrediting the experiments with statistical arguments and by resorting to what should be called an attempt of destabilization.

It was for this reason that J. Randi was quickly back in action and his sense of the staging was then utilized. One should not forget that J. Randi was first of

all a man of spectacle. He knew what a show was. He took part to television programs in the 50s, participated in a tour with rock star Alice Cooper in the 70s peppering the spectacle of surprising special effects, playing in particular on scene the role of a crazy dentist and that of an executioner (yes, it is indeed about the same artist of variety show who came to exercise his talents in a laboratory of Inserm). Therefore J. Randi also known as "The Amazing" had showmanship. Naturally, he was the one who had the idea of sticking the envelope on the ceiling. But what was the sense of this dramatization since it was a simple code made by W. Stewart who could have kept it in his pocket? J. Randi did not hide that it was a trap. Speaking about the envelope, he explained:

> "Normally, it would have been necessary to give it to a bailiff. Or better to post it at the address of the lab, so that it would have been returned to us the next day without anybody being able to touch it. But I had been called in this place for a precise purpose: to assess all personalities.
>
> I thus decided that the envelope would be stuck on the ceiling of the laboratory. So nobody could read the code without obvious trace. If somebody wanted to cheat, I would know it. To reach the envelope, it was necessary to use a ladder which was against a wall. Without anybody knowing about it, I made marks on the ground with a pencil to locate the exact position of the ladder." [42]

The following morning, he noticed that "the ladder was moved by several meters". But, according to J. Benveniste: "the explanation is simple: my collaborator Yolène Thomas, penetrating the next day into her laboratory and seeing this ladder in the middle of the room, had considered logical to replace it where it usually rested." [43]

Others were able to move it, including the housekeeper! Indeed, contrary to the words of J. Randi who asserted: "there was no cleaning team. The lab was closed from our departure to our return" [44], on one hand, a housekeeper came early in the morning and, on the other hand, there was not only J. Benveniste who possessed the keys of the laboratory and the code of the alarm. The alarm concerned all the Inserm building which housed several laboratories. Furthermore, anybody in the building could easily penetrate into the Unit 200. The number of people who would have been able to approach the ladder (and the envelope) was thus potentially high. Finally, if we take the assertions of J. Randi literally, it meant accusing J. Benveniste himself! When the investigators returned on Thursday morning with J. Benveniste, they were certainly not the first ones to penetrate into the Inserm building.

We see which types of arguments – closer to a novel of Agatha Christie or Conan Doyle than to a scientific expertise – the investigators used. But here again – since we are on the same lines of logic like in detective novel – it is necessary to wonder who benefited from the crime. Indeed, when the envelope was stuck on the ceiling, the experiments had been prepared and the plates of cell cultures were in the cold room, waiting to be counted. One could not change anything. One does not understand for what purpose the code would have been useful since W. Stewart distributed himself the samples to be counted under a new code (for an unclear reason since he held both successive codes…). As the journalist M. de Pracontal correctly pointed out:

> "Randi seems to be a victim of the self-deception that he denounces in others: he is so sure of the reality of the fraud that he does not seem to take into account the inconsistencies of his demonstration." [45]

In spite of the numerous criticisms directed toward *Nature* and the inconsistencies of its investigators, there was now a doubt in the media. The media wave which followed upon the publication of the report vanished with the summer. J. Benveniste must now tackle year 1989, because as announced in the press release of Inserm of July 27th, 1988, the Unity 200 of Inserm had to be evaluated.

It was soon in front of his peers of Inserm that J. Benveniste had to explain himself, the stake being the survival of his laboratory and his position as director.

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Notes of end of chapter

[1] J.Y. Nau. Nouvelles polémiques sur la « mémoire de la matière ». Une commission d'enquête conteste les résultats du docteur Benveniste. *Le Monde*, July 27th, 1988.

[2] F. Nouchi. Passe-passe au laboratoire. *Le Monde*, July 27th, 1988.

[3] Press release of Inserm of July 27th, 1988.

[4] J. Maddox. A too polite silence about shoddy science: why scold those who expose error. *New York Times*, September 26th, 1988 (page A23).

[5] M. de Pracontal. Les mystères de la mémoire de l'eau, p. 42.

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

[7] It was not a "double-blind" experiment but two successive codes (which were both known to W. Stewart…)

[8] Letter of J. Randi to J. Benveniste of August 6th, 1988.

[9] In the same article, J. Benveniste answered to these charges in these terms: "This new revelation underlines the internal contradictions of the group supposed to check our research work and demonstrates that they did not still arrive a tangible conclusion".

[10] G. Pial. Nouveau trouble pour la mémoire de l'eau. *Libération*, October 3rd, 1988.

[11] M. de Pracontal. Les mystères de la mémoire de l'eau, p. 47.

[12] P. Alfonsi. Au nom de la science, p. 81.

[13] W. Sullivan. Water that has a memory ? Skeptics win second round. *New York Times*, July 27th, 1988, p. A14.

[14] M. de Pracontal. Les mystères de la mémoire de l'eau, p. 66.

[15] In fact, an attentive reading of the report of *Nature* of July 28th, 1988 shows skillful equilibrium with veiled charge followed by an ambiguous denial. Here is how is described the opening of the envelope during the meeting of Friday: "Opening sealed envelopes is Randi's expertise. He found that the sealed flap of the envelope had detached itself at a surprisingly straight angle when the scoth tape attaching the code to the ceiling was pulled away, but inspection of the aluminium foil allowed him to pronounce himself satisfied that the code had not been read." In summary, if there was attempt, it did not succeed…

The scene of the opening of the envelope was filmed by J. Benveniste and can be seen into in the episode dedicated to J. Benveniste in the documentary series "Heretics" of BBC2 and first broadcasted on July 15th, 1994.

[16] M. Alfonsi. Au nom de la science, p. 31.

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

[18] The Nature of Science (Editorial). *The Los Angeles Times,* August 7th, 1988.

[19] E. Garfield. Contrary to *Nature* ? *The Scientist*, September 5th, 1988.

[20] The complete reference quoted by E. Garfield is: "R. Hudson. Nature debunks piece it just published that supported homeopaths' claims. *Wall Street Journal*, July 27th, 1988."

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

[22] R. Pool. More squabbling over unbelievable result. *Science*, August 5th, 1988, p. 658.

[23] A.S. Relman. *New York Times*, October 17th, 1988, p. A20.

[24] W. Sullivan. Water that has a memory? Skeptics win second round. *New York Times*, July 27th, 1988, p. A14.

[25] Quand l'eau fait frémir les scientifiques. *La Recherche*, September 1988, p. 1005.

[26] H. Metzger and S. Dreskin. Only the smile is left. *Nature*, August 4th, 1988, p. 375.

[27] J. Maddox. When to publish pseudo-science. *Nature*, August 4th, 1988, p. 367.

[28] Interview: Walter Stewart. *Omni*, February 1989, p. 65.

[29] Dalek are extraterrestrial robots in a famous British TV series (Dr Who).

[30] S. Young. Breaking the laws of Science. Is Dr Benveniste a genius or a cheat? *Telegraph Week End Magazine*, (no date), p. 25.

[31] J. Palca. Research, misconduct and Congress. *Nature,* February 9th, 1989, p. 503.

[32] Letter of J. Randi to J. Benveniste of August 6th, 1988.

[33] Interview: Walter Stewart. *Omni*, February 1989, p. 65.

[34] Have the fraudbusters gone too far. *New Scientist*, July 11th, 1988.

[35] B.J. Culliton. A bitter battle over error. *Science,* 1988;241:18.

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

[37] M. Alfonsi. Au nom de la science, p. 29.

[38] F. Nouchi. Passe-passe au laboratoire. *Le Monde*, July 27th, 1988.

[39] R. Pool. More squabbling over unbelievable result. *Science*, August 5th, 1988, p. 658.

[40] M. Alfonsi. Au nom de la science, p. 72.

[41] J. Maddox. Plus vrai que « Nature ». *Le Monde*, July 26th, 1989.

[42] P. Alfonsi. Au nom de la science, p. 41.

[43] J. Benveniste. Ma vérité sur la mémoire de l'eau, p. 68.

[44] M. de Pracontal. Les mystères de la mémoire de l'eau, p. 46.

[45] *Ibid.*, p. 49.

Chapter 14. "A laboratory curiosity"

"That is an impressive list"

To prevent the negative consequences of the investigation of *Nature*, J. Benveniste suggested to the administration of Inserm the immediate organization of a counter-inquiry:

> "[…] Philippe Lazar, the Director General of INSERM, with whom I did not really get along, seems to want to let things rest and send back the evaluation of the research of the Unit 200 to the "legal" deadline of the four-year examination planned at the beginning of year 1989. But to counter effectively the devastating effects of the botched investigation published by *Nature*, it would have been necessary that another inquiry commission – a serious one – be immediately appointed. Its composition could have been established in dialogue between Inserm, my team and possibly other partners such as the CNRS *[National Center for Scientific Research]* and the Academy of Science. A rigorous protocol of check of my experiments and the observations performed in the foreign laboratories would have allowed rebalancing the situation. But, in total convergence with the mandarins of the French research whom I met a few weeks before at the Minister of Research, the administration of Inserm refuses the immediate creation of such a commission. *Business as usual*, as if the intrusion of a bunch of bounty hunters in a state laboratory was commonplace." [1]

In spring 1989. J. Benveniste knew that many of his colleagues sitting in Inserm commissions where the renewal of the units of the Institute were decided, waited to catch him out. Numerous members of the commissions of Inserm wished an exemplary penalty because they considered that the credibility of Inserm and French research was at stake. But both the commission and the administration of Inserm faced with a difficult problem. Indeed, how could J. Benveniste be punished when the production of his laboratory was unanimously acknowledged and while he wore the halo of the discoverer of the paf-acether?

Furthermore, after the turmoil of the summer 1988, the *Current Contents* of Philadelphia – an independent organism that broadcasts databases concerning scientific articles and performs bibliometric studies – wrote: "Professor

Benveniste has a substantial scientific reputation as judged by his publication and citation record":

> "A check of the *Science Citation Index* revealed that Benveniste has written dozens of papers, including at least 13 that are cited more than 100 times […]. That is an impressive list. He has written the second most-cited paper ever published in Comptes Rendus de l'Académie des Sciences. And certainly a paper from the Journal of Experimental Medicine cited more than 640 times is an outstanding achievement." [2]

These comments made the task of the "peers" of J. Benveniste particularly difficult for assessing his scientific activity. Their work would have been largely facilitated if J. Benveniste was an unknown researcher without a prestigious past, without a productive laboratory around him and without scientific and political networks. What arguments the Commission could put forward without giving the impression of an "official" scientific censorship. Only the ability and the skill of P. Lazar allowed protecting the institution and not making a martyr of science at the same time. But what scientific arguments were used for this purpose?

The report of the Specialized commission [3]

In April, 1989, a delegation of the commission of Inserm (*Specialized scientific commission n°2* or *CSS2*) attended a presentation in Clamart made by the scientists of the Unit. Then, the members of the commission visited the premises. A report was available on April 25th, 1989 in which one can read the following extract:

> "Concerning the controversial domain of high dilutions, the CSS2 recommends:
> - Stop as fast as possible (or get rid of it) the activity concerning the pharmacological effects at high dilutions. The reasons of this last recommendation are the following ones:
> 1) This activity represents, according to Mr Benveniste, only a quite small fraction of the total activity of the Unit and employs no researcher with permanent position;
> 2) At present, the team does not seem to be ready to use biological models other than basophil degranulation;
> 3) The possible biophysical interpretations of the experimental observations exceed at present the skills of the current team.
> For all these reasons, it is obvious that this issue can only move forward at a snail's pace. It seems thus urgent that the problem changes hands.

> - Any relation with the media concerning high dilutions must be immediately stopped. It is clear, in the opinion of Mr Benveniste himself, that the controversial facts cannot be considered as definitively established. The considerable importance given in media to these results, as well as the permanent polemic associated to the problem:
> 1) damages the necessary outside collaborations that the team needs to preserve in other scientific domains constituting the key point of its activity (paf-acether)
> 2) will probably damage recruitment of researchers for this team from public agencies and will make the search of an industrial employment for the young PhD students more difficult [4]
> 3) probably damages the scientific reputation of the strong part of the team (paf-acether)
> 4) damages the image of Inserm and more generally the image of the French scientific community."

The vote of the Commission n°2 on June 6th reflected well the perplexity of its members in front of the administrative management of the issue: for the theme of the paf-acether, the votes were widely favorable (22 favorable votes and 1 reserved); for the theme of "high dilutions" the ratio was inverted (1 favorable, 3 reserved, 16 unfavorable and 3 abstentions). The global vote concerning the scientific activity of the unit led to 3 yes and 20 abstentions. And for the question of the renewal of the mandate of director, the rate of abstention was also massive: 1 yes, 6 no and 13 abstentions.

Bis repetita

In front of this division of the votes, a second visit of the unit was decided for June 27th. But this time, it was a delegation of the Scientific Council of Inserm, the supreme scientific authority of the Institute, which went to Clamart. It was unusual, but two foreign experts joined the commission. One of these experts was the American H. Metzger which was an eminent member of National Institute of Health. He was the same who evaluated the first manuscript for *Nature* on high dilutions. Once the article was published in June 1988, he wrote to *Nature* that it was shameful to publish such absurdities. The other expert was the English A.B. Kay of National Heart and Lung Institute of London.

The day before the coming of this commission, J. Benveniste sent a letter to P. Lazar to express his fears about "the purpose of this visit and its conditions of organization". Thus, he wrote about the foreign experts:

> "We received no official notification of the name of the experts chosen by the Council. These names are circulating all over Paris

> and came back to us by numerous sources, but we had no possibility of discussing this choice and, possibly, of suggesting other experts for a second opinion. One of them, Barry Kay, is not one of our friends for strictly scientific reasons. A reliable source, since he is the personal doctor of Queen Elisabeth (*sic*), recently told me that Kay was ideologically opposed against any research on high dilutions. The other one, Henry Metzger, scientist of much better quality, became famous for sending a letter to Nature […] describing a single experiment, performed in a system totally different from our own, allowing him to categorically deny the existence of any effect at high dilutions. It is to say the impartiality of the chosen experts and the impartiality of the choice." [5]

About the theme of high dilutions, he pursued:

> "Mr Lhoste who manages the delegation of the Scientific Council pointed out to me that the research on high dilutions would not be examined during this visit. This seems very inconsistent to me. Indeed the C.S.S. N°2 "emitted a favorable vote on the activity concerning the paf-acether". The unfavorable vote is only for "the activity which concerns the pharmacological effects of high dilutions". A visit of the unit by the Scientific Council is necessary only if there is an unfavorable vote of the commission and it is exactly the part that was the object of an unfavorable vote which would not be examined."

J. Benveniste then considered the possibility of giving up the study of high dilutions:

> "I remind you my position which is the one of the laboratory council of U.200: if deemed necessary, I agree to give up, within the framework of my activity of research in Inserm, any research on high dilutions. Things being what they are, any decision which could appear as a penalty to a laboratory of Inserm which published 10 articles in the Journal of Immunology during the last four years would provoke an enormous national or international scandal in which nobody has interest, self-destructing in passing the system of evaluation of Inserm. I am counting on your wisdom, to avoid such turbulences in U.200 and in Inserm. However, the appointment of these "experts" and the fuzziness of tomorrow's visit worry me. Obviously, an operation gets ready, but which one?"

The report of the Scientific council

Contrary to what J. Benveniste anticipated, the Scientific council was not as negative as he had imagined. In its conclusions, the Scientific council indicated that "the scientific activity of Unit 200 remained at a high level, in an original and important domain, which is inflammation. […] We are certainly not in favor of depriving it from the means necessary to pursue most of the studies, even less to scatter it". Then, the main subject of the report was finally reached:

> "Without entering the debate, the delegation wished to analyze with lucidity the place and the effects of the research on the theme of high dilutions led in the Unit, or in the immediate neighborhood, for several years. Let us remind first that they constitute only a small portion (5%?) of the global activity of the group. Well informed about various aspects, scientific or not, about this activity, the members of the delegation were unanimous to underline the disproportion of the facts with their interpretation and judgments expressed in all circles. As they were described, with the recent developments which were presented to us, the results of the team of J. Benveniste appear only as a curiosity of laboratory to which satisfactory explanations are not yet given and the impact of which will remain limited."

The reader probably noted the expression "curiosity of laboratory" that is surprising coming from scientists to describe the experiments on high dilutions. He also noted this strange conception of the scientific research: only facts for which one has an explanation have to be the object of research. The report continued:

> "These observations contradict some of the best established laws of physical chemistry; thus they require an open mind and even temper. Every experimental researcher is familiar with unexpected, even unusual, observations and the signature of a creative and responsible scientist is to know how to distinguish the facts that are significant among those who finally appear trivial, what is sometimes difficult. The observation of this group, the sincerity of whom we will not question, can correspond to the one or the other one of these categories. One could hope, even demand, that this team will make an effort of analysis in order to conclude with certainty on the meaning and the importance of these observations. For several years, the team supports its conclusions on a type of cells and a test, which is disputed to say the least. Only the extension to other simpler cellular or biochemical

> systems would allow generalizing these curious results before asserting that certain phenomena escaped 200 years of research in chemistry. The director of the laboratory did not answer all these objections in a satisfactory manner, so the relevance of the facts could not be considered as established […]".

During its meeting from July 4th to 6th, 1989, the scientific council recommended to maintain the Unit 200, but to postpone the renewal of director's mandate of J. Benveniste "because the program and the scientific perspectives were insufficiently structured and because the answers to the serious scientific objections were insufficient."

"The refusal of any ideological censorship as guarantee of any creativity"

In an open letter, which he gave directly to J. Benveniste after having met him, P. Lazar explained the reasons of his decision, first of all the preservation of the Inserm's laboratory:

> "The convergent opinions of the Specialized scientific commission and the Scientific council on the internationally recognized quality of most of the work made in your laboratory lead me quite naturally to this decision." [6]

Then P. Lazar expressed his wish to maintain J. Benveniste at the head of the laboratory but "to postpone the official confirmation" of this new mandate for the following reasons:

> "At first I think necessary to reaffirm clearly that, subject to the scientific quality of their works, the freedom of the researchers in the choice of their hypotheses and their working methods could be limited only by the rules of the common law and by the respect for the ethics and the moral code. Consequently, we must accept the possible consequences of this deliberate refusal of any ideological censorship, irreplaceable guarantee of any real creativity".

A declaration of principles which one would like to see engraved above the front door of any laboratory! But – indeed this type of introduction is often followed by one "but" – this freedom has for consequence, P. Lazar continued, the exercise of the responsibility of a laboratory director who, because of the public character of the research institute, "also commits the scientific community to whom he belongs". Besides, the Director of Inserm added on, it was necessary "to consider with the biggest attention the criticisms and the convergent recommendations of both authorities of evaluation of Inserm during the *a posteriori* four-year examination of their activity […] which

guarantees the good employment of the means granted by the nation to his researchers". He then added:

> "It is clear that the two scientific authorities that successively examined the work of the Unit 200 with – for the second one – the help of foreign experts, have expressed strong reservations about your works concerning "high dilutions".
> These reservations are related to the content of these works, an analysis of the results which was insufficiently critic, their adventurous interpretation, the conditions of their public expression and the worrisome consequences of the publicity which was then given to them regarding the unfounded strengthening of the credibility of some forms of therapeutic practices".

Then P. Lazar came to the role of sound box played there by *Nature* – which was not directly named – in the affair:

> "The conditional publishing, by a high-level international journal, of an insufficiently supported article and the surprising behavior of this journal, to say the least, after this publication – the unprecedented decision to organize a visit of the laboratory by representatives of the journal, the strangeness of the composition of the committee of visitors, the unfriendly contents of the report published as a result of this visit, the doubtful justifications of the journal on its real motivations – constitute extenuating circumstances towards the team of Unit 200. They do not however absolve their own responsibility."

This quite clear criticism of the attitude of *Nature*, presented as an "attenuating circumstance", is the first public position of Inserm on the "affair in the affair" [7]. That was in stark contrast with the press releases of Inserm which seemed to contemplate at a distance the "scientific debate" in spite of the involvement of some of its members.

Having expressed the necessary "duty of confidentiality" of the researchers towards the population and the "rational doubt" and the critical mind which the latter should permanently exercise, P. Lazar proposed to J. Benveniste a kind of road map for the next six months at the end of which the renewal of the mandate of the director of the Unit 200 would be decided or not. First of all, about his scientific activity towards the high dilutions:

> "On the basis of the scientific authority which is recognized to you, I ask you to work, during the period which opens, to completely resume your role in a scientific community which does

> not, in principle, try to reject you – as shown by the views emitted by our authorities of evaluation – but which rightfully expects from you the proofs of your desire not to deliberately marginalize from it. I do not ask you to give up your ideas and the studies which result from it. Such an act of authority would seriously violate the principle of freedom which I expressed above. I perfectly understand moreover that a researcher who thinks he has highlighted a new phenomenon cannot agree to classify the file without clearing up the reasons of these observations. But if you really want to achieve this clarification, please agree to dedicate as a priority your reflection to systematically look for the experimental biases which might have escaped until now and which can, in all likelihood, explain your unusual observations: you will thus find again a behavior which could not be criticized by your peers because in compliance with the true essence of the scientific thought. It is not excluded in fact that the highlighting of such a bias could present in itself a scientific interest."

Finally, concerning the attitude of J. Benveniste towards the media, P. Lazar added:

> "The code of good practice which I recommend to you presumes in particular that you give up, for a while, expressing yourselves on this subject except in high-level scientific journals – the necessary time for reconstituting the capital of confidence which you have today, you may or may not admit it, largely dissipated in the eyes of your colleagues.
>
> I hope very sincerely to be understood by you, to observe the next signs of a significant change of attitude, in order to follow up the intention which I announced you at the beginning of this letter as regards the renewal of your mandate before December 31st, and thereby to assure the viability of your laboratory. I will be very sorry to give this up."

It was not thus strictly speaking about a penalty but of a kind of testing that allowed the administration of Inserm to let time take its course and to calm things down by maintaining the media at a distance.

"Certainly, I was dreaming sometimes"

In an "opinion" in the journal *Le Monde* entitled "The forbidden dream", J. Benveniste expressed his satisfaction after this decision and commented on the conditions which were imposed on him:

> "As one could foresee, the wisdom and the courage have prevailed. The final decision maintains the U200 in its integrity. It leaves to the researchers their most fundamental right, the freedom to search, without which discovery is not possible. I did not doubt Philippe Lazar's attitude on this point, even if it led him to implicitly deny the conclusions, admittedly arbitrary, of the CSS2 (and, it seems, of the Scientific council) forbidding without reason a research subject.
>
> This was merely very normal. However, there are two conditions. Firstly, I must dedicate as my priority a reflection to look for experimental biases… What else did I do the previous years by informing the Scientific council and the administration of Inserm about these strange results? Did I do anything else when I asked the most famous French scientists for help and when I submitted, after seven working years and after check by five laboratories around the world, these results to the journal *Nature*? Did I do anything when I accepted the only French scientist who presented himself, showing him my books, making with him the necessary checks with, naturally, the same positive results? [8]
>
> The public opinion must know that, among the numerous scientists who shout that French research was dishonored, no one came in the laboratory to comment scientifically on these scientific results. It indicates that the debate is not, has never been, scientific; it is partisan, personal, maybe economic and especially theological." […] [9]

Then he addressed the recommendation not to express himself in the media any more:

> "The second condition which is imposed upon me is the absence of communication with the media. I point out that, from 1985 (first disclosure in the press) to 1988, I remained silent under, sometimes, a torrent of insults. I published first before speaking, and it is *Nature* that, instead of doing its work of editor, gave a considerable impact inside and outside the journal and continued after this publicity. I followed up. What would have been said if I had refused to explain? I always made it, I believe, in the dignity and by specifying every time: "if it is true".
>
> Certainly, I sometimes dreamed: the key in the Seine, the electromagnetic fish. I did not know at that time that the physicists who touch the infinity have the right to dream and not those soft scientists who are the biologists! Now I know it."

"A little more humor would be needed in this story"

Even if P. Lazar was not convinced of the interest of high dilutions – it is an euphemism – nevertheless the delicate management of the affair probably fed his reflection on the role and the functioning of the administration of research as well as the role of scientific journals. Thus, in a book published in September 1989, he wrote that "when one gets off the beaten track, one takes real risks, starting with the risk of not being able to quickly publish results". In order to avoid innovative ideas slip away, he proposed "to try to set up a procedure which would, experimentally, allow financing every year a small number of projects recognized as at "high risk", out of quota." With a scoffing attitude, one could interpret this proposition as the implicit recognition that the projects that are usually financed by Inserm are neither risked nor very innovative…

In the same book, he confirmed his reproaches concerning the behavior of *Nature* by naming the journal directly this time:

> "The journal *Nature* should never have agreed to publish an article by having the intimate conviction, as its director will explain later, that it deliberately released an example of "second-category research"! In reality, there is every reason to think that it imagined having to deal, in one way or another, with a deliberate deceit: otherwise how could one explain that the journal took the deliberate risk to be deeply criticized for this choice, obviously inconvenient if the existence of trickery could not be demonstrated? It had to be really sure of itself and of the trick it played, in passing, to the French science." [10]

In a less formal way, at the same time, P. Lazar shared his thoughts with the journalist M. de Pracontal about "the affair":

> "[…] Philippe Lazar points out that there are not two Benveniste, "One Doctor Jeckyll who would do wonderful works on paf during the day and Mister Hyde who would devote to obscure research on the memory of water during the night". Lazar does not personally believe to the memory of water: "I think that there is an artifact, something like a "magic trick". Nevertheless, I think that Benveniste is in a situation which deserves respect: he thinks he has pinpointed out something. My message is not easy to pass through. In this affair, my wish is that Benveniste does not drown himself in his own bowl of water. I cannot change his character or his way of overestimating his own work and depreciating those of others. I cannot blunt Jacques Benveniste. There are no solutions to all the problems on Earth when we refuse censorship. The ideal

> would be that somebody explains what is happening in these experiments and discovers the experimental bias. But a little more humor would be needed in this story. A number of my colleagues have no sense of humor." [11]

In 2004, p. Lazar reaffirmed his opinion on the work of J. Benveniste:

> "Philippe Lazar […] sees, above all, in Jacques Benveniste a first-rank scientist who remained honest but who was a victim of a murky affair. He also considers that the man "was not critical enough in the interpretation of his results." "The phenomenon which he noticed, he judges, could result from another cause than from a dilution of the studied substances, for example a repetitive contamination from tube to tube." " [12]

It is important to note that these comments dated October 2004 did not take into account the later developments when contamination was no longer an issue (see second part). If there was an artifact, its highlighting would have to be much more subtle and more original than a simple "repetitive contamination from tube to tube". We will nevertheless examine in the next chapter the arguments in favor of possible artifacts.

Notes of end of chapter

[1] J. Benveniste. Ma vérité sur la mémoire de l'eau, p. 86.

[2] E. Garfield. Citation Perspective on Jacques Benveniste - Dew Process at Last? *Current Contents*, March 27th, 1989, p. 3–7.

[3] Members of the Specialized Scientific Commission n°2 : M. Richard Rips (President), M. Jean-Paul Tillement (Vice-President), M. Raymond Bazin, M. Pierre Bechtel, M. Emile Bisagni, M. Denis Blache, Mme Francine Bourgeois, Mme Marie-Françoise Cachera, M. Etienne Delain, M. René Devilliers, M. Guy Dirheimer, Mme Evelyne Eschwege, M. Jean-Charles Fruchart, M. Yves Guidicelli, M. Jean-Pierre Henichart, M. Jean-Pierre Kantelip, M. Pierre Laduron, M. Michel Lagarde, M. Michel Ladzunski, M. Gérard Leclerc, M. Jacques Robert, M. Jean-Michel Scherrmann, M. Gérard Siest, M. Camille-Georges Wermuth.

[4] About this issue, J. Benveniste pointed out: "Other inconvenience that the committee would dread was the impact of the media debate about the memory of water "will probably damage recruitment of researchers for this team from public agencies and will make more difficult the search of an industrial employment for the young PhD students." On the question of the recruitment of PhD students coming from my laboratory, the future, as we will see, will show that the commission was right. Retrospectively, such prescience seems to me admirable". (J. Benveniste. Ma vérité sur la mémoire de l'eau, p. 90).

[5] Letter of J. Benveniste to P. Lazar of June 26th, 1989.

[6] Letter of P. Lazar to J. Benveniste of July 11th, 1989.

[7] J. Maddox answered the critics of P. Lazar about the attitude of *Nature* in *Le Monde* of July 26th, 1989 (J. Maddox. Plus vrai que « Nature »). He pointed out, about the works of J. Benveniste, that in spite of the criticisms of P. Lazar on the attitude of *Nature*: "both committees of Inserm criticized his works on high dilutions with more or less the same arguments as ours".

[8] This scientist was Alfred Spira (see Chapter 16).

[9] J. Benveniste. Le rêve interdit. *Le Monde,* July 12th, 1989.

[10] P. Lazar. Les explorateurs de la santé. *Odile Jacob* (1989), p. 160.

[11] M. de Pracontal. Les mystères de la mémoire de l'eau, p. 140.

[12] M. Albertganti and J.Y. Nau. Jacques Benveniste. Un biologiste hors norme. *Le Monde*, October 6th, 2004.

Chapter 15. "The explanation is very simple"

In contrast with other famous scientific controversies of the history of the sciences, the "Benveniste affair", as we have already pointed out, did not succeed in going beyond the stage of a polemic. It was indeed not a controversy because, as J. Maddox insisted, there were no results! The director of *Nature* expressed this idea very explicitly in the last paragraph of conclusion of the text, which intended to close the "debate" in the columns of his journal:

> "So what is the truth about INSERM 200's claim on behalf of high-dilution anti-IgE? One correspondent chided us with having impeded the discovery of the true explanation. My own conviction is that it remains to be shown that there is a phenomenon to be explained." [1]

Therefore, there was no reason to look for an artifact since there was no fact for the simple motive that *it could not exist*. We have seen that the investigation report of *Nature* tried to demonstrate the non-existence of an effect of high dilution and results were assimilated to simple statistical fluctuations of the background noise. It is however pleasant to notice that after this report, *Nature* published the letters of readers for numerous weeks explaining what was the artefact responsible for the observed effect!

Thus let us examine the various suggestions of artefacts which were then proposed. Most suggestions came from the considerable correspondence which was sent to the journal during ten weeks after the publication of the investigation report.[2] The reader will notice that some of the proposed alternative explanations were often more unlikely and more fanciful than the hypothesis of a "memory of water". These proposals had another feature: they were always expressed in a supposing manner "if we suppose that… then it is possible that in fact…" However each author of these proposals did not go farther than this "thought experiment" and never performed – except one – an experiment to try to confirm the hypothesis. .

The cork of molecules

This hypothesis was proposed by J. Ninio, researcher to the CNRS, who during summer 1988 tried to popularize it with the editorial staffs of various Parisian newspapers. According to this researcher, the molecules of anti-IgE, from a certain dilution, stayed at the surface of water and were thus transferred from one tube to the next one. The consequence was that there was no real dilution,

but a transfer of anti-IgE from tube to tube. To express his thought, he used the following analogy:

> "Uncork an old wine bottle. Pour a little, by a funnel, into another bottle. Complete by a liter of water. You will have actually diluted the wine… But not the dust of cork which was on the surface, and thus almost entirely transferred from a bottle to the other one." [3]

An analogy remains however an analogy and by which experiments was this scientist able to demonstrate that the molecules of anti-IgE really behaved like this? None. He proposed nevertheless a test to assess his hypothesis:

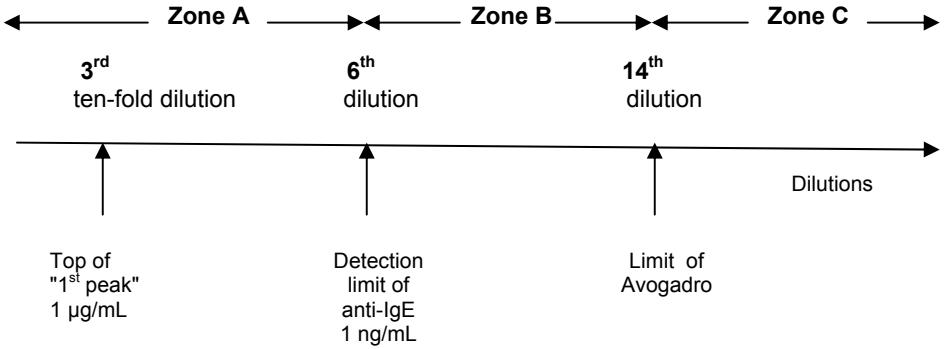
> "Let's take again the example of the wine bottle and pour two cups: the fragments of cork are found in the first one, which thus has not the same content as the second one. In the experiments of Mr Benveniste, the dilutions are made by manual pipetting and I suppose that only the first pipetting is used. Nowhere it is mentioned what occurs if the first pipetting is systematically discarded and that the following ones are used." [4]

To put it more simply, the idea of J. Ninio is that anti-IgE is transported from one tube to the next one and that the supposed concentration decrease is not respected (in particular when the concentration of anti-IgE is low). The consequence is the contamination of all tubes of the series of dilutions. The tubes which are supposed to contain only "organized water" would be in fact contaminated unknown to the experimenter by molecules of plain anti-IgE.

If we follow this reasoning, how can one explain that the heights of the peaks of the degranulating activity were similar on the entire series of dilutions? Indeed, one would expect that anti-IgE ran out gradually from tube to tube, which was not the case. Moreover, the analogy with the wine bottle seemed to suggest that the molecules of anti-IgE were transported all together (the "dust of cork" passes from a tube to the other one). In this case, all molecules of anti-IgE shall be found in the last dilution. Yet an activity was also present in the previous tubes.

But, one could object that it is possible the traces of anti-IgE were actually transported throughout the series of dilution and that these traces were sufficient to cause degranulation. We can indeed never exclude a tiny contamination.

This is quite certain, but detecting traces of anti-IgE is not enough and anti-IgE must be at a *sufficient concentration* in the presence of the cells. Here is a figure where various marks have been placed on a series of anti-IgE dilutions:



The marks on this scale allow defining 3 zones:

- Zone A is the "classic" zone (up to the 6th dilution). It is the zone that corresponds to the "first peak". Whatever the method of dilution (with or without shaking), the biological effect is the same and the dilutions of the antibody are in keeping with the successive ten-fold decreases.

- Zone B is an intermediate zone (from the 6th to the 14th dilution) where there are still anti-IgE molecules, but where they cannot be detected and where anti-IgE does not have any activity anymore (except when the dilutions are shaken).

- Zone C is the zone where there are no anti-IgE molecules.

The examination of this scale allows answering the argument about possible traces of "active" anti-IgE. Indeed, if we observe a peak of degranulation of approximately 30-40%, then – if it is indeed anti-IgE which is responsible for this activity – the presence of anti-IgE molecules should be detected after dosage. The threshold of detection of this last one is indeed of the order of 1 ng/mL. At this concentration (corresponding to the 6th ten-fold dilution of the initial antiserum), there is typically no degranulating activity anymore.

Consequently, we can reply that it is possible that the explanation of the problem of the claimed "high dilutions" is in the zone B. In this zone, the molecules of anti-IgE are present, but in undetectable small quantities. The fact of shaking them would make them much more effective for a reason which remains to discover. Therefore, we can conclude – according to this logic – that it is quite possible that traces of antibody due to a tiny contamination,

undetectable by classic methods, would be nevertheless active! One does not need to hypothesize any "memory" to explain these results.

Well, it would be indeed the end of the "memory of water" with the advent of a very big discovery! It would mean that one can transform traces of antibody into "super antibody" having the same properties as monoclonal antibodies that the pharmaceutical industry produces at high cost. It would be indeed sufficient to dilute antibodies up to traces and to shake them violently between each dilution step. And if this hypothesis applied to other molecules, pharmaceutical industry would be destabilized!

Let's dream and imagine that this explanation is the correct one. In that case, *exit* the "memory of water". We should recognize nevertheless that the initial observations of J. Benveniste deserved to be brought to the attention of the scientific community. Thanks to this debate, an important discovery would have been made. Leaving Europe to draw a new road to India and discovering America is frequent in the history of sciences and does not deserve discredit. On the contrary. But this process is possible only if "error is decriminalized" and if one does not ostracize the one who observed a fact but was not able to interpret it correctly.

To my knowledge, no patent was filed and no industrial application was developed based on this idea, rich in applications if it was true. There were however arguments – quoted in the article of *Nature* of June 1988 – that were against the hypothesis of the "efficient undetectable traces": heating at 70°C, action of ultrasounds and freezing-defrosting destroyed the effects of the high dilutions; in contrast, the active high dilutions were not modified after passage through a molecular filter that blocked plain anti-IgE but not water molecules. Taken together, these results thus suggested that the observed effects did not possess the properties that molecules – even as trace contaminants – should have possessed.

The molecules which stick on the tube (and unstick…)

At the end of 1991, Pierre-Gilles de Gennes had just received Nobel Prize in Physics. J. Benveniste – whose a family member was in the professional circle of the physicist – asked advice through a letter. In a very brief answer, P.-G. de Gennes suggested a possible artefact for high dilutions in these terms:

> "I nevertheless wonder if the adsorption of proteins at the wall water/glass does not upset the nominal concentrations (note also that this adsorption is often reversible at high dilutions)." [5]

P.-G. of Gennes decided however to interrupt these brief exchanges in spite of several reminders of J. Benveniste who would like to benefit from knowledge of the Nobel prize laureate on "soft matter", the specialty of this scientist.

The idea that molecules of anti-IgE could adhere to the walls of the tube – and consequently to falsify the ratios of dilutions – was also reported by physicists questioned by the journalist M. de Pracontal. The latter suggested the possibility for the anti-IgE molecules to adhere to the walls of the tube: "[…] from the fifth or sixth dilution, an important fraction of molecules can remain adsorbed on the walls of the tube or on the surface of the liquid." [6]

This "explanation" of the possible artefact by an adsorption on the wall of tubes does not seem very logical. Indeed if molecules stick on walls, then the diminution of the concentrations should be more rapid than expected. Consequently we should achieve the limit of Avogadro more quickly.

Paradoxically, this explanation brings rather arguments in favor of an absence of molecules in high dilutions because the test tubes which serve to make the dilutions would contribute to eliminate the contaminant plain anti-IgE. Let us remind indeed that the test tube (with the possible anti-IgE antibodies stuck on its intern walls) were not in contact with cells. The tube is simply discarded after a fraction of its contents has been taken with a pipette.

Memory of heparin

Was it a hoax? Even if the author of this correspondence to *Nature* did not express his proposal of artefact under the form of a "memory of heparin", the reading of his explanations gave a bizarre feeling. Indeed, J. Leslie Glick of the *Bionix Corporation* company in the USA noted that the physiological medium used in the article of *Nature* contains heparin. He explained that heparin molecules stick on numerous molecular structures and form aggregates that are stabilized by water and ionic environment:

> "I propose that anti-IgE antibody (or any of the other immunological stimuli noted in the paper, that were responsible for basophil degranulation) might have acted as a template for heparin, thereby inducing a specific conformation of the heparin molecule. […] Upon dilution with heparin-containing Tyrode's solution, the stabilized heparin conformation, although lacking biological activity, would itself serve as a template, effecting a new heparin conformation which would mimic the three-dimensional structure of the antigen-binding site of anti-IgE antibody (or other immunological stimulus". [7]

According to this hypothesis, heparin would be a kind of "photocopy machine" for biological molecules. Once again the pharmaceutical industry might be afraid for its future. Nevertheless no patent or publication tried to exploit this admirable "discovery". Did its author really believe in it?

If one makes nevertheless the bet that this proposal of artefact was seriously given out, one could answer that the experiments with high dilutions had been performed with other physiological mediums that did not contain heparin without changing the results.

The masked agent

For M.J. Escribano of the CNRS, a "very simple explanation" could exist for the reported phenomenon [8]. One could simply suppose a molecule with degranulating properties that would be fixed to one of the components of the physiological medium, for example to albumin. Agitation would release this molecule and degranulating activity would be thus observed and wrongly attributed to high dilutions of antibody.

The answer to this argument is much simpler than the "very simple explanation": there is no effect noticed with the control solution that was shaken in the same conditions.

The masked agent (bis)

This explanation was a more sophisticated version of the previous one with a "masked agent" that, in this case, would be present in the wall of the tube. Indeed, here is what A. Danchin of the Institute Pasteur proposed:

> "Since it is well known that antibodies strongly (and often specifically) interact with surfaces, it is possible that they extract some ion (or contaminant molecule), which in turn acts as a trigger for further extraction (in the absence of antibody). This would account for the requirement of strong agitation." [9]

We cannot reproach the supporter of this possible artifact not to be generous with *ad hoc* hypotheses. First, it is necessary to suppose, on one hand, that anti-IgE antibody is capable of extracting "something" from the wall of the tube, but, on the other hand, that anti-IgG is not capable of doing the same (what *per se* would be particularly interesting), that this "something" would have degranulating properties (direct or indirect) and that it would be capable of auto-extracting of the wall. One must also add – and it is the last condition – that it is necessary that agitation alone could not extract this "something" if the latter (or anti-IgE) was not already present in the solution.

The explanation being thus completely reinforced on all sides, the only possible answer is that experiments with high dilutions were performed with various types of materials (tubes in polypropylene, polyethylene, glass) and with various molecules (anti-IgE antiserums, antigens, deganulating peptides, ionophores, histamine, phospholipase A2, etc.) We could certainly imagine a specific hypothesis for each of these various biological substances and materials by copying the above reasoning. But is it still science?

The contaminating sprays

Here also a contamination is proposed by I. Lasters and M. Bardiaux [10] of the company *Plant Gentic Systems* in Brussels. But the contamination would take place not at the time of the realization of the dilutions but when the high dilutions are put in contact with the cells. This contamination would occur step by step, from a well to the other one.

The best answer is to put emphasis on the blind experiments where "active" and "inactive" wells were both present on the same plate of cell culture.

The fragments of antibody

For R.M. Schilling, the results of the experiments with high dilutions could "be easily explained" [11]. Shaking would be responsible for the formation of fragments of antibody. To summarize the thought of this reader, one believes to use molecules of anti-IgE and in fact there are fragments – some keeping degranulating properties – which are transported through the dilution process.

However, even for fragments, the limit of Avogadro applies and the serial dilutions finally exhaust the supposed stock of fragments.

The free radicals

K.S. Suslick of the University of Illinois suggested that shaking of liquid locally creates bubbles of cavitation and high temperatures that induce chemical reactions with the following consequences:

> "We suggest that the degranulation observed by Benveniste and coworkers is an artefact of cell damage caused by reactions with small amounts of OH°, H°, H_2O_2, HO_2, etc., produced by their use of vortex turbulence." [12]

The simplest answer once gain is that controls prepared in the same manner do not induce degranulation.

Autoantibodies anti-IgE

The English scientist F. Shakib [13] pointed out that a source of anti-IgE antibody is not taken into account: anti-IgE autoantibodies, which are present in variable quantities according to the individuals. These antibodies fixed to the IgE on the basophils could be responsible for a "spontaneous" degranulation.

Here again, if this hypothesis would be correct, one should observe this phenomenon also with controls.

The oxidation of toluidine blue

The only hypothesis for which the author made the effort not only to perform an experiment, but also to publish his hypothesis of artefact was due to Jean Jacques, chemist, scientist at CNRS. We will talk in detail on this article published in 1990 in Chapter 19, because this scientist by writing this article helped J. Benveniste in a very involuntary manner. One will see how was refused to J. Benveniste on this occasion something which could have been considered as the start of a constructive controversy.

Notes of end of chapter

[1] J. Maddox. Waves caused by extreme dilution. *Nature*, October 27th, 1998, p. 760.

[2] *Nature* of July 28th, August 4th, 18th and 25th, September 8th, 15th, 22nd and 29th septembre, October 13th and 20th, 1988.

[3] M. de Pracontal. Les mystères de la mémoire de l'eau, p. 93.

[4] *Ibid.*, p. 97.

[5] Letter of P.G. de Gennes to J. Benveniste of October 31th, 1991.

[6] M. de Pracontal. Les mystères de la mémoire de l'eau, p. 96.

[7] J. Leslie Glick. *Nature*, August 4th, 1988, p. 376.

[8] M.J. Escribano *Nature*, August 4th, 1988, p. 376.

[9] A. Danchin. *Nature*, July 28th, 1988, p. 286.

[10] I. Lasters et M. Bardiaux. *Nature*, July 28th, 1988, p. 285.

[11] R.M. Schilling. *Nature*, October 13th, 1988, p. 584.

[12] K.S. Suslick. *Nature*, August 4th, 1988, p. 375.

[13] F. Shakib. *Nature*, October 20th, p. 664.

Chapter 16. "It is the same girl, still as beautiful"

"At this moment the Unicorn sauntered by them, with his hands in his pockets. 'I had the best of it this time!' he said."

Lewis Carroll. *Through the looking glass.*

As Russian dolls, which are placed one inside the other, each of the "crucial" demonstrations that J. Benveniste hoped definitive to convince the scientific community resulted inevitably in a new "nested experiment". Constrained to a permanent headlong rush in the quest of the experience that would be convincing for all, J. Benveniste dreamed about the last Russian doll which still remained inaccessible. Thus, after the investigation of *Nature*, he intended to demonstrate that in strictly blinding conditions while maintaining acceptable experimental conditions, the effect of high dilutions persisted.

The opportunity to wipe out the disastrous consequences of the *Nature*gate came from Alfred Spira, an epidemiologist, director of the Unit 292 of Inserm. The latter, during summer 1988, wrote to J. Benveniste to express his support after the "mockery of evaluation" of *Nature* because, he wrote, "our survival as researchers with scientific ethics is at stake". [1]

He then confirmed this "declaration of faith" one year later in an open forum of *Le Monde* – a few days after the decision of P. Lazar concerning the Unit 200 and his director – where he explained the reasons of his commitment with J. Benveniste:

> "The results on the high dilutions are inexplicable? Let us try to explain them! The researchers made a mistake, we have been deceived? Let us give ourselves the means to show it! […] Personally, this is what I decided to do since a year. It is necessary to clarify the problem we are faced with, which is the possible transmission of information by non molecular supports. […]
>
> Scientific errors are more frequent than big discoveries and maybe we are confronted once again with error. It is not in the logic of the research to give up a problem at the middle of a crossing point […] I will thus continue to work with Jacques Benveniste as long as we will have not demonstrated that his results are false or exact." [2]

Owing to the rarity of such a public statement and personal commitment, J. Benveniste could not neglect them. Another important point is that P. Lazar, the director of Inserm, and A. Spira are both epidemiologists having belonged to the same "school", that of Daniel Schwartz who introduced the use of statistics in the area of health and biological sciences in France in the 50s. The direction of Inserm can only favorably look – if it did not arouse or at least encourage – this collaboration between U200 and U292 which could allow forming an opinion, peacefully, on the reality of the controversial results. A. Spira took nevertheless precautionary measures and he asked to check his work by a statistician from Inserm who remained in the shadows.

This conjunction of interests led to the collaboration for the design of an experimental protocol. This new attempt of reproduction of the effects of high dilutions should be carried out without methodological criticisms and must take into account the lessons of the past. A protocol of 23 pages minutely describing step by step the experiments was drafted. This new expertise was aimed to be diametrically opposite of the investigation of *Nature*. Thus, the blind procedure was systematic. A. Spira thought for a moment to call for a bailiff and then gave up preferring to consider his participation as a normal scientific collaboration.

The protocol planned to define *a priori* quality criteria before including each experiment in the statistical analysis: percentage of degranulation above a given value for the first peak indicating that basophils were reactive enough, absence of important variation between controls, etc. Let us insist once more that these quality criteria were applied before unblinding and statistical analysis. The selection of the experiments was hard to understand for the investigators of *Nature*. For them, this selection was leaving the door open to all manipulations. It was in fact a misunderstanding of the rules of the scientific methodology and this method was simply a quality control as practiced in numerous industrial sectors. Let us imagine a racing driver who notices before the departure of a Grand Prix that the engine of its car falters. Nobody thinks of blaming him for preferring to use another car whose engine is properly running and which is planned to prevent the breakdowns of the first one.

On the field in Clamart, Béatrice Ducot from the Unit U292 was in charge to blind and supervise the experiments which were performed by E. Davenas and by a newcomer, Sylvie Gonnord, trained to the technique of basophil degranulation. The experiments were performed from September to December 1989.

At the end of December 1989, the first results of the statistical analysis began to leak out. J. Benveniste declared then:

> "Everything suggests that the trial led with Spira is going to be super positive. Once again, we find again the results published in *Nature*. It is the same girl, still as beautiful. She lacks just a little makeup. Beautiful and faithful, it is rare." [3]

This information was confirmed – in a less flowery language – by A. Spira in January 1990:

> "We reproduced the results published in *Nature*. Our work thus answers to the methodological arguments of the investigation of July 1988. As far as we can, the results of Benveniste cannot be explained by a rough experimental bias. If the team worked haphazardly, we would have noticed. In substance, all that I may assert is that, in the conditions of the laboratory of Clamart, the phenomenon exists. We did not prove that he does not exist. Now, it would be necessary to work on other models, in other places."

And what about the famous error of sampling? A. Spira noticed that actually, the variability between the counts hardly varied:

> "It is surprising, unusual. It cannot be related to a bias of observation, because everything was performed blind. Too big variations could always be understandable by an external factor. Here, I do not understand".

Were the results as "super positive" as stated by J. Benveniste? Why this small reservation in his statements when he said that "she lacks just a little makeup"?

Notes of end of chapter

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[1] Letter of A. Spira to J. Benveniste of August 15th, 1988.

[2] A. Spira. Recherche et Vérité. *Le Monde*, July 13th, 1989.

[3] M. de Pracontal. Les mystères de la mémoire de l'eau, p. 200.

Chapter 17. "She only lacks a bit of makeup"

Light years away from the investigation of Nature

The protocol drafted in common by Benveniste's and Spira's teams intended to reproduce first of all the experiments reported in *Nature* with high dilutions of anti-IgE antiserum (ten-fold dilutions from $1/10^{21}$ in $1/10^{30}$). As a control, anti-IgG antiserum, ineffective on basophil degranulation, was diluted in the same conditions.

Another series was performed including experiments with inhibition of the first degranulation peak by high dilutions of *Apis mellifica*. One remembers that experiments with this homeopathic product were initially included in the manuscript intended for *Nature* and then had been finally published in another journal (see Chapter 4). The inhibitory experiments with *Apis mellifica* performed during the collaboration with A. Spira contained 6 dilutions (ten-fold dilutions from $1/10^{30}$ in $1/10^{40}$) of the initial solution of *Apis mellifica* the effect of which was compared with the solvent of this solution diluted in the same conditions.

The experiments were performed by E. Davenas (ED) and S. Gonnord (SG) from October to December 1989. As already said, the protocol planned to select for analysis only the experiments which met a series of quality controls concerning minimal number of basophils in control wells, significant percentage of degranulation of the first peak and absence of spontaneous degranulation of basophils. Among 45 experiments performed in the first series, 18 were included in the analysis according to the predefined selection criteria and among the 38 experiments performed for the second series with inhibition, 19 were included. The readers can make their own analysis with the counts of basophils obtained during this study that are given in the appendix of the first part.

The effect of high dilutions was confirmed

Overall, the statistical analysis highlighted that high dilutions of anti-IgE were associated with counts of basophils lower than high dilutions of anti-IgG. In other words, it was as if high dilutions of anti-IgE had a degranulating effect on basophils. Therefore, the main result of the article of *Nature* was reproduced. It was thus an essential result. As J. Benveniste said, degranulation with high dilutions was present, "beautiful and faithful".

Indeed, the statistical analysis performed by the team of A. Spira indicated that the observed differences were not simply due to statistical fluctuations (for the familiar reader of the statistical tests, a value of $p < 0.01$ was achieved). To make these results more concrete, we will build several figures.

The figure below represents all counts in terms of percentage of degranulation with anti-IgE at high dilutions. The percentage of degranulation associated with each of the 10 high dilutions of anti-IgE was calculated in comparison with the mean of the 10 anti-IgG (controls) [1]. Let us remind that each of these points was counted blind. Consequently, if only chance was at work, one should obtain a cloud of points centered on the horizontal line (corresponding to degranulation equal to 0%). We notice that ED's cloud is moved upward, indicating that chance was "biased" towards the positive values. In other words, it was as if high dilutions of anti-IgE (compared with high dilutions of anti-IgG) had a degranulating effect on basophils. The statistical analysis confirmed this observation. It was a very important result. In contrast, for the experimenter SG, the cloud remained centered on the line 0% of degranulation.

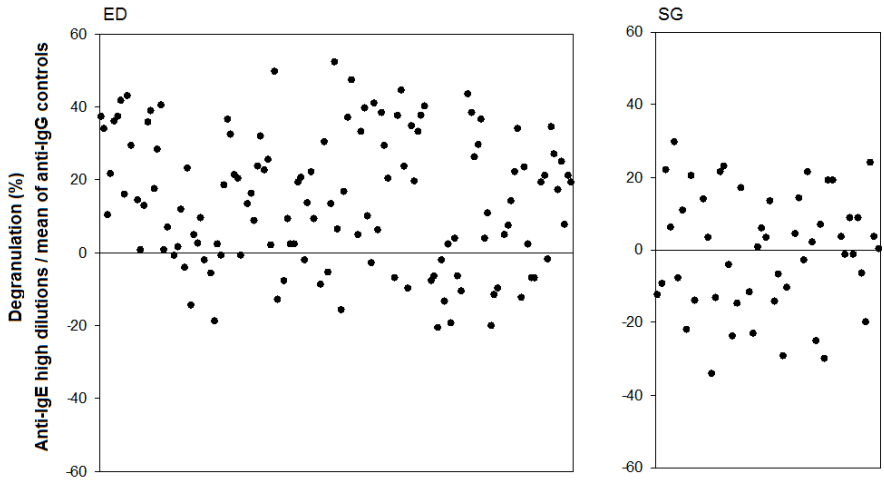


Figure 17.1. Each point is the percentage of basophil degranulation in the presence of high dilutions of anti-IgE assessed by experimenters ED and SG. The calculation of the percentage of degranulation corresponding to a well X is made in the following way:
(mean of the 10 anti-IgG counts – count of the well X) / mean of the 10 anti-IgG counts
The values of the counts of basophils are given in Appendix 4.

We can also sketch these clouds of points in a more concise manner by calculating the distributions of the percentages of degranulation with high dilutions of anti-IgG and with high dilutions of anti-IgE (Figure 17.2). This type of summary clearly highlights that the "behavior" of the basophils was not the same if they were in the presence of high dilutions of anti-IgE or the inactive

controls, namely "high dilutions of anti-IgG". We can also separate ED's and SG's results (Figure 17.3).

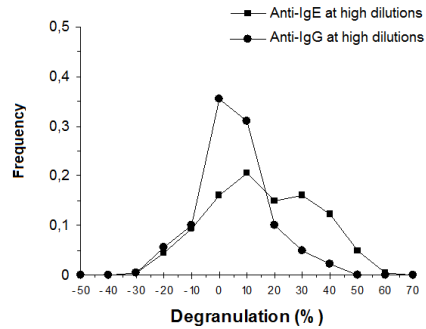


Figure 17.2. This figure presents the results as the distribution of the percentages of degranulation obtained with anti-IgG and anti-IgE. The percentages of degranulation of anti-IgE at high dilutions are calculated as indicated in Figure 17.1 by taking as controls the mean of the 10 anti-IgG controls. For high dilutions of anti-IgG, the mean is equal to 0 by definition. We observe that basophils that were incubated with high dilutions of anti-IgE were more frequently "degranulated".
(NB. On this figure and the next ones, each value of the *x*-axis corresponds to the upper limit on the interval).

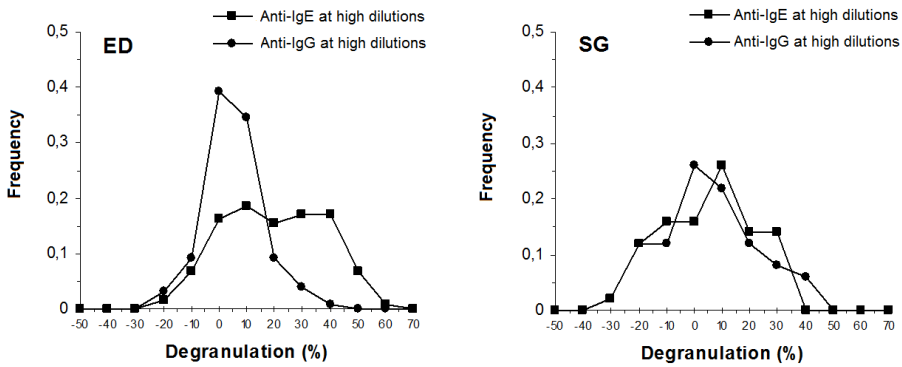


Figure 17.3. These two figures are built exactly as for Figure 17.2. Simply the results of both experimenters (ED and SG) are separated. We notice that both "measurement instruments" did not achieve comparable "performances". In particular the important dispersion of anti-IgG at high dilutions (control) on the right figure suggests that getting a "signal" with SG would be more difficult.

Both experimenters thus obtained very different results. What was striking with SG was the wide dispersion of the percentages with anti-IgG controls. Obviously there were two "measurement instruments" with very different "performances". It was possible that the detection of the loss of affinity of basophils for the staining agent required a good or specific view of colors. The manual dexterity or even the sensory acuteness of the experimenter could be crucial. These are only hypotheses. However if we were to speak about physics instruments, this would seem obvious. These results illustrate the difficulties to achieve a good reproducibility for some experiments in biology, even, as depicted here, within the same laboratory.

J. Benveniste attributed these differences to the different duration of practice for basophil counting of both experimenters.[2]

But where are the "sinusoids" of yesteryear?

The above presentation of the results does not take into account however the rank of the dilution, only the characteristics "high dilution of anti-IgE" or "high dilution of anti-IgG" was considered. One can also show the percentages of degranulation of the dilutions of anti-IgE by taking into account the rank of the dilution from $1/10^{21}$ to $1/10^{30}$. The 18 experiments are shown in Figure 17.4.

What is striking is the chaotic aspect of the results. One is very far from the regular curves that had been previously reported and had very much intrigued. As J. Benveniste noticed: "she lacks just a little makeup". Nevertheless, as we have seen before, points are more often above the line 0% (for ED) than allowed by chance only.

The inhibitory experiments with Apis mellifica

Let us examine now the results performed with the homeopathic product *Apis mellifica*. We represented the effect of this product as percentages of degranulation inhibition (Figure 17.5). Here again, if only chance were at work one should have an equal distribution around the line 0% inhibition. We notice here again that better performances were obtained with ED compared to SG. The latter obtained nevertheless an inhibitory effect of the homeopathic product, but less marked than her colleague.

The distribution of these points is also shown in Figure 17.6 (results of ED and SG are not separated). One notices as expected that, overall, the high dilutions of *Apis Mellifica* had an inhibitive effect.

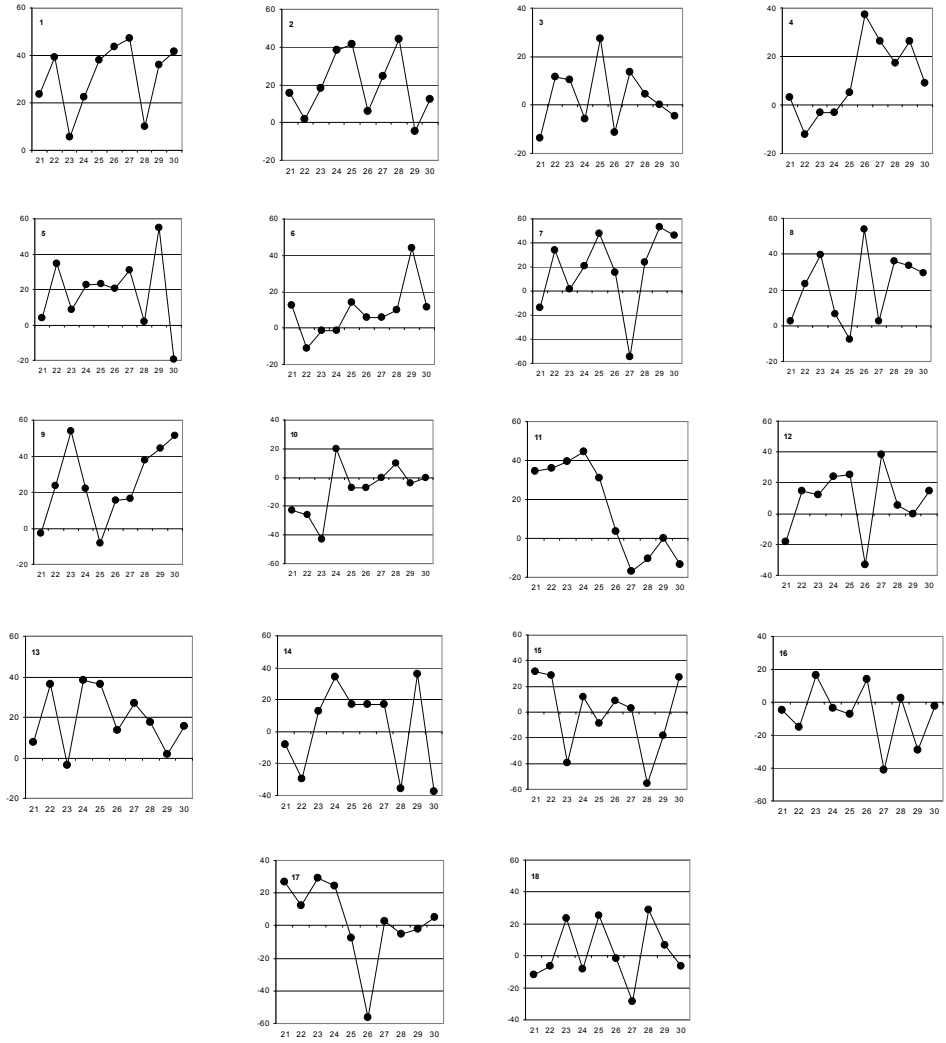


Figure 17.4. The 18 experiments are shown separately on this figure (n°1 to 13 for ED and n°14 to 18 for SG). Overall, there is an impression of chaos that prevails and one observes only rarely "sinusoids" or regular "waves". Nevertheless, overall, there is a statistically significant effect. In other words, points are more often above the line 0% of degranulation (in approximately two-third of cases) than allowed by chance (if only chance was at work we should have comparable numbers of points on each side of this line).

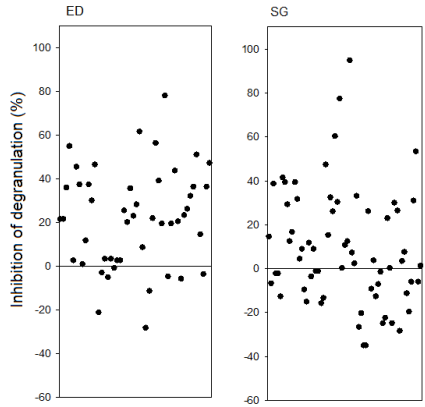


Figure 17.5. Each point is the percentage of inhibition of basophil degranulation by *Apis mellifica* assessed by the two experimenters ED and SG.

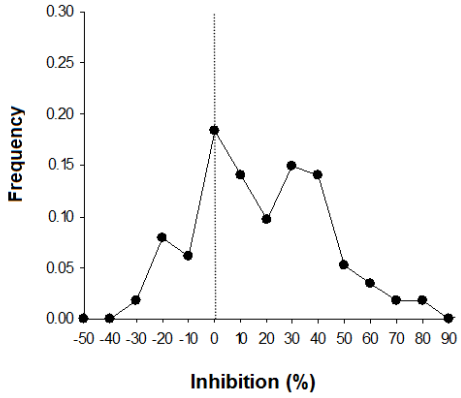


Figure 17.6. This figure summarizes the results of inhibition of degranulation by *Apis mellifica* as the distribution of all experimental values. We observe that the percentages of degranulation are more frequently on the right of the *x*-axis 0% thus indicating an overall inhibitory effect. If there was no overall inhibition (null hypothesis), then the distribution should be centered on 0% of inhibition.
The counts of basophils are given in Appendix 4.
(Each value of the *x*-axis corresponds to the upper limit on the interval).

A. Spira and his collaborators analyzed the results, dilution by dilution, and found a statistically significant effect (from $p < 0.05$ to $p < 0.01$) for the dilutions $1/10^{30}$, $1/10^{32}$, $1/10^{34}$ and $1/10^{40}$. We can draw the profile of

inhibition according to the dilutions of *Apis Mellifica* in the following way (Figure 17.7).

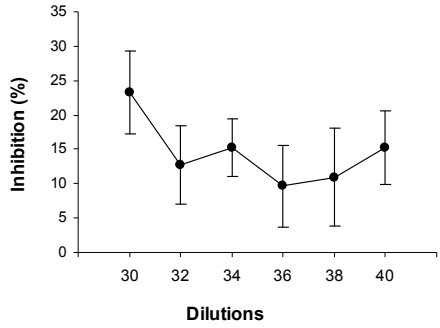


Figure 17.7. This figure is another representation of the results with *Apis mellifica*; the inhibitory effect is represented for each dilution of this product. Each point is the mean ± standard error of the mean of 19 experiments of inhibition of the degranulation with *Apis mellifica*. If the results obtained were only due to random fluctuations, we should find points on both sides of the horizontal line corresponding to 0% of inhibition.

As above, the results of both experimenters can be shown separately. If we consider results of ED who overall found a higher inhibition, 6 dilutions gave results which were statistically not different between them (Figure 17.8).

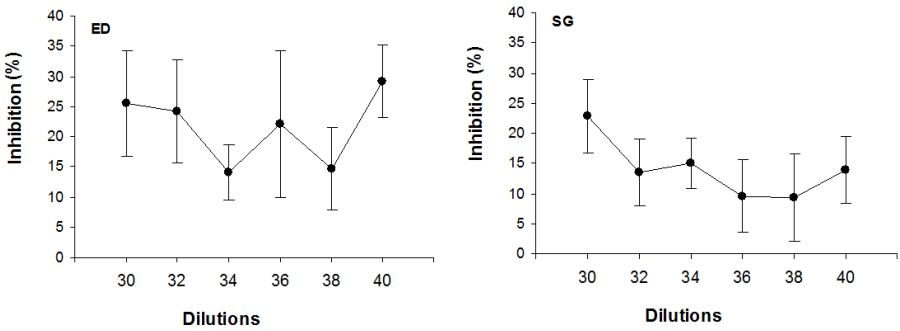


Figure 17.8. These figures show the same results as those of Figure 17.7. Simply, the results of ED and SG are shown separately. It is difficult to conclude that a given dilution has higher efficacy, even if overall the inhibition is statistically significant.

What about the law of small numbers?

As in Chapter 12, we can study the distribution of the ratio variance/mean for the 10 anti-IgG controls in each of the 18 experiments of the first series of experiments (Figure 17.9).

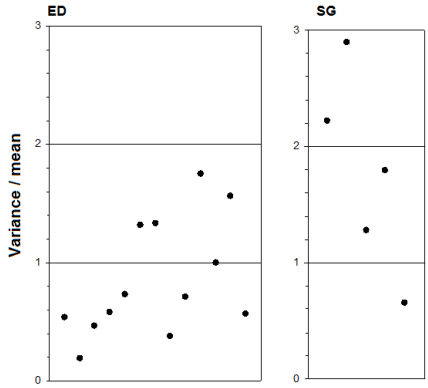


Figure 17.9. The distribution of the ratio variance/mean of the controls (anti-IgG at high dilutions) of the experiments with "direct" activation by anti-IgE is represented on this figure. Each point is the ratio of the variance of 10 anti-IgG controls divided by their mean. For the experimenter ED, we notice that the variance is lower more frequently than the mean (variance/mean < 1). See Chapter 12 for explanations concerning the interest of this representation.

One thus notices that in the 13 experiments performed by ED, 9 had a variance which was lower than the mean. In the 5 experiments of SG, 4 had a variance which was higher than the mean and two of them had a variance which was at least twice the mean. Therefore, with the "successful" ED experimenter, one finds again this notion of weak variability (here for 69% of the counts). Let us remind however that with a sampling of n=10 we should expect that 56% of the variances would be lower than the mean (cf. Chapter 12). These results are thus not incompatible with the law of small counts (if one does not take into account a possible added statistical noise).

In the conclusion of the article, the authors mentioned this issue of the conformity of the results with the law of small numbers:

> "Indeed, the variability for each of the 18 experiments of the number of basophils counted for the dilutions 21 till 30 of anti-IgG, showed that in 15 cases the test was compatible with the law

> of small numbers; in 2 cases the variance was higher to a variance conform to the law and in 1 case was lower."

This precision, which insisted on the compatibility with the law of small numbers, differed a little bit from the initial statement of A. Spira quoted at the end of the previous chapter ("It is surprising, unusual") when the first analysis were just done.

A consequence of the collaboration with A. Spira

At the end of December 1989, P. Lazar announced that he maintained J. Benveniste in his functions of director of Inserm U200 until June 30th, 1992.

According to the journal *Le Monde*:

> "This decision, taken in the context of the affair of the "memory of water", puts thus an end to the kind of testing imposed last July to Doctor Benveniste by Mr Lazar (*Le Monde* of July 8th and 12th, 1989). The latter had then recommended to Doctor Benveniste to adopt a "code of good practice" supposing in particular that he gives up for a while expressing himself on the effects of high dilutions except in high-level scientific journals in order to reconstitute a reliable capital "largely dissipated" in the eyes of his colleagues, said Mr Lazar.
> As well as Doctor Benveniste actually refrained since last July from making statements in the media, the decision of the director of INSERM could be also motivated by the fact that the results of the "second opinion" expertise led jointly for several months by doctors Benveniste and Alfred Spira (director of the unit 292 of INSERM) confirm for the moment the data published in June 30th, 1988 in the journal *Nature* on the molecular effects without molecule." [3]

There was however an important obstacle necessary to overcome: informing the scientific community on these results.

Notes of end of chapter

[1] One could also calculate for each high dilution of anti-IgE the degranulation with regard to anti-IgG at the same corresponding dilution. Close results are obtained that change nothing to the demonstration.

[2] In the first versions of the manuscript, the initials of the two experimenters were reported. In the version published in the *Comptes Rendus de l'Académie des Sciences* (cf. Chapter 19), only overall results were presented. The difference of results between SG and ED was explained in these terms in the early version of the manuscript of March 6th, 1990: "These differences of performance can be probably attributed to the longest experience of manipulation and counting of basophils of E.D. (five years) compared with that of S.G., a newcomer in this area (6 part-time months)."

[3] F. Nouchi. Une décision du directeur général de l'INSERM. Le docteur Benveniste est maintenu dans ses fonctions jusqu'en 1992. *Le Monde*, January 3rd, 1990.

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 U.S. 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

[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.

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" [1]. 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" [2].

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."[3]

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." [4]

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." [5]

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." [6]

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!" [7]

"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?" [8]

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." [9]

The note was finally sent during summer. It was returned on September 5th, 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". [10]

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." [11]

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." [12]

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 30th, 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, [13] 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"." [14]

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." [15]

"It seems that it is neither a plain artifact nor a simple error of manipulation"

The publication of these results on February 28th, 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" [16] or more macabre: " "Ghost molecules" theory back from the dead." [17]. 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." [18]

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." [19]

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." [20]

Regarding the journal *Nature*, it simply ignored this article. In a correspondence with Nature of 1991 [21], 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." [22] 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* [23], *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." [24]

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." [25]

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.[26] 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." [27]

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 19th 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.

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

[1] J. Jacques. La "mémoire de l'eau" : remarques sur le test utilisé. *C R Acad Sci (Paris)* vol 310 series II (1990) p. 1437.

[2] J.M. Lehn. *Le Monde*, June 30th, 1988. Interview by J.Y. Nau.

[3] J. Benveniste. Ma vérité sur la mémoire de l'eau, p. 103.

[4] Letter of J. Benveniste to J.M. Lehn of June 14th, 1990.

[5] Letter of J.M. Lehn to J. Benveniste of June 22nd, 1990.

[6] Letter of J. Benveniste to J.M. Lehn of July 2nd, 1990.

[7] M. Schiff. Un cas de censure dans la science, p. 144.

[8] Letter of J. Benveniste to P. Potier of July 5th, 1990.

[9] Letter of J. Benveniste to P. Lazar of July 10th, 1990.

[10] Letter of J. Benveniste to P. Potier of September 21st, 1990.

[11] Letter of J. Benveniste to P. Potier of December 3rd, 1990.

[12] J. Benveniste. Ma vérité sur la mémoire de l'eau, p. 104.

[13] 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.

[14] Press release of *Agence France Presse* of March 1st, 1991.

[15] M. Schiff. Un cas de censure dans la science, p. 118.

[16] M. Vigy. Quand la mémoire de l'eau refait surface. *Le Figaro*, March 1st, 1991.

[17] D. Concar. "Ghost molecules" theory back from the dead. *New Scientist*, March 16th, 1991.

[18] 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 2nd, 1991.

[19] Letter of J. Benveniste to P. Lazar of February 27th, 1991.

[20] Letter of P. Lazar to J. Benveniste of March 29th, 1991.

[21] H. Timmerman. *Nature*, August 29th, 1991, p. 751.

[22] J. Benveniste. Publicity and controversial data. *Lancet* 1990;336:944.

[23] J. Benveniste. *Nature*, October 1991, p. 787.

[24] E. Fottorino, La mémoire de l'eau. Du rêve au soupçon. *Le Monde*, January 21st, 1997.

[25] Julien Naël. Portrait : Alfred Spira, la santé publique en bandoulière. *La Recherche*, March 2001, p. 25.

[26] 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 21th, 1997).

[27] J. Benveniste. Ma vérité sur la mémoire de l'eau, p. 210.

Chapter 20. The revived passion of *Nature* for high dilutions

"Our results contain a source of variation for which we cannot account"

One would have thought that *Nature* had turned over a new leaf on "Benveniste's affair". It was the case indeed for any result from the laboratory of Clamart. Nevertheless, the works of other scientists on high dilutions were obviously considered by *Nature*. The condition, of course, was that their conclusions should be in keeping with the editorial team of the journal. [1]

Indeed, early December 1993, an article signed by researchers of London (J. Hirst, N.A. Hayes, J. Burridge, F.L. Pearce and J.C. Foreman, of *University College London*) was published in *Nature*. The article was a remake of the article on high dilutions of 1988. Its conclusion was – one could expect it – at the opposite of the article of 1988.

Strangely, as an ultimate ceremony of purification, the journal once again used the famous unusual column entitled *Scientific Paper* and the title of the article was the same as the one in 1988, but under a negative form. Except the layout of the journal which changed between these two dates, the comparison of both titles, with a 5-year interval, is eloquent:

Nature June 28th, 1988


816 SCIENTIFIC PAPER NATURE VOL. 333 30 JUNE 1988

Human basophil degranulation triggered by very dilute antiserum against IgE

E. Davenas, F. Beauvais, J. Amara*, M. Oberbaum*, B. Robinzon†, A. Miadonna‡, A. Tedeschi‡, B. Pomeranz§, P. Fortner§, P. Belon, J. Sainte-Laudy, B. Poitevin & J. Benveniste‖

Nature December 9th, 1993


SCIENTIFIC PAPER

Human basophil degranulation is not triggered by very dilute antiserum against human IgE

S. J. Hirst*, N. A. Hayes*, J. Burridge†, F. L. Pearce‡ & J. C. Foreman*§

Departments of * Pharmacology, † Statistical Science and ‡ Chemistry, University College London, Gower Street, London WC1E 6BT, UK

The only bibliographical reference quoted in the article of Hirst *et al* was the article of *Nature* of 1988. The article of 1991 in the *Comptes Rendus de l'Académie des Sciences* was ignored contrary to the most elementary scientific and academic rules.

The method used to present the results was the same as for the investigation report of 1988: the conclusion was given at the beginning so that the reader saves time.. Indeed, having looked at the title in the negative form, the reader knew, from the first paragraph onwards, the conclusion of the article:

> "We have attempted to reproduce the findings of Benveniste and co-workers […]. The results were contrary to conventional scientific theory and were not satisfactorily explained. Following as closely as possible the methods of the original study, we can find no evidence for any periodic or polynomial change of degranulation as a function of anti-IgE dilution. Our results contain a source of variation for which we cannot account, but no aspect of the data is consistent with the previously claims."

The readers who pursued the reading beyond the title and the first paragraph were surely not many to do so. Furthermore, the article was rather unclear and it was necessary to be extremely motivated to be able to understand all the experimental details. It is what we will do in the next chapter and, in particular, we will try to decipher what the authors meant by this mysterious "source of variation" that they could not explain. In the present chapter, we describe only the circumstances of the publication of this article and its consequences.

Of course, in this issue of *Nature* there was not any question of a possible on-site inquiry with diligent investigators and self-proclaimed "experts". Because the data fitted the "expected" results, it was – in the logic of goat and unicorn as developed by J. Randi – naturally useless. Indeed, with the article of Hirst *et al*, one was obviously in the case of the goat. As for the unicorns (namely, effects of high dilutions), everybody "knows" that they do not exist. One would then wonder, if these results were totally expected, why they were published in *Nature* which is always parsimonious of its editorial space.

When fair play is not British any more

J. Benveniste was furious. After the refusal of the article cosigned with A. Spira, it was a new affront of *Nature* which took advantage of its position of power. J. Benveniste noted that the experimenters introduced numerous technical variations which could jeopardize the success of the experiment. To better understand the reported results, in particular to understand what was this strange "source of variation", he requested in writing to J. Burridge, the

statistician of the team, and to the other authors, to quickly communicate the raw data of the counts of basophils to him in order to analyze these results and then to send an appropriate answer to *Nature*:

> "Professeur Spira and myself ask you to kindly communicate the raw data corresponding to the recent Nature article by the fastest means available, including using our telecopy […] or sending a computer disquette [*disk*]. We are ready to send you our data of the 1991 C. R. Acad. Sciences and to come to London to compare our data with yours." [2]

J. Benveniste pursued his letter by criticizing the modifications of the original protocol and the absence of reference to the article of the *Comptes Rendus*. The answer at the request of J. Benveniste arrived only on January 11th although the letter was dated December 14th. It was signed by all authors of the article:

> "We are really only prepared to give our raw data to an independent, professional statistician. The raw data was offered to the reviewers of our Nature paper. We have no comments to make on the methodology except to say that that we followed as closely and carefully as was possible the method in your original Nature paper;
>
> We do not accept that there has been any misrepresentation, in our article, of your Nature paper.
>
> We conducted our study at the request of the Research Council for Complementary medicine. We do not intent to pursue any further investigation and, as far as we are concerned, our contribution is complete and the matter closed." [3]

J. Benveniste immediately and briefly answered that "Prof. Spira, an independent professional statistician, is awaiting the data" while specifying that "there are 14 points of discrepancies between our methods and yours." [4]

Of course, J. Benveniste and A. Spira newer saw the raw data. J. Benveniste drafted nevertheless with A. Spira an answer to *Nature* resuming each of the litigious points. The answer of J. Maddox to these comments arrived on… July 22nd and a letter of J. Benveniste, B. Ducot and A. Spira was finally published on August 4th, that is eight months after the article of Hirst *et al.* A text of J. Maddox (unsigned) accompanied the response of J. Benveniste. In his text, J Maddox reminded that many "discoveries" have never been reproduced and have now been abandoned. He ended by:

> "It is unfortunate, and a little sad, that Benveniste and his colleagues do not appreciate the parallel. Correctly, Hirst *et al* did not conclude in their article that Benveniste was mistaken, but merely that their reasonable test of his conclusion failed to support it." [5]

And if, one more time, the key for reading of J. Maddox prevented him to see an unexpected aspect of the results of Hirst *et al* (well hidden in the article, admittedly)?

Notes of end of chapter

[1] In 1989, in an unsigned editorial, *Nature* returned on "the affair" at the moment when the direction of Inserm decided the fate of the Unit 200. The author of this editorial – J. Maddox apparently – noted: "*Nature* in the past year has been sent for publication a single paper reporting similar observations with a different system, now with its authors for further clarification, but may well have discouraged others by its treatment of Benveniste's contribution" (Can heresy be real? *Nature*, July 13th, 1989, p. 82).

With a disarming frankness, the editorial writer thus recognized that the "treatment" of high dilutions by *Nature* could indeed have dissuaded other researchers to undertake research in this field or to submit their results to *Nature*. We will see in this chapter that all scientists were not "discouraged" if their conclusions were at the opposite of those of J. Benveniste.

[2] Letter of J. Benveniste to J. Burridge and other coauthors of December 9th, 1993.

[3] Letter of S.J. Hirst, N.A. Hayes, J. Burridge, F.L. Pearce and J.C. Foreman to J. Benveniste of December 14th, 1991.

[4] Letter of J. Benveniste to S.J. Hirst of January 11th, 1994.

[5] Replication defined. *Nature*, August 4th, 1994, p. 314.

Chapter 21. "A source of variation for which we cannot account"

The extreme skeptic pays no attention to the simple common sense, he knows that when the presumed order of the world seems threatened, the reason grants him an unlimited overdraft."

B. Méheust[1]

Nature having successively killed the article of 1988 and the article written in association with A. Spira – mainly on statistical arguments – one could suppose that the article of S. Hirst *et al* was indisputable on this point. Of course, one would be curious to know the comments and remarks of the experts who reviewed this article. Unfortunately, we did not get the pleasure of reading them.

However, although the raw data were not released by the authors, we can find rather easily the experimental outcomes that allowed the statistical analysis, through the graphs of the article. Furthermore, a statistical report of J. Burridge from the department of Statistics was drafted in March 1992 and noticeably enlightens these results. [2, 3]

It is thus by confronting the text of the article, all results deducted from figures and the statistical report of J. Burridge that we are going to be analyzing this article and showing that this latter could be a textbook case.

The experimental protocol

Thirty-six working sessions were performed by Hirst *et al* for the 3 types of dilutions (Table 21.1). One session was performed in one day.[4] The first experiments began on early June 1990. The samples of blood were obtained from 11 blood donors who could participate in more than one session: five participated once and one participated nine times. Basophils were counted by a single "trained" experimenter.

	Type A Dilutions of Anti-IgE (shaken)	*Type B* Dilutions of anti-IgE (not shaken)	*Type C* Dilutions of solvent (shaken)
1 control + 1 anti-IgE dilution 10^2 + 8 high dilutions $1/10^{12}$, $1/10^{14}$ … $1/10^{26}$ = 30 counts	5 sessions	4 sessions	3 sessions
1 control + 1 anti-IgE dilution 10^2 + 8 high dilutions $1/10^{30}$, $1/10^{32}$ … $1/10^{44}$ = 30 counts.	5 sessions	4 sessions	3 sessions
1 control + 1 anti-IgE dilution 10^2 + 8 high dilutions $1/10^{46}$, $1/10^{48}$ … $1/10^{60}$ = 30 counts.	5 sessions	4 sessions	3 sessions

Table 21.1. Summary of the plan of experiments of Hirst *et al.* There were 36 sessions. Each session corresponds to one working day with the preparation of cells, preparation of the series of dilutions, incubation of cells with dilutions and finally counting of basophils. Each session was dedicated to the study of a series of 1/100-dilutions for one of the types of dilution (antiserum anti-IgE diluted with shaking, antiserum anti-IgE diluted without shaking, solvent diluted with shaking) and for one of the 3 ranges of dilutions (3 ranges were defined between $1/10^{12}$ and $1/10^{40}$).

Each session included 30 counts of basophiles. The report of J. Burridge gives an example for a session "diluted and shaken anti-IgE" (Figure 21.1). The continuous lines between tubes were intended to show how tubes were "connected" by the successive dilutions. Consequently, to each dilution (of anti-IgE or solvent), 3 counts of basophils corresponded. It is the means of these triple counts that are presented in the figures of the article.

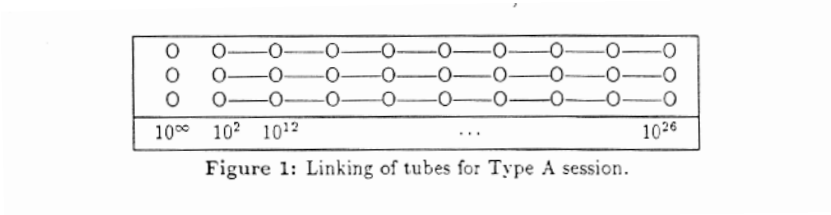


Figure 1: Linking of tubes for Type A session.

Figure 21.1. This figure extracted from the report of J. Burridge corresponds to an experiment of Type A (diluted and shaken anti-IgE) and of "rank 1" (i.e. high dilutions from $1/10^{12}$ to $1/10^{26}$). The sessions of Type B were identical except that tubes were not shaken between each dilution. For the sessions of type C, *the only tubes that contained dilutions of anti-IgE were 3 tubes at dilution $1/10^2$*; the 27 other tubes of the sessions of Type C contained the solvent serially diluted in solvent with shaking between each dilution.

A textbook case

Before going farther, we have to overcome the hurdle of Figure 1. Indeed, the first figure, which the reader saw on the first page after having read the title and possibly the lead paragraph, is reproduced in Figure 21.2.

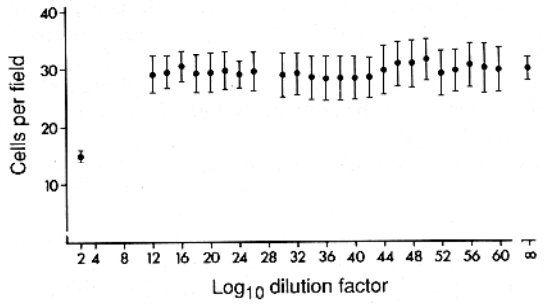


FIG. 1 Mean cell densities (with standard errors) as a function of dilution for all the data. The data for succussed anti-IgE, unsuccussed anti-IgE and succussed buffer have been combined. For the buffer control (10^{∞}) and anti-IgE dilution 10^{2}, $n = 108$; for the other anti-IgE dilutions, $n = 36$.

Figure 21.2. Comment: *succussed* = shaken according to the homeopathic wording that names "succession" the shaking of solution between each dilution.

At first sight, this first figure of the article was coherent with the title because a quick examination seemed to indicate that high dilutions hardly modified the counts of basophils. However, an attentive reading of the text and the figure legend showed that in fact the results of the three series of data were – contrary to usual and good scientific practices – presented by their *common means*! The legend of the figure indeed specified that the data "have been combined"!

But, this way of "presenting" results did not apply to anti-IgE with a classic dose (which is the point on the extreme left of the graph: $1/10^{2}$)! Indeed the latter was present in all sessions (whatever the type of session: A, B or C). The first impression was thus strengthened since the number of basophils in the presence of anti-IgE with classic dose ($1/10^{2}$), an active one, had considerably decreased. The reader who was accustomed to "normal" presentations of scientific graphs was deceived because he supposed that classic doses of anti-

IgE at high dilution of anti-IgE *were presented on an equal footing, which was not the case.*

It is useless to impute motives, but if one did not want to highlight a "signal" by flooding it in the "background noise", one would not have done so otherwise. [5]

Some very different clouds

Let us resume the results of the article which are represented in the form of the means of the 3 percentages of degranulation corresponding to each dilution (see figure 21.3).

To each dilution of anti-IgE (or solvent), there were 3 counts of basophils (= a triplicate). The article reported the averages of these triplicates. For 30 sessions, there were thus 8 × 30 = 240 percentages of degranulation with high dilutions. If there was no difference between a "control" well and a "high dilution" well, we should expect that the percentages of degranulation fluctuated around 0%, because, according to this hypothesis, high dilutions were supposed to have no effect. In statistics, this is known as the null hypothesis.

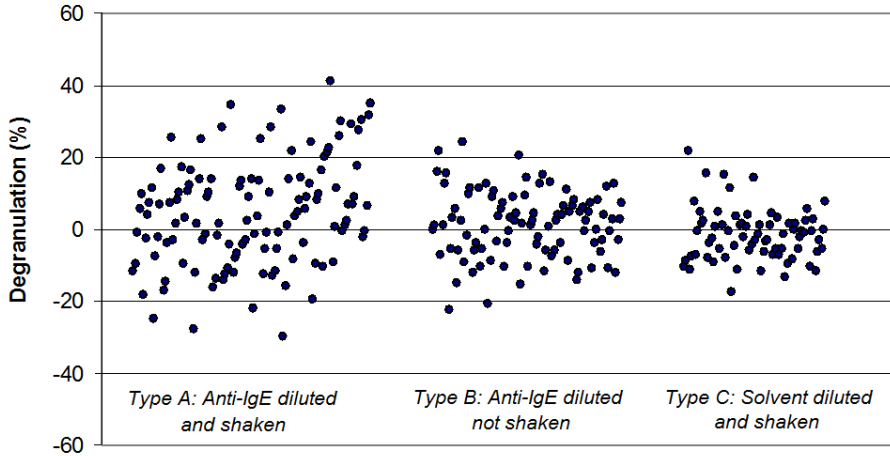


Figure 21.3. Degranulation corresponding to each experimental point was obtained from Figure 2 of the article of Hirst *et al* (1993). Each point is the mean of 3 experimental points with high dilution. We notice that the 3 "clouds" have very different shapes. This suggests that the type of high dilutions had an influence on the counts of basophils.

Nevertheless, even a non-experienced eye notices that the 3 series of experiments (diluted and shaken anti-IgE, diluted and not shaken anti-IgE and

diluted and shaken solvent) did not identically behaved (Figure 21.3). The percentages of degranulation of the diluted and shaken solvent seemed less scattered. In contrast, the cloud of points of diluted and shaken anti-IgE was very scattered and it seemed to contain more positive than negative percentages. The cloud of points corresponding to diluted and not shaken anti-IgE was in an intermediate situation. The calculation of the averages and the standard deviations confirms this impression:

Diluted and shaken anti-IgE:	4.5 ± 14.7 %
Diluted and not shaken anti-IgE:	1.1 ± 9.3 %
Diluted and shaken solvent:	-1.7 ± 7.1 %

Let us build the distributions of the results

As regards the evidence of an effect with high dilutions, the A and C series (diluted and shaken anti-IgE and diluted and shaken solvent) are enough for this analysis (indeed, series B tested the necessity of shaking tubes to obtain an effect). Let us classify each of the points: degranulation from 0 to 9%; 10 to 19%; 20 to 29%, etc. and let us count how many points belong to each class. We then obtain the distributions of Figure 21.4.

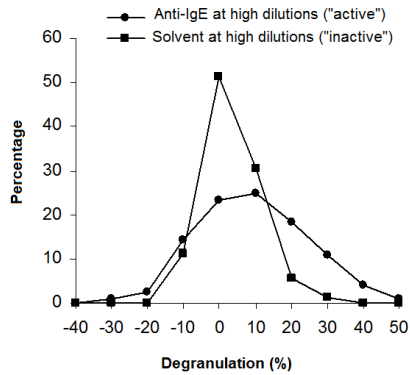


Figure 21.4. This figure is built from the results of Figure 21.3 for diluted and agitated anti-IgE (type A) and for diluted and agitated solvent (type C). The frequency of the counts is calculated for every class of percentage (every point on the *x*-axis corresponds to the upper limit of the interval). One clearly highlights here (whatever was the cause) a difference of the distribution of counts according to high dilutions of anti-IgE (supposed to be "active") or high dilutions of solvent (supposed to be "inactive") prepared in the same conditions. Nevertheless, the authors of the article refused to envisage the possibility that these differences were an argument in favor of an effect of high dilutions of anti-IgE.

We thus notice that the two populations are different. We observe a shift of the distribution towards higher degranulations when basophils were in the presence of high dilutions of anti-IgE. A statistical analysis shows that both populations are significantly different. In other words, it looks like an effect of high dilutions of anti-IgE!

Furthermore, thanks to the series of diluted but not shaken anti-IgE (type B; not represented on the Figure 21.4), the authors showed that high dilutions obtained with shaking were more active than high dilutions, which were performed without shaking! It is difficult to completely homogenize a solution by not shaking it, what could explain the small "degranulating" activity – although statistically not significant – that seems to have been passed on during the process of "dilution without shaking".

The three series of measurements thus appeared to be very different and it was indeed what the statistical calculations of Hirst *et al* indicated! Indeed, the authors reported this table that summarized the p-values (statistical significance) after an analysis of variance according to the type of treatment (Table 21.2).

Table 6: ANOVA Tests*(*p*-values) For Differences Between Dilutions Separately For Each Session

Treatment Type	High Dilution Range		
	$10^{12} - 10^{26}$	$10^{30} - 10^{44}$	$10^{46} - 10^{60}$
A	0.34	0.028	0.34
(combined "Fisher"	0.066	0.018	0.21
p-value = 0.0027)	0.14	0.42	0.17
	0.0043‡	0.42	0.21
	0.70†	0.80	0.40
B	0.56	0.25	0.27
(combined	0.27	0.97	0.27
p-value = 0.086)	0.0073**	0.76	0.16
	0.084	0.48	0.44
C	0.92	0.80	0.66
(combined	0.25	0.25	0.21
p-value=0.85)	0.65	0.91	0.72

* ANOVA tests used the one-way F-test with (8, 18) degrees of freedom, using control and high dilution treatments in each session, ie the 10^2 dilutions were excluded.

† The missing value in this session means that the F-test used (8, 17) degrees of freedom.

‡ See Fig. 6.

**See Fig. 7.

Table 21.2. This table comes from the report of J. Burridge. It was reproduced in the article of Hirst *et al* without major change. There are the same data in Table 21.3 in a simplified and commented version.

Treatment	*p*-value (statistical significance calculated by J. Burridge)	Interpretation (not in the article)
Treatment Type A (anti-IgE diluted and shaken)	0.0027	Very significant
Treatment Type B (anti-IgE diluted but not shaken)	0.086	Not significant (trend)
Treatment Type C (solvent diluted and shaken)	0.85	Not significant

Table 21.3. Simplified and interpreted version of Table 21.2. The statistical tests (variance analysis) performed by J. Burridge indicated (whatever was the cause) that high dilutions of anti-IgE did not have the same effect – with a high statistical significance – compared to control dilutions performed in the same conditions. Interestingly, one notes that agitation appears necessary to observe an effect with high dilution. In spite of these results, Hirst *et al* concluded that the significance of these tests was probably the result of a "statistical artifact".

In other words, the percentages of degranulation were not null for high dilutions of anti-IgE. In contrast, high dilutions of solvent were not significantly different from 0. If there was no experimental bias, this indicates that cells did not have the same behavior in the presence of high dilution of anti-IgE or in the presence of a control.

In the statistical report, J. Burridge commented on these results:

> "According to conventional scientific theory there should, within a session, be no differences between the control treatment and the eight high dilutions "treatments". […] Such an hypothesis can be tested, separately for each session, by applying the conventional ANOVA F-test to the mean counts for each tube […]. The resulting p-values are given in Table 6. These results are curious. They should, if the null hypothesis is correct, to be uniformely distributed between 0 and 1. This does not seem to be the case for treatment A and B for which the p-values are collectively too small."

J. Burridge even considered a possible effect of high dilutions!:

> "Table 6 and Figure 6 and 7 suggest that triples differ from each other. The reasons for this are at present obscure. One interpretation is that there are, after all, differences between treatments – for some sessions and subjects at least."

Let the reader relish this "after all". Having quickly pushed aside this hypothesis which seemed obviously unthinkable to him – but what his statistical analysis was nevertheless supposed to assess! - J. Burridge pursued:

> "The most plausible explanation of these effects is that some as yet unidentified feature of the experimental procedure tends to make triples differ from each other in some random or haphazard way. It is possible that the serial dilution procedure is responsible for this effect – although it is hard to see how."

If we summarize the method of J. Burridge, our reason forbids us to consider the possibility of an effect with high dilutions, therefore another cause exists – but an "unidentified" one – related to the experimental procedure! Once again, the spirit of Descartes paradoxically crossed the Channel: "And the demonstrations are so certain that, even if experience seemed to show us the contrary, we would nevertheless be obliged to place more faith in our reason than in our senses." [6]

The criticisms (not published) of the statistician J. Burridge towards the article, of which he was co-author

Obviously, the expertise of the statistician J. Burridge was used *after* the results were completed. What seems certain is that he did not participate to the design of the experimental protocol. He repeatedly complains in his report about defects in the design of the protocol thus leading to a delicate analysis. His main criticisms were the following ones:

1) No randomization between sessions:

> "[…] there are some features which make analysis somewhat awkward and others which make the interpretation problematic at times. For example, no attempt appears to have been made either to randomise the time order of the sessions or to balance the ranges within each treatment type with respect to volunteers. Thus the type A sessions were done first, the type B followed by type C. Similarly, within each type, range 1 sessions were done first, then range 2 followed by range 3. The allocation of volunteers to sessions was unavoidably haphazard. The lack of randomisation of the order of the sessions is an inconvenient feature of the experiment and mean that certain "treatment" effects could be attributable to trends over time (due in particular, perhaps, to learning effects acquired by the experimenters during the course of the experiment".

2) The "links" between the dilutions were "broken":

> "[…] for most sessions the tubes were "linked" by the serial dilution procedure. Such linking means that the results for successive dilutions might be serially correlated within a series of nine dilutions so that ideally these series should be analysed as single entities with their own mean and covariance structure. However, the linking was not recorded during the subsequent randomisation procedure and so cannot be properly accounted for in the statistical analysis."

Yet, concerning this second point, one of the results highlighted in the article is that there was no periodicity for degranulations according to dilutions. Nevertheless, J. Burridge implicitly recognized that the authors of the article did not give themselves the means to analyze this precise point. Indeed, when tubes were blinded, it has been not noted to which of the three serial dilutions these tubes belonged (see the "links" between the dilutions for each of the three series of dilution on Figure 21.1). It is quite possible that the authors of the article did not think that they would need to analyze the periodicity because they did not envisage that a significant global effect would be observed. It is likely that the differences of effect of the various treatments surprised the authors of the article and that they tried "to sweep them under the carpet" by insisting on the absence of degranulation "waves" as described in the article of *Nature* in 1988.

How did the authors of the article overcome this difficulty to nevertheless "demonstrate" – in spite of their results – that high dilutions of anti-IgE were without effect?

A "statistical artefact"…

Of course, these criticisms of J. Burridge about the issues of methodology were not reported in the article. Even though the authors correctly summarized the description about the different behaviors of the 3 treatments (corresponding above to "According to conventional scientific theory… the p-values are collectively too small"), they never considered the possibility that the observed effect could be due to high dilutions of anti-IgE. To explain these unexpected differences between treatments, the authors introduced a new and curious notion: a "statistical artifact":

> "Although it is possible that these observed effects are a statistical artefact, some unidentified part of our experimental procedure might account for them. It is an interesting feature of our data but it does not, of course, lend any support to the findings of Davenas et al., and serves once again to underscore the complexity of the analysis of variance in an assay of this type."

The very original notion of "statistical artifact" played the role of a wild card. As unexpected results were obtained, the "statistical artifact" allowed refuting them without explanation. Furthermore, the authors seemed to complain that everything could not be checked, that the experimental protocol could play tricks on them and that these analyses were so complicated…

But all these considerations did not prevent the authors to impudently conclude the article with this sentence:

> "We have been unable to find any evidence that very high dilutions of anti-IgE, succussed or unsucussed, cause any reproducible effect on the degranulation of human basophil leukocytes."

This conclusion was thus in disagreement with the reported results. If the authors were aware that their experimental protocol contained weaknesses and was not thus capable of answering the question that was asked, they were free to explain it (by reporting the criticisms of the report of J. Burridge on which the article is tongue-tied). But would their results then have deserved to be published in the pages of *Nature*? In the end, it is the strategy "everything but the results of Benveniste" that has prevailed.

The arguments of J. Benveniste and A. Spira

It was on a unique column that J. Benveniste and A. Spira gave their comments in *Nature* and, as already said, eight long months after the publication of the article.[7] They noted fifteen differences between the methodology of Hirst *et al* and the one of the article of *Nature* of 1988 but, given the limited space, they only pointed out the most important differences. Thus, Hirst *et al* included in their analysis all experiments, including those for whom the percentage of degranulation with anti-IgE at a classic dose was low. J. Benveniste explained again that, if one did not observe a degranulation with anti-IgE at classic doses, there was little chance to observe an effect with high dilutions of anti-IgE.

Another criticism expressed by J. Benveniste and A. Spira was about assessing in separated experiments the various treatments that one wished to compare. It was the most importing reproach because it is at the heart of the reasoning in experimental biology to vary only one factor at the same time. The correct procedure would have been to compare the high dilutions of anti-IgE and high dilutions of the solvent in the same session. Finally, a step of centrifugation had been added after cell incubation with high dilutions. This procedure might have increased the variability of the counts.

Secondly, J. Benveniste and A. Spira questioned the statistical method and pointed out the "tactics" used to mask the statistically significant differences.

Finally, they insisted that the authors refused to communicate the raw data of the experiments.

The exercise of the criticism was however delicate. One could not indeed blame the authors for not having respected the original experimental protocol and asserting at the same time that the results proved nevertheless the existence of an effect of high dilutions.

In the press, J. Benveniste expressed himself in a more direct way by asserting that Hirst *et al* "committed several methodological and ethical errors".[8] For the famous "Figure 1" in particular, he considered that it was "a manipulation unprecedented in the history of science (combination of results of active and control samples)."

Then, he continued:

> "Also unethical […] is the fact that I was not approached for the adjustment of the numerous details necessary for the good practice of so complex experiments and that I learnt the existence of this article only by the press. It is extremely surprising to see a journal as *Nature*, which portrays itself as an archetype of the excellence and of the scientific integrity, be engaged in such a manipulation. The question is: what are the real motives?"

More technical, A. Spira declared:

> "All in all […] I do not think that these results are contradictory with ours and I think that it would be necessary that we can exchange our raw data so as to compare the results of both series of experiments by using the same strategy of statistical analysis".

Exchanging data, comparing results, is not this called doing research? But was it the concern of the authors and those who promoted the publication of this article? [9]

Comparison with the results of the article of the Comptes Rendus de l'Académie des Sciences

The comparison of these results with those of the study done with the collaboration of the team of A. Spira and published in the *Comptes Rendus de l'Académie des Sciences* is quite unexpected. Indeed, the presentation of the results as distributions of percentages of degranulation leads to similar profiles (Figure 21.5).

It is extremely strange to notice that results, which in fact are very similar, were interpreted with opposite conclusions. In both cases, high dilutions had a behavior different from that of control dilutions and the "sinusoidal" curves

were not present. We remember that J. Benveniste had said: "once again we obtain the results published in *Nature*. It is the same girl, as beautiful as ever. She only lacks a bit of makeup." [10] But for Hirst *et al* this absence of "makeup" is a decisive argument to state: "We can find no evidence for any periodic or polynomial change of degranulation as a function of anti-IgE dilution" and that consequently in no case one could assert that the results of J. Benveniste had been confirmed. [11]

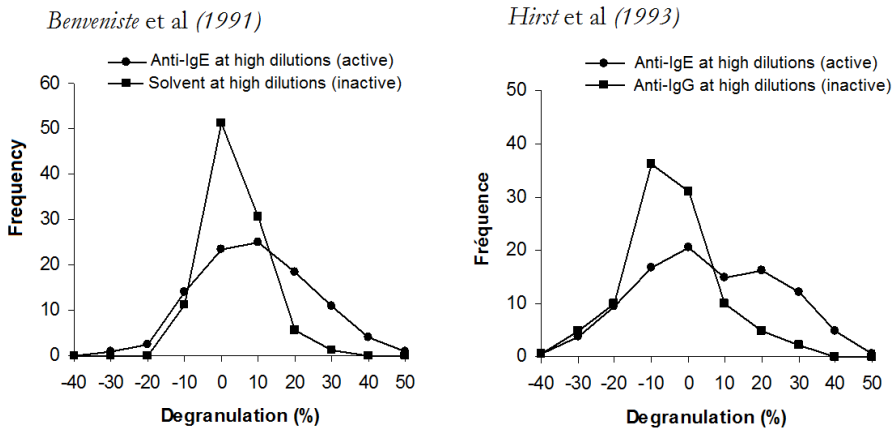


Figure 21.5. Comparison of the results of the article of J. Benveniste and A. Spira [12] of 1991 in the *Comptes Rendus de l'Académie des Sciences* and those of Hirst *et al* of 1993 in *Nature*. Very close results were obtained but the conclusions of the authors were diametrically opposed for a possible effect of anti-IgE at high dilutions.
(Each point on the *x*-axis corresponds to the upper limit of the interval).

J. Maddox and the "Popperian spirit"

To finish on the relationship of J. Benveniste and the journal *Nature*, we will conclude on a thought, in the form of a prediction, that J. Maddox had inserted into the long final comment of four pages that he wrote (not cosigned by the other investigators) in the issue of *Nature* of October 27th, 1988.

Indeed, in September 1988, J. Maddox wrote to the Israeli, Italian and Canadian teams to ask them if they wished to comment on the events of the previous months.[13] The team of Toronto answered in particular that it pursued the research on high dilutions in a "Popperian spirit". J. Maddox added in his final text of October 27th that he would be "glad to publish as Scientific Correspondence the general conclusion of any or all of these groups when they are ready." [14] Then, about J. Benveniste and his team, he formed the wish that

this latter "will now counting basophils in replicate, following the standard procedure for controlling sampling errors, and will be eliminating unavoidable observer bias by making blind experiment a routine".

Finally, he concluded:

> "I expect that these results will not differ substantially from those obtained in the three blind experiments (each with two observers) at Clamart on 9 and 10 July (*sic*)[15]; it will be extremely interesting if it should be otherwise, but no doubt that Dr Benveniste would prefer to publish in some other journal."

The first prediction of J. Maddox did not come true. Indeed, during the series of experiments done in association with A. Spira and his team an effect associated with high dilutions was observed in much more rigorous experimental conditions than for the experiments quoted by J. Maddox.

The second prediction did not come true either. Indeed, as we saw above, the manuscript reporting these experiments has been indeed proposed to *Nature*. We have noticed how J. Maddox again disqualified these results. We saw how in contrast the article of Hirst *et al* crossed the barrier of the experts apparently without too many difficulties despite legitimate questions that should have been raised if the same criteria had been applied as for the article of J. Benveniste and A. Spira.

The Popperian spirit consists in questioning and in testing one's own convictions in the light of the experiment. It seems that for J. Maddox the Popperian spirit applies to all scientists, except however for the director of *Nature*.

Notes of end of chapter

[1] B. Méheust. Somnambulisme et médiumnité, tome II, *Les Empêcheurs de Penser en Rond / Synthélabo*. 1998.

[2] J. Burridge. A repeat of the "Benveniste" statistical analysis. Department of Statistical Science. University College London. Research Report N° 100, March 1992.

[3] This report was kindly communicated to me in 2001 after simple request to the secretariat of the Department of Statistics of *Royal College of London*.

[4] The experimenters cut the experiments according to this design most probably because they considered that an experiment including 30 wells was sufficient for one working day. It is a pity that they did not benefit from any advice and assistance of W. Stewart who had a more Stakhanovite conception of the counting of basophils…

[5] A possible explanation of this statistical "approach" could be that the variance of the counts would be increased if some "active" dilutions modified the numbers of the basophils in comparison with the "inactive" dilutions. It remains that this approach is quite unusual.

[6] R. Descartes. Principes de la philosophie (1644).

[7] J. Benveniste, B. Ducot and A. Spira. Memory of water revisited. *Nature*, Auguts 4th, 1994, p. 322.

[8] F. Nouchi. Une équipe de chercheurs anglais n'a pu reproduire les travaux du docteur Benveniste sur la « mémoire de l'eau ». *Le Monde*, 11 décembre 1993.

[9] Nevertheless, it seems that the manuscript required some improvements since it was received by the journal on April 16th, 1993 and accepted on October 22nd, 1993.

[10] M. de Pracontal. Les mystères de la mémoire de l'eau, p. 200.

[11] This incoherence between the results and the conclusions of the authors was nevertheless noticed by some scientists. In particular independent analyses from Italo Vecchi as well as those of Jean-Pierre Pharabod could be read on Internet shortly after the publication of the article of Hirst *et al.* These analyses led to the same conclusions, namely that the null hypothesis (i.e. no difference between controls and "active" samples) must be rejected; consequently the results contradicted the title of this article.

[12] For the results of J. Benveniste and A. Spira, the percentages of degranulation within every experiment are calculated with the mean of the counts of highly diluted anti-IgG.

[13] The Israeli team answered in two waves. First of all, B. Robinzon explained that it was difficult for him to comment on an investigation which he did not attend (letter of September 18th, 1988 to J. Maddox). Then, while commenting on several technical points, he reaffirmed his conviction that "a biological phenomenon was observed, not an artifact, although it is one for which there is no explanation". He concluded: "I did not comment until now […] since I do not think that it is for us to prove if the phenomenon we observed was real or an artifact, especially after your report discredited us". He asked however to J. Maddox not to publish his letter. J. Amara and M. Oberbaum answered after at lenghth by resuming several technical points and they complained too about the treatment by the British journal of the works on the high

dilutions which according to them "is not such as befits a journal of *Nature*'s calibre regarding scientific work" (letter of J. Amara and M. Oberbaum to J. Maddox of December 11th, 1988).

The Italian team answered at the beginning of October to J. Maddox and blamed the "unfair" treatment of its contribution.

[14] J. Maddox. Waves caused by extreme dilution. *Nature*, 27 octobre 1988, p. 760.

[15] The investigators left on Friday, July 8th, 1988; J. Maddox meant about Thursday, 7th and of Friday, 8th.

Chapter 22. "Their baby is in my bath"

"Benveniste should have recognized this anteriority"

Even if J. Benveniste in advance assumed all the risks related to the highlighting of his person, his assertive attitude as the only one to be able to extract the research in homeopathy from the darkness where, according to him, it stagnated was a motive of irritation for some "homeopaths" who participated in these studies. As a consequence, there were many repeated attempts to remind him that he was not the first one to experiment in this domain and thus – implicitly – that he could not take advantage of having "invented" the high dilutions, what his statements sometimes suggested.

To understand these questions of anteriority, which seem to have fed certain resentment, it is necessary to return to the origins of the story. We have already seen at the beginning of Chapter 2 that two research programs were simultaneously performed for both rival homeopathic firms Boiron and LHF (Boiron absorbed LHF in 1988).

Here is the chronology of the events that according to P. Belon, scientific director of Boiron, led to the experiments with high dilutions on basophils:

> "Jean Sainte-Laudy worked with us [Boiron] since 1981 on high dilutions inhibiting degranulation. We looked for an independent laboratory to duplicate these results. In 1982, we met Benveniste. He hesitated before accepting it the next year. In 1984, during a scientific congress in Florence, we presented our model and published an article in the *Journal de l'homéopathie*. This time, Benveniste lost his mind. He decided to publish on the subject. The affair with *Nature* harmed us a lot." [1]

And he specified:

> "If the first version of the article of *Nature* article, which was based on the model in inhibition, had been published, then Benveniste should have recognized this anteriority."

These words made J. Benveniste blow up:

> "Their baby is in my bath! Saying that the system would work in inhibition but not in activation is anti-scientific. Finally, Sainte-Laudy cannot have the anteriority. I have been working on degranulation since 1975. He practices my test. He even paid me royalties at the beginning. In 1984, at the Congress of Young

> Researchers, at Lille, I signed a paper on inhibition with Bernard Poitevin and Professor Aubin, then another one in the Journal of Clinical Pharmacology." [2]

We certainly are not discussing questions of anteriority concerning the discovery of insulin or the elucidation of DNA structure. Furthermore, it is about a phenomenon which has not yet found a satisfactory explanation. It is also advisable to add that, for the reader who is not really familiar to the habits of the scientific community, these considerations can seem rather narrow-minded. Nevertheless, this precision allows us to correct the cliché which was very widespread in this context of a research "bankrolled by the homeopathic industry". The reality was, as we can see, obviously different.

It is indeed indirectly that J. Benveniste became interested in homeopathy. It was by the common point of high dilutions that he was connected with it. In fact – and he expressed it on numerous occasions – he did not look "to prove homeopathy". If there were some points of convergences, this did not disturb him. But for him, the approach of Hahnemann – "father of homeopathy" – was not a scientific and rational approach. According to J. Benveniste, if the effects of high dilutions eventually were to be proven, this could be nevertheless the end of homeopathy. For homeopathic physicians and industrialists of homeopathy, this point of view was naturally unthinkable. For them, high dilutions were certainly an aspect of homeopathy, but it was not the only one. They also mentioned the "law of similars" and they insisted on this specificity of homeopathy, a "global" medicine according to them, very far from "classic" medicine which they call "allopathic".[3]

"He wedged his model"!

As everyone knows, "victory has many fathers, but defeat is an orphan". In 1997, the main protagonists of the "affair" were questioned by E. Fottorino for *Le Monde* which told the "affair" in three long articles from 21 to 23 January 1997. The unspoken feelings could then be freely expressed. The scientific director of Boiron gave a free rein to his resentment:

> "Philippe Belon considers that the faux pas of 1988 in Nature entailed a delay of ten years in the recognition of high dilutions. "We were branded as a shame of the science", he says. On the works of doctor Benveniste, his opinion is clear: "He wedged his model (*sic*). The peaks of activity are not stable. The only possible conclusions must be statistics. Yet the summation of his results is not significant. Elisabeth Davenas had pushed too far. Benveniste leaned on a single experiment which worked. If he had redone it a thousand times, there would have been no problem. But what he

> published in Nature, he does not know how to reproduce it, even in his laboratory. And nobody knows." [4]

About the article of *Nature*, P. Belon declared that "the published text is not the one that he had signed":

> " "Since 1982, we worked with Benveniste on the test of degranulation of basophils which he unquestionably developed. But our researches concerned the inhibition of the phenomenon and not the direct cell activation. I agreed with the first two versions of the text sent to Nature, because they dealt with inhibition. The final text described a direct activation, I did not read it" Why didn't he say it? "I was in an awkward position. I preferred to keep silent about it and continue working on our initial model"."

As for B. Poitevin, he "did not agree with the article of the Academy of Sciences":

> "On the activation of basophils, only one experimenter, Elisabeth Davenas, obtained results. It did not work with the other one. Benveniste offended her. I repeat: it was necessary to say that the phenomenon was difficult to reproduce. As for the model of inhibition, it worked in both cases."

He too seemed to deny an article of which he was nevertheless signatory. One also finds in these words the same emphasis to distinguish the effects "in inhibition" from "direct" effects. He pursued:

> "When Elisabeth worked "open-label", we noted an avalanche of good results. I believe that technical errors could increase the chances of obtaining positive data. But the curves of activities were not imaginary. It was only necessary to finalize the reproducibility of the system and to say that it was difficult to repeat as long as all parameters were not mastered. Benveniste refused."

It is difficult however to understand how the same method was acceptable "in inhibition" and would be to blame for all the troubles "in activation".

For the reader who could be a little misled in front of these arguments, we can summarize the point of view of the "homeopaths" – without betraying their thought I think – by saying that there would be, on one side, a good research in homeopathy – "in inhibition" in the case of basophils – with homeopathic products (or with histamine which, under the name of *histaminum*, is also a

homeopathic product sold in pharmacies…) and, on the other side, the research "*à la* Benveniste" which did not care to be in agreement with the principles of Hahnemann and would risk to make lose its soul to homeopathy.

It is also possible that the mistrust towards J. Benveniste, as expressed by the "homeopaths", was related to the fear of being exposed behind Benveniste who only dreamed to confront in a challenge worthy of him on the international scientific scene. For the "homeopaths", there was a great risk that one sees that the "king was naked" or at least very slightly dressed.

"Is it Benveniste-like without Benveniste, as water would produce a molecular effect without molecule?"

These articles in *Le Monde* in 1997 brought nevertheless important information. Indeed, the reader of *Le Monde* could learn with interest that on the initiative of Boiron Laboratories and their scientific director, P. Belon, an international study concerning the effects of high dilutions on basophil degranulation was performed and that the results were positive!:

> "Professor at the University of Louvain, biochemist and toxicologist Marcel Roberfroid recognizes to have coordinated the experiments of four European laboratories on high dilutions (in France by doctor Sainte-Laudy, in Italy, in Holland and in Ulster). But, he specifies: "My purpose is not to know whether Benveniste is right or not. I apply the test of Sainte-Laudy, not that of Benveniste. This last one had no knowledge about our works." [5]

What is the difference between the "test of Sainte-Laudy" and the "test of Benveniste"? J. Sainte-Laudy replaced the blue of toluidine which was the staining agent of basophils by another one, namely alcian blue. But how this technical modification was decisive in the study of high dilutions? Was it only a simple change of a biological test or was this modification crucial in the case of high dilutions? This question was already raised by the journalist M. de Pracontal a few years before. With a lot of goodwill, he candidly asked J. Sainte-Laudy why he had changed the staining agent in the method of basophil counting. He then answered:

> "In 1986, I changed the staining agent because there were major problems with toluidine blue […]. From 1986 to 1988, I confirmed that the results obtained with toluidine blue were also observed with alcian blue. I think that persisting with toluidine blue is a scientific and diplomatic error. The technique with toluidine blue can be performed but in conditions less good than the technique with alcian blue." [6]

The journalist, who was brought down by this convoluted answer, added: "In brief, it works without working, while working nevertheless. Make sense of that if you can.".

Besides the change in the staining agent, the experiments of the European study were performed in "inhibition" (with histamine) and furthermore on the "first peak" of degranulation. Consequently:

> "Professor Roberfroid, the scientific director of Boiron, Philippe Belon, and Jean Sainte-Laudy rely on this difference to deny Benveniste the right to claim some confirmation of his own experiments.
>
> Is it Benveniste-like without Benveniste, as water would produce a molecular effect without molecule? No, Roberfroid answers, who considers the expression "memory" of water as a "speculation". "I will not take a position. Science does not still admit the effect of high dilutions. Then, speaking about memory…"
>
> Philippe Belon recognizes that the publication of the works of the Belgian professor will help Benveniste, while insisting on the difference of method. "That of Sainte-Laudy preceded that of Benveniste"."

The determination to keep away from J. Benveniste was clearly present in these words. We were thus again in the presence of the strategy "anything but Benveniste", but this time, from what an outside observer would consider as the "natural" camp of J. Benveniste. It is true that J. Benveniste, *volens nolens*, was almost automatically associated at this time with any allusion to high dilutions or to "memory of water". Justified or not, these technical subtleties or these battles of egos were difficult to understand for anyone was not directly involved in this research. For an outside observer, any positive experiment in favor of "memory of water" was always followed by the idea: "and if Benveniste was right?" The article of *Nature* was the reference which everybody remembered. Previous articles published in "minor" or confidential journals were forgotten even if in fact they said nothing very different. As J. Benveniste did not hesitate to claim, these articles were only "farts of rabbits in the stratosphere". He was the only one, according to him, who could bring this research theme on the baptismal fonts of science.

However, when he heard about this international study, the reader of *Le Monde*, who did not grasp technical quibbles and questions of egos, could wonder: "and if Benveniste was right?"

Notes of end of chapter

[1] E. Fottorino. La mémoire de l'eau. Une vérité hautement diluée. *Le Monde*, January 23rd, 1997.

[2] E. Fottorino. *Ibid.*

[3] We do not envisage in this book the question of homeopathy as therapeutic practice.

[4] E. Fottorino. La mémoire de l'eau. Du rêve au soupçon. *Le Monde*, January 21st, 1997.

[5] E. Fottorino. La mémoire de l'eau. Une vérité hautement diluée. *Le Monde*, January 23rd, 1997.

[6] M. de Pracontal. Les mystères de la mémoire de l'eau, p. 184.

Chapter 23. "Benveniste-like experiments without Benveniste"?

J. Benveniste liked to say that "nine pregnancies of one month do not make a baby". The publication of the results of the study impulsed by the laboratories Boiron and coordinated by M. Roberfroid was – whatever the reasons –- long to deliver!

The announcement in 1994

One finds a first allusion to this study by one of the participants, F. Wiegant. The latter, in August 1994, sent a letter to *Nature* concerning the article of Hirst *et al* evoked previously. This letter is interesting because the sequence of the ideas explicitly unveiled the strategy to strictly keep away from J. Benveniste and his results.

First step: F. Wiegant announced that he agreed with the conclusion of Hirst *et al* and he indicated that his group of research published the same negative results two years ago.[1] This team had then noticed differences in the counts of basophils of two experimenters. He added that this fact could explain the absence of positive results with high dilutions.

Second step: F. Wiegant then specified that one of the signatories of the article of *Nature* of 1988, J. Sainte-Laudy, modified the initial method of basophil degranulation and used at present alcian blue "which allows rapid and clear-cut basophil counts without time-consuming training." .

Third step: F. Wiegant indicated that with this modified method, J. Sainte-Laudy reproduced the results published before, namely the inhibitory effect of histamine at high dilutions on basophil degranulation.

Fourth step: F. Wiegant announced that blind experiments using this model were in progress in five laboratories in United States, Ireland, Italy, France and the Netherlands. These experiments were coordinated by Marcel Roberfroid of the University of Leuven in Belgium.

He ended then: "the last word has not yet been spoken". Let us remind that one was then in 1994. But, it will be necessary to wait until 2004 to see these results published in the journal *Inflammation Research*! [2]

The results unveiled in 2004

The signatories of the article [3] of 2004 were from four laboratories (the U.S. laboratory had disappeared). There were first of all the former two signatories of the article of *Nature* of 1988, P. Belon, scientific director of Boiron, and

J. Sainte-Laudy (CERBA, France) as well as Fred Wiegant (University of Utrecht, Netherlands) and two other researchers who had not previously been involved in this research: Madeleine Ennis (Queen University of Belfast, United Kingdom) and Pier Francesco Mannaioni (University of Florence, Italy). The study was coordinated by M. Roberfroid, professor of biochemistry who also blinded the dilutions to be tested. The results were analyzed by Jean Cumps, statistician (Catholic University of Leuven). The laboratories having performed the degranulation tests were French (laboratory 1), Dutch (laboratory 2), English (laboratory 3) and Italian (laboratory 4).

High dilutions of histamine were tested at 10^{-30}, 10^{-32}, 10^{-34}, 10^{-36}, 10^{-38} mol/L (there are of course "theoretical" concentrations). The effect was assessed on three concentrations of anti-IgE corresponding to the first peak (1; 0.2 and 0.04 µg/mL). Overall – and it was a remarkable result – the statistical analysis showed that the percentages of degranulation were smaller for the samples that contained histamine at high dilutions. Figure 23.1 is a summary of all results. One notices that, taken as a whole, the percentages of inhibition were observed more frequently than by chance with positive values. The statistical tests indicated a very high degree of significance ($p < 0.0001$).

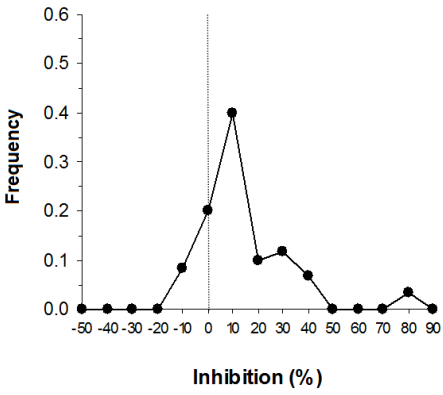
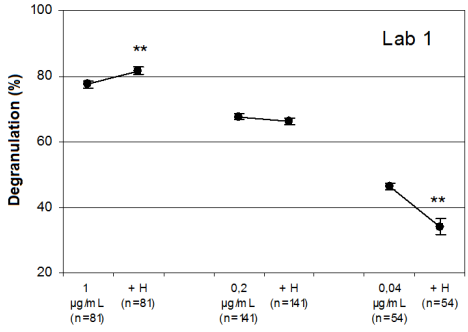


Figure 23.1. This figure shows the overall results of inhibition by histamine at high dilutions in the European study. The figure has been performed using the means reported in the article for each experimental condition (an experimental condition being, for example, inhibition by histamine at 10^{-30} mol/L with antiserum anti-IgE at 0.2 µg/mL for the laboratory 1). One notices that the percentages of degranulation are "moved" towards the right of the point 0% of the *x*-axis. If there was no inhibition (null hypothesis), the distribution curve should be centered on 0%.
(Each point of the *x*-axis corresponds to the upper limit of the interval).

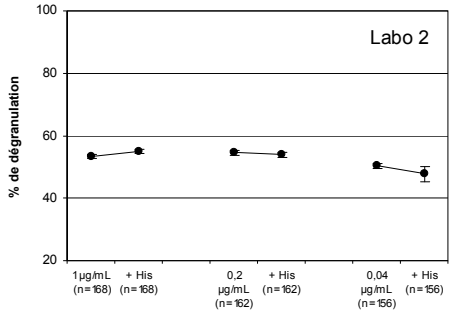
The results obtained in each laboratory are represented on Figure 23.2. One notices that the results are considerably different according to laboratories. First of all, there was no significant effect of high dilutions of histamine for the laboratory 2. This was the laboratory of F. Wiegant whose group of research had already published on the same subject and did not observe any effect of high dilutions on basophils (in the article of Ovelgonne *et al* of 1992; cf. note 2). Nevertheless, it was this laboratory that supplied the higher number of experiments. Only laboratories 1 and 4 observed an effect with the highest dose

of anti-IgE (1 µg/mL). But strangely degranulation was increased in the presence of high dilutions for laboratory 1 whereas it decreased for laboratory 4. Finally, laboratory 4 distinguished itself compared to the three others for its "efficiency": an inhibitory effect with high dilutions of histamine was observed with all concentrations of anti-IgE.

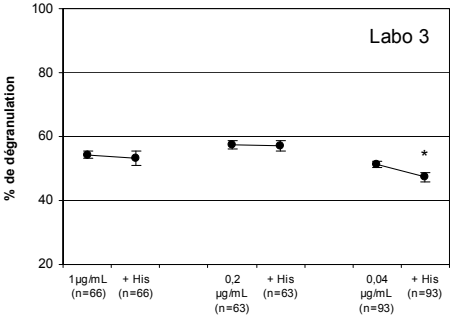
Laboratory 1 (Jean Sainte-Laudy, France)



Laboratory 2 (F. Wiegant, The Netherlands)



Laboratory 3 (M. Ennis, United Kingdom)



Laboratory 4 (P. Mannaioni, Italy)

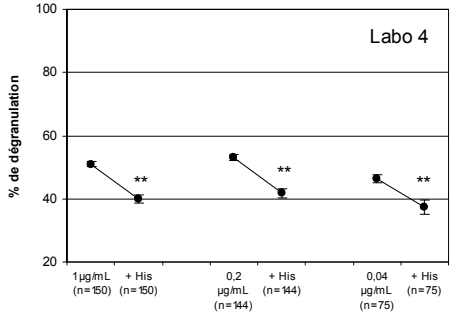


Figure 23.2. The analysis of the European study with four laboratories concluded that overall high dilutions of histamine significantly inhibited degranulation ($p < 0.0001$).
The results shown here were obtained from the data of the article published in 2004 in *Inflammation Research*, for each laboratory. The effect of high dilutions of histamine (+H) on degranulation induced by anti-IgE at various concentrations (0.04; 0.2 and 1 µg/mL) is compared with the effect of anti-IgE alone at the same concentrations (+His). It must be noted that this representation does not allow highlighting – and risks even to mask – the classic "waves". We observe nevertheless significant differences (* $p < 0005$. ** $p < 0001$) for some results, more frequently for the lowest concentration of anti-IgE (0.04 µg/mL). That is why we summarized in Figure 23.3 the results with this concentration of anti-IgE in the presence of all dilutions (from 10^{-30} to $1/10^{-38}$ mol/L).
The results are given as mean ± standard error of the mean.

Three laboratories among the four obtained significant effects with the lowest dose of anti-IgE (0.04 μg/mL). Since the inhibitory effect was the most marked with this concentration of anti-IgE, it is interesting to study the results according to each dilution of histamine as shown in Figure 23.3.

When one looks at Figure 23.3, one can notice that the results of the European study – in "inhibition" on the first peak and with the alcian blue method – were poorly reproducible between the four laboratories. Furthermore, the differences between "active" samples and controls were small and the peaks of activity had fainted. We remember that P. Belon had depreciated the results of the article in *Nature* of 1988, in particular because "the peaks of activity were not stable". The reproducibility was also not reliable according to him. The method with alcian blue and the experiments "in inhibition" were supposed to produce better results. Even if globally a significant effect persisted for this study, one notices here again that the blind procedure abolished the differences between the various high dilutions (i.e. there was no "dose-response").

Even J. Sainte-Laudy did not reproduce, in these blind experiments, the spectacular results that he previously reported. Furthermore, in contradiction with the results of the other laboratories and with his own previous results, with the highest concentration of anti-IgE (1 μg/mL), he observed an *increase* of basophil degranulation.

Yet, the new technique with alcian blue was supposed to allow counting basophils with a better reproducibility and the biological system "in inhibition" was considered as fully tried and tested. Great expectancies were therefore put on this protocol. On arrival, it was – as for the article of the *Comptes Rendus* of J. Benveniste and A. Spira – the same perplexity: one undoubtedly obtained an overall significant effect on the statistical plan, but the "message" was blurred if one considered the results in details, for each dilution. Here again, the "measurement instruments" had very different performances.

Questioned in 2001 about the results of this study which had been reported at a congress, J. Benveniste – who abandoned at that time basophils several years before to dedicate himself to what he named "digital biology" (cf. second part) – declared: "They've arrived at precisely where we started 12 years ago! " [4]

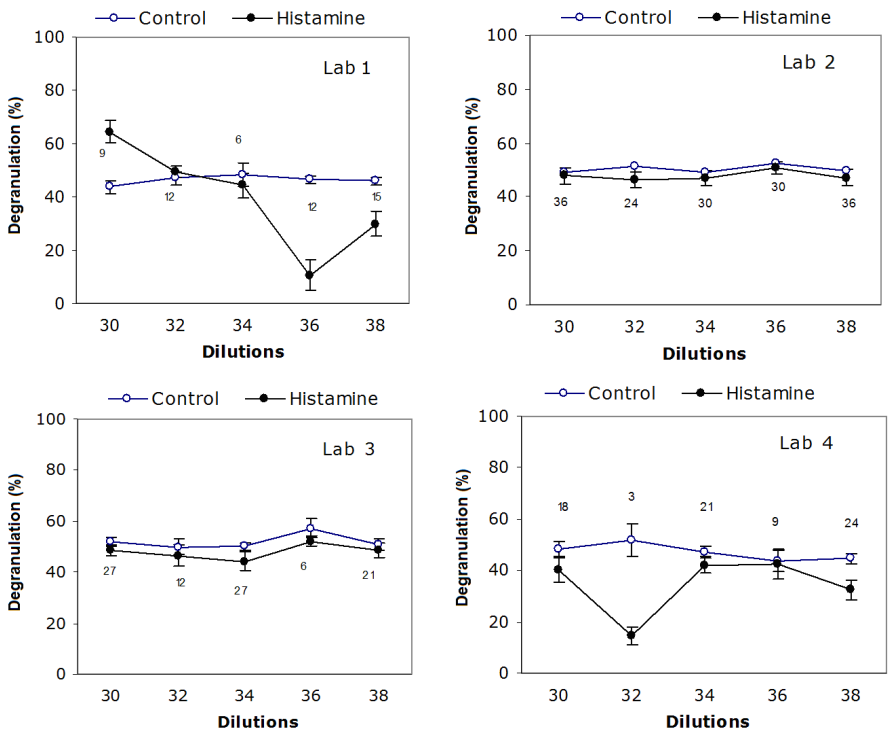


Figure 23.3. . This figure corresponds to the results of Figure 23.2 for anti-IgE 0.04 µg/mL. Indeed it was at this concentration of anti-IgE that most significant results were observed in the European study. Degranulation induced by anti-IgE 0.04 µg/mL is presented in the presence and in the absence (control) of histamine (from 10^{-30} to 10^{-38} mol/L). The results are thus very different according to laboratories and even if a significant global effect is found, one does not observe "waves" of inhibition. Even within each laboratory, one could not conclude if a given dilution of histamine was an "active" one. This contrasts with the previous results reported by J. Sainte-Laudy and P. Belon.
The numbers under each of the symbols are the number of experimental points (for every point, there are as many points of histamine at high dilutions as samples of corresponding controls).
On *x*-axis, dilution "30" corresponds to 10^{-30} mol/L.

"The scourge of homeopathy"

This experiment with several European laboratories nevertheless allowed converting a "non-believer", namely M. Ennis of Belfast who managed one of the four participating laboratories. Here is how Mr. Ennis was described in *New Scientist*:

> "Madeleine Ennis, a pharmacologist at Queen's University, Belfast, was the scourge of homeopathy. She railed against its claims that a chemical remedy could be diluted to the point where a sample was unlikely to contain a single molecule of anything but water, and yet still have a healing effect. Until, that is, she set out to prove once and for all that homeopathy was bunkum. In her most recent paper, Ennis describes how her team looked at the effects of ultra-dilute solutions of histamine on human white blood cells involved in inflammation. […] The study, replicated in four different labs, found that homeopathic solutions – so dilute that they probably didn't contain a single histamine molecule – worked just like histamine. Ennis might not be happy with the homeopaths' claims, but she admits that an effect cannot be ruled out." [5]

One knows that recent converts are often proselytes! They do not hesitate to tell the conditions of their "conversion" in terms such as "I did not want to believe it but the results were there". M. Ennis reported her evolution in the following manner:

> "I was incredibly surprised and really had great feelings of disbelief, but I know how the experiments were performed and I couldn't see an error in what we had done." [6]

At another occasion, she declared:

> "Despite my reservations against the science of homoeopathy […] the results compel me to suspend my disbelief and to start searching for a rational explanation for our findings." [7]

In order to explore these results in more detail, M. Ennis set up in her laboratory a method which avoided counting basophils manually. To put it simply, this method was based on the measurement of a molecule from basophil granules which is "transported" on cell surface during the degranulation process. Specific fluorescent antibodies recognize this molecule and therefore degranulation could be quantified. This method had already been used by J. Sainte-Laudy [8] and M. Ennis applied his experimental protocol. In 2001, M. Ennis published, in the form of a communication at a congress, preliminary results using this method; the results were in favor of an effect of high dilutions of histamine. [9]

The results of M. Ennis generated some publicity in United Kingdom because during a television program of the BBC2, an attempt of replication of these – preliminary – results was presented. The initiative did not come from

M. Ennis, but from the producer of the scientific series *Horizons*. The purpose was to win the million dollar prize offered by the foundation chaired by J. Randi (still him). This prize was intended for anyone who can prove the reality of a "paranormal" effect (high dilutions being apparently filed under this denomination…) A scientific team was constituted (unrelated to M. Ennis and her laboratory) and the emission was broadcasted on November 26th, 2002. The result was considered as a failure and the million dollars stayed in the bank account of J. Randi…

Not long after a debate developed because the protocol which had been followed by the scientists in charge of the study was apparently not the one that M. Ennis used.[10] Moreover, none of the scientists "recruited" for the occasion had a particular skill concerning this research area.

We will not comment beyond these "studies" for which we only have indirect information because the results of the experiment and the protocol were of course not published. Once again we can notice here a recurrent and now familiar situation: auto-appointed experts, atmosphere of circus where science is done on stage with the media as witnesses. Finally, it is the confusion of the ideas that prevails and the truth – if there is a truth – cannot find its way.

Notes of end of chapter

[1] This article was the following: Ovelgonne JH, Bol AW, Hop WC, van Wijk R. Mechanical agitation of very dilute antiserum against IgE has no effect on basophil staining properties. *Experientia* 1992; 48:504–8 (Department of Molecular Cell Biology, State University of Utrecht, The Netherlands).

In fact, in this article, Ovelgonne *et al* compared two series of anti-IgE at high dilutions (from $1/10^{21}$ to $1/10^{30}$) in 24 experiments. One of the series of anti-IgE was shaken and the other one was obtained "by pipetting very gently and tilting the test tubes 10 times to mix the contents after diluting". Unfortunately, the authors did not perform a series of controls (without anti-IgE). The method of "soft" dilution was thus not controlled and it was consequently difficult to know to which extent a certain "activity" of anti-IgE was not present in these high dilutions. We saw in the article of Hirst *et al* that the dilutions performed without shaking had an activity which was intermediate between that of "true" controls (i.e. shaken control samples) and "true" high dilutions of anti-IgE (i.e. shaken dilutions of anti-IgE).

[2] There was a congress abstract in 1991 in *Inflammation Research* 48 (Suppl 1): S17-8. The article of 2004 was submitted to *Inflammation Research* in December 2002 and accepted in November 2003.

[3] Belon P, Cumps J, Ennis M, Mannaioni PF, Roberfroid M, Sainte-Laudy J, Wiegant FA. Histamine dilutions modulate basophil activation. *Inflammation Research* 2004; 53:181–8.

[4] L. Milgrom. Thanks to the memory. *Guardian*, 15 mars 2001.

[5] Michael Brooks. 13 things that do not make sense. *New Scientist* n°2491, March 19th, 2005.

[6] Interview of M. Ennis during the TV program *Horizons* of BBC2 of November 26th, 2002.

[7] L. Milgrom. Thanks to the memory. *Guardian*, 15 mars 2001.

[8] Sainte-Laudy J, Belon P. Analysis of immunosuppressive activity of serial dilutions of histamine on human basophil activation by flow cytometry. *Inflammation Research* 1996; 45 Suppl 1:S33–4.

[9] Brown V, Ennis M. Flow-cytometric analysis of basophil activation: inhibition by histamine at conventional and homeopathic concentrations. *Inflammation Research* 2001; 50 Suppl 2:S47–8.

[10] Robert Matthews. TV homeopathy trial was 'flawed'. *New Scientist*, 7 décembre 2002.

Chapter 24. Some questions without answers

Can we say that the results of the article of Nature of 1988 on high dilutions have been reproduced?

In other words, can we say that "Benveniste was right"?

The results of the experiments intended to confirm or not the effects of high dilutions (i.e. the study coordinated by M. Roberfroid and published in 2004 in *Inflammation Research*, the study of J. Benveniste and A. Spira of the *Comptes Rendus de l'Académie des sciences* of 1991and the study of Hirst *et al* published in *Nature* in 1993) remind us of the story about the glass being half full or half empty depending on an optimistic or pessimistic view point. For some people, there was certainly a statistically significant difference, but the results were incomplete: what happened to the smart "sinusoidal" curves that fascinated so much? For other people: "Undoubtedly, one did not really find the famous oscillations again, but nevertheless the experiments were overall statistically significant. It is thus the proof that there was a real effect of high dilutions!"

For those who attended the first experiments where high dilutions appeared to defy all controls (including blind tests), the results of these "reproductions" are – one must agree –disappointing at first sight. Indeed, the regular curves, the mountainous profiles on the horizon of a new world full of promises are now partially fainted in the mists of the large-scale blind experiments and their statistical analyses. The analyses now compare "noise vs. noise". The fact that a statistically significant difference remains is however very disturbing. But it is also disturbing to observe that "blinding the experimenter" modifies the results. The only word which could qualify the state of mind of an observer who would try to be impartial is perplexity.

Contrary to appearances, reproducibility is a very difficult issue from an epistemic point of view. Indeed, what are we talking about? What is supposed to be reproduced? Is it necessary to reproduce the experiments of *Nature* of 1988 in their slightest details? We know that it is always practically impossible. J. Benveniste did not hesitate to raise methodological differences when experiments performed by other teams were negative. When the observed results fitted with the "expected" results, this last one was prone to see on the contrary a confirmation of his own results. In this case, the methodological differences ceased to be a problem. It must be recognized that a "positive" experiment does not have the same status as a "negative" one. But, somewhere

in the universe, is there a big book which lists all possible experiments and indicates if they must be considered as "positive" or "negative"? In fact, it is the reading grid of the scientists which decides this. As a consequence, the race for the "crucial experiment" does not make sense.

Moreover, a study such as the one of *Nature* of 1988 has a scientific interest only if the result can be generalized and is not limited to a unique experimental model. We cannot blame researchers for not having tried to reproduce it literally but to have verified if this claim was not restricted to basophils by using experimental models that they knew well.

Nevertheless, one must be cautious because there are many discoveries in the history of science that are accepted today and which, in those days, had difficulties being recognized because there were issues to reproduce them. We can quote the decomposition of colors by Newton's prism or the measure of the electrostatic forces using Coulomb's torsion balance. On the contrary, we can also evoke experiments which were reproduced those days by other scientists and which are today considered as errors. Thus, the experiments that "evidenced" the N-rays of Blondlot were reproduced by some laboratories at the beginning of the 20th century. In spite of these reproductions, this "discovery" is now a chapter of the history of the sciences intended to illustrate the auto-illusion of some scientists.

The answer to the initial question of this part is thus: in blind controlled conditions, statistically significant variations of the counts of basophils in the presence of high dilutions were reported after 1988 in other laboratories. It is an important point.

What kind of "memory" are we talking about?

The compounds which are highly diluted in the experiments are often complex mixtures. Thus, *Apis mellifica* is made of whole bee macerated in alcohol; *Lung-histamine* is prepared from an extract of lung of guinea pig after an allergic shock. Even anti-IgE antiserum contains not only anti-IgE immunoglobulins but also numerous constituents of plasma. Furthermore, a molecule such as anti-IgE is a huge protein. If water has a "memory", it should keep the "trace" not only of the molecule involved in the experiment but also those of all other dissolved molecules. Furthermore, when one uses solutions containing thousands of different molecules, as for example in an extract of crushed bee, how the "memory" of these numerous molecules with all their details would be stored? How do these various "traces" not interfere?

We do not have an answer to this question (assuming that this question has a meaning and is relevant). It is often said that water is poorly known and that

there is no explanation on the liquid state of water at usual temperature. One can only subscribe to this assertion, but one must recognize at the same time that this does not prove that "memory of water" exists. To explain the properties of high dilutions, J. Benveniste frequently quoted the studies of Giuliano Preparata and Emilio Del Giudice in theoretical physics which suggested that water molecules could organize in "coherent domains" around the dissolved compounds.[1] However, this theory has never been used to improve Benveniste's experiments or to build hypotheses in the framework of these experiments. This physical theory frequently served as argument from authority ("physicists showed that…"). This theory moreover seems to envisage only a single type of molecule. What happens in the presence of "soups" of molecules that are frequent in biology? What then become the "coherent domains" in front of a mountain of information which must be stored?

Even if we forced ourselves about not raising the issue of homeopathy as therapeutics, a question deserves nevertheless to be raised because it concerns the physical properties of high dilutions. Indeed, homeopathic medicines sold in pharmacy are most often in the form of granules. The latter are constituted by lactose on which a homeopathic solution has been pulverized. Undoubtedly, "memory of lactose" has poetic effects which are less powerful than "memory of water", but it is nevertheless mainly under this form that the homeopathic products are administered. Yet, if we break these granules, they seem as dry as a sugar cube. Are we still speaking of "memory of water"? The answer of the homeopathy manufacturers concerning this paradox is generally the following one: it is in fact very difficult to evaporate all water molecules adsorbed on a surface and temperature much higher than ordinary temperature would be required for all water molecules to escape from the granule. This is quite possible, but concentration of water is then very weak and few water molecules are adsorbed on the surface of a solid. Is water in these conditions not completely destructured? Where could be stored the "information" in these "almost dry" conditions? Is "information" transferred to the lactose of the granule?

Moreover, the manufacturers of homeopathic medicines insist on the numerous quality controls which take place throughout the production of granules, but nothing is said (and one can understand why…) on the ultimate and essential control which would be to verify that a biologic activity is present in a few samples of a batch. In the absence of such controls, are some batches sometimes recalled, for example because of an absence of efficiency noticed by homeopath doctors? In the area of health, the homeopathic industry is probably the only one where there is no control of the finished product.[2]

To end, let us imagine by a thought experiment that a facetious goblin systematically replaced each tube of homeopathic pills which leaves the factory by a tube of "neutral" granules with nevertheless the same "label". How much time would it take for the subterfuge to be noticed? Would one ever notice it?

Why is there no simple and reproducible experiment?

As one has probably understood, J. Benveniste was not the first one to be interested in the effects of high dilutions. Today, after the publicity made around the article of *Nature* of 1988, it is difficult not to know this marginal current of research. Nevertheless, if these researches were so old, it is surprising that despite decades of research, not one simple experiment, which many laboratories would have been able to perform, was defined. No test which would have allowed quality control of homeopathic granules was invented. Nevertheless the number of biological systems which were explored is impressive, from the vegetable to the animal kingdom (not to mention the question of the clinical trials in humans or in animals).

To speak only about *in vitro* or *in vivo* biological models, one finds studies with substances at high dilutions on germination of diverse seeds, consumption of oxygen by vegetables, reaction rate of varied enzymes, contraction of the gastrocnemian muscle of frog, isolated heart of rat, liver of rat, synaptosomal preparations of rat brain, slices of rat brain, isolated intestine of rat, isolated fragments of trachea of guinea pig, isolated fragments of human bronchi, learning in rat, behavioral tests in mouse, tumoral growth in rat, proliferation of *in vitro* tumor cells, edema of rat paw, UV-induced erythema in rat, liver toxicity in rat, experimental arthritis in rat, intestinal transit in mouse, wound healing in mouse, metamorphosis in batrachians, elimination of various toxins in diverse laboratory animals, experimental diabetes in mouse, toxicity of heavy metals on cell lineages, proliferation of lymphocytes, production of diverse mediators by polymorphonuclear neutrophils, production of antibodies in mouse, etc.

Despite this list which is very far from being exhaustive, not the slightest simple experiment, not the slightest biological well-defined test on which a consensus could be built.

Did the "Benveniste affair" change anything in the field of research on high dilutions?

There are some associations or foundations that bring together researchers who study the effects of the homeopathic dilutions, most frequently in the more general frame of "complementary" medicines. The reading of the reports of the congresses or meetings organized by these groups is interesting. One indeed notices that most of the experimental studies that are reported remain phenomenological: an effect *X* is observed in a biological system Y in the

presence of high dilutions of a product *Z*. This phase of the experiment does not seem to be able to go over. It is nevertheless paradoxical, after so many years of research, that elementary results about characterization of high dilutions – for example the effect of the exposure of high dilutions to heat – are not known. There is no consensus today on what "erases" the effect of high dilutions (or even possibly what increases them). Today, we should know the action of heat, ultrasounds, electromagnetic waves or other radiations on the "traces" left in water by molecules during the dilution-agitation process. Instead of this, there are still the same types of experiments with the everlasting final wish of future investigations by other researchers. Everything is going as if the research in this domain was a never-ending beginning.

This situation does not prevent the organization of colloquiums or symposia which play probably an important social role because they allow consolidating the feeling of belonging to a small circle of "enlightened" people being right against "official science" and against the other narrow-minded scientists. Moreover, some of the researchers who attend these circles complain about the ostracism of their works since "the Affair". But, in fact, did something really change? Is it not on the contrary an ideal pretext to be in the company of all scientists who were not understood in the past but are now in the pantheon of the science (Galilee remaining the gold standard on this matter)? Did these researchers have an easier access to the high-level scientific journals before the "Benveniste affair"? This attitude also avoids raising questions on the relevance of this research area and on the real role of water in this story.

To go out of a purely phenomenological description, great expectations seem to be based on the demonstration of modifications of physical properties of water. Maybe this hope is due to the prestige of physics. But, after the wave of enthusiasm which invariably welcomes the promotion of new results, supposed to be a definitive answer ("is homeopathy just about to be proven and explained?"), another new physical method, generating renewed hopes, is investigated. There were thus the dielectric constant of water, infrared spectroscopy or spectroscopy Raman-laser. More recently, one could observe enthusiasm for nuclear magnetic resonance, "crystals I_E" or thermoluminescence. Soon after, some issues related to reproducibility, artefacts and cruelty of blind experiments were raised. In the end, one assists to the transposition, from biology to physics, of the difficulties of high dilutions.

What can we do?

Despite these reservations, a statistically significant effect persisted in the experiments that we described in this text. This is *the* scientific fact that emerges from this story and encourages to pursue the study of the phenomenon. The

term "phenomenon" must then be understood in broader terms. Because the perspective has changed, the question is no longer "how water could have a memory", but rather "how could one obtain these results" or more exactly "how could one bias chance even in blind experiments". The hypothesis of "memory of water" would be only a hypothesis among other ones. One can discard the possibility that this hypothesis would be finally rejected. This hypothesis would have nevertheless played an important "historical" role by having crystallized around it these unusual observations. After the rejection of this hypothesis, observations awaiting a satisfactory explanation would nevertheless remain.

This approach needs to come out from a purely descriptive and pragmatic attitude ("it works, thus it is true") and at the same time not to sink into narrow-minded skepticism because these phenomena appear at first sight to lack of credibility or because the explanation adopted by those who support them does not satisfy us ("it is impossible, thus it is false"). To sum up, there is something interesting to study, these results are not trivial, but maybe the most immediate explanation is not relevant. One could thing that there are smart circumlocutions in order not pronouncing the word "artifact". As we will see in the second part of the present text, in spite of the abandon of the basophil model, the effects of "memory of water" persisted in new experimental systems. We will consequently see that, if there is an artifact – i.e. an effect generated by the experimental procedure itself – its explanation remains a challenge which is at least as exciting as the observation of the effects attributed to the "memory of water" in its early stages.

Notes of end of chapter

[1] E. Del Giudice, Preparata G, Vitiello G. Water as a free electric dipole laser. *Physical Review Letters* 1988; 61: 1085.

[2] There is also another difference. In contrast with pharmaceutical industry, there is no pharmacovigilance and no record of adverse events for homopathic medicines....

Epilogue of the first part

From 1990, J. Benveniste explored other experimental models in order to avoid some of the inconveniences of the basophil model. A new experimental system appeared to be very promising. With this new device, no intermediary human "counter" – both experimenter and measuring device – was needed. This new model – the system of Langendorff – consisted of a classic preparation which allows physiologists to study the functioning of an isolated heart of rat or guinea pig. Its main advantage was that one could directly "see" the effect of high dilutions without any intermediary. The public that attended demontrations could thus be observer, actor and witness at the same time.

This "spectacular" biological system allowed J. Benveniste to propose new concepts such as "electronic transmission of molecular signal" and "digitization of molecular signal" in the framework of a hypothetical "digital biology". This new approach contributed to further marginalize him from both scientific community and his former supports in homeopathic circles. Most scientists considered that J. Benveniste had definitely crossed the lines and was too far from the limits of what is reasonable. Nevertheless, J. Benveniste repeatedly thought during this period that he was about to succeed "within six months".

These results – less broadcasted and not as well known as the results on basophils – are certainly more surprising and more destabilizing. We describe them in the second part of this book. We will see the promises, the hopes, the surprises, the perplexity that these new experiments have induced. We will also analyze their limits that bring *a posteriori* an odd light on the overall story.

Appendices of the first part

Appendix 1. The world of basophils and allergy

Basophils, mast cells and allergy

Blood while cells contain less than 1% of basophil polymorphonuclear cells (we will call them basophils in short). The cells contain granules (a kind of small bags) that can release their content outside the cell. This phenomenon is called degranulation. Histamine which is thus released is responsible for some of clinical symptoms of allergy: redness (due to the increase of blood flow in capillary vessels dilated by histamine), local swelling (due to liquid leakage from blood to tissues) and tingling and itching (due to stimulation of nerve ends). Other cells – such as mast cells – share the same characteristics, but contrary to basophils they are located in tissues.

In the case of a individual who suffers from hay fever (or allergic rhinitis), the symptoms are due to the following sequence of events: pollen irritates the nasal mucosa, mast cells are "stimulated" and they release histamine and other compounds that participate to the allergic reaction; basophils are attracted by some chemical mediators on the site of inflammation and they also release the content of their granules thus participating to the inflammatory reaction. In the case of hay fever, the consequence of inflammation is nasal discharge, tingling and sneezing.

But, outside allergic phenomena, what is the role of these cells since anybody – allergic or not – possesses mast cells and basophils? These cells play a role in the control of the diameter of small vessels (and thus control blood flow) and in the early phase of immune response in tissues. Paradoxically, the physiology of these cells is better known in allergic individuals than in healthy ones.

These two cell types, basophils and mast cells, are thus studied to better understand and hopefully control allergic reactions. Basophils have the advantage that they can be obtained by taking a simple blood sample. However their purification is difficult and only small numbers are obtained.

Another actor of the allergic reaction: IgE.

Why some individuals are allergic but others are not? Allergic people have high amounts of antibodies called IgE (= Type-E immunoglobulins). These antibodies synthesized by the immune system when the body encounters some molecules contained, for example, in pollens, animal hair, food, etc. Non-allergic people synthesize also these antibodies, but at considerably lower levels. IgE antibodies have an important property: their "foot" binds at the surface of

basophils and mast cells, whereas their "head" remains free, in order to "catch" foreign molecule for which they have been specifically synthesized. When an allergenic molecule is close to specific IgE molecules, they bind all together due to the complementarity of their surfaces (lock and key model). Thus, IgE molecules immobilize allergens as Velcro strips does. An important difference with Velcro is however specificity. Thus, IgE molecules that "recognize" only cow milk antigens are not able to bind to pollen molecules. When an IgE molecule binds to a molecule, other IgE molecules – due to their mobility on cell membrane – come in close contact with the allergen molecule and progressively an aggregate of antibodies is forming around the allergen molecule. This immobilization of IgE molecules is responsible for the triggering of a series of enzymatic reactions that lead finally to the onset of "degranulation".

Tests for allergy diagnosis

This reaction can locally be induced in the skin of the allergic subject. Indeed, even though the initial contact between allergen (pollen) and the body is located in nasal mucosa (in the case of allergic rhinitis), IgE that are synthesized by the immune system spread out the whole body and bind on basophils and mast cells whatever their localization. If the sensitizing allergen is introduced into the skin of an allergic individual, it is "recognized" by specific IgE molecules and maintained at the surface of mast cells present in dermis. As described above, histamine and other pharmacologically-active compounds are released by mast cells and induce a small inflammatory reaction where allergen has been introduced with redness (the diameter of blood capillaries increases), formation of a small bubble that lifts up the epidermis (edema due to fluid leak outside capillaries) and itching (nerve ends are stimulated). This method is the basis of a diagnosis test used by allergy specialists (skin tests).

Scientists like to reproduce *in vitro* the *in vivo* biological mechanisms in order to manipulate them easily. Thus, let us put into a tube maintained at 37°C: 1) blood from an individual allergic to pollen; 2) the specific allergenic. After about 15 min, histamine can be measured at the outside the cells. Of course, if we do the same experiment without adding allergenic extract we have no histamine outside the cells. This last experimental condition is called a "control". It allows checking that allergen is indeed responsible of the release of histamine. This notion of control could seem obvious. This is the case indeed in this simple example. This notion is however very important in any experimental procedure. It is a constant obsession in experimental sciences to wonder whether the observations are "real" and have not been created by the

experimental conditions themselves. It is important to know what a control is to understand some of the arguments during the controversy on "high dilutions".

Staining of basophils and their degranulation

Basophil granules have the property to bind some stains (called basic stains). Toluidine blue is one of them. It is precisely because basophils "like" basic stains that they receive this name. Due to electrostatic charges, toluidine blue binds on structures that have many electronegative charges, such as basophil granules. When these stained structures are observed under a microscope, they appear as dark red. This shift from blue to red is called metachromasia. Basophils that appear red after staining with toluidine blue can be counted under a microscope.

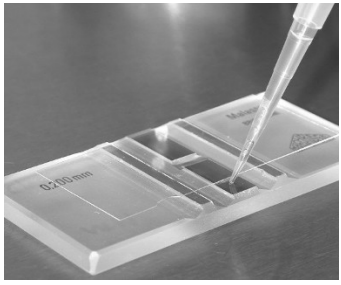
What is the consequence of the "degranulation" of the basophil? Not only histamine is released, but degranulated basophils cannot be stained. It is the basis of the basophil degranulation test that can be used for diagnosis purposes or for experimental research. In particular, there is a kind of "universal allergen" that allows inducing basophil degranulation as an allergen does. It is an anti-IgE antiserum that contains antibodies able to bind the IgE at the surface of basophil membrane. This binding of antibodies to IgE "mimics" the effect of an allergen.

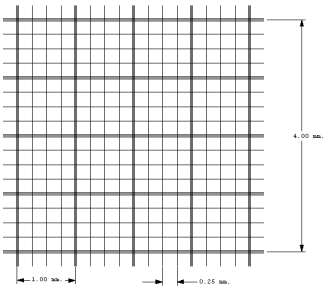
How to assess degranulation?

How to induce basophil degranulation with allergen of anti-IgE? In a first step, some simple handlings (blood sedimentation, recovery of supernatants, centrifugation) – that we will not detail – allow obtaining a concentrate of white blood cells suspended in physiological medium. Remember that this cell concentrate contains about one basophil for hundred white blood cells. Small volumes of this concentrate are put in tubes or more often in wells of plates designed for cell culture and widely used in biology labs ("96-well plates"). Then the allergen at different concentrations is placed in each well. The plate is then warmed at 37°C for half an hour.

After the time is up, a fixating and staining solution is added in each well. This solution allows also to get rid of contaminating red cells that disturb counting. Basophils are then counted under a microscope. Because one tries to assess the percentage of basophils that have degranulated in comparison with a control (which is a well prepared in the same conditions except that no allergenic extract was added), it is very important to count basophils in comparable volumes. Therefore basophils are counted by using a hemocytometer that allows the biologist to count cells in an accurate volume. A

small volume of the content of a well is placed under the coverslip of the hemocytometer and cells are counted on the grid pattern engraved in glass. On the left image below, we can see what a hemocytometer looks like. We see the two surfaces that are recovered with a coverslip before placing fixed blood cells in each of the two chambers. On the right, there is the grid pattern seen under a microscope (here at low magnification). Basophils are counted by scanning systematically the whole surface row by row.





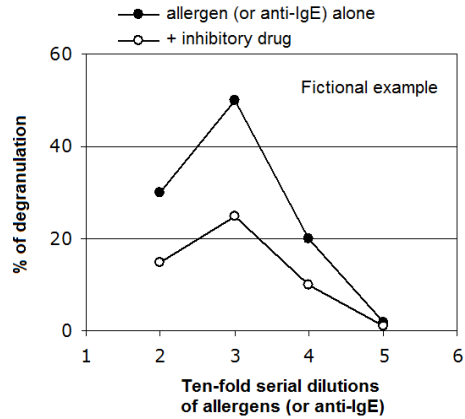
Suppose that the following results have been obtained (of course by counting the same surface for each result). For simplification, we suppose that each experimental point was performed only once.

Well 1: control	60 basophils
Well 2: allergen diluted 1/100	42 basophils
Well 3: allergen diluted 1/1000	30 basophils
Well 4: allergen diluted 1/10.000	48 basophils
Well 5: allergen diluted 1/100.000	59 basophils

We observe that, in comparison with control, the number of basophils decreases according to the dilution of anti-IgE antiserum. We can show these results as above, but it is often more demonstrative to express the results as percentages of degranulation, namely the percentage of basophils that are no more visible. For this purpose, one calculates the difference of basophils in control well and in well to be calculated and one divides by the number of basophils in the control well. For example, for the well 1/100, we obtain: (60 – 42)/60 = 30%. A graph is useful to show these results. The percentages have been calculated below for the same wells. In *y*-axis, we put the percentages of degranulation of the different dilutions.

Well 2: antiserum anti-IgE diluted 1/100	30% of degranulation
Well 3: antiserum anti-IgE diluted 1/1000	50% of degranulation
Well 4: antiserum anti-IgE diluted 1/10.000	20% of degranulation
Well 5: antiserum anti-IgE diluted 1/100.000	2% of degranulation

One can also slightly modify this biological model for the study of substances or drugs that inhibit the allergic reaction. The drug to be tested is added in wells containing the allergen (or anti-IgE) and results with and without the study drug are compared.



Release of histamine and degranulation

Of course, reality is rarely as simple as in textbooks. Moreover, what is not yet in textbooks is a possible definition of research. In particular, we showed at Inserm U200 in some experimental situations (not detailed here) that it was possible to get basophil "degranulation" evidenced by toluidine blue staining without simultaneous release of histamine. In other words, the basophil granules remained in place with their histamine content, but the granules nevertheless lost their capacity to retain toluidine blue. We thus hypothesized that the decrease of the ability to retain the dye was the consequence of ion movements. We all know for example that depolarization of nerve cells is – schematically – the consequence of an entry of sodium ions in nerve cells. This entry of sodium is an example of ion movement. There are many cell models where the first step of "cell activation" is an entry of ions into the cell though "ion channels". In the case of a "degranulation" without histamine release, our hypothesis was that an entry of ions was evidenced (no fixation of the dye to electronegative charges), but that the activation of the cell stopped. One

possibility was that obtaining release of histamine required "stronger" stimuli. The demonstration of this hypothesis was not completely achieved. Nevertheless, we published several articles, more particularly on the inhibitory role of extracellular sodium on the release of histamine and on ion channels present on basophil membrane. [1]

As described in this text, we observed that degranulation associated with high dilutions was not accompanied with a relapse of histamine. If histamine had been released, the reproduction of the high dilutions experiments by other laboratories would have been more comfortable. We thus proposed that high dilutions were "weak stimuli" that induced physicochemical changes of granules evidenced by the loss of affinity for the dye but were not able too induce the release of histamine. This is generally the case with people allergic to drugs, for example. This does not prevent allergy specialists to use this test for the diagnosis of drug allergy.

The use of the word "degranulation" has been criticized when the article has been published in *Nature*. It has been argued that a "true" degranulation must be accompanied, by definition, with a release of histamine. Afterwards, we coined the term "achromasia", which was purely descriptive and did not prejudge the release of histamine.

How to make "high dilutions"

Homeopathic dilutions are traditionally given as CH (Hahnemannian centesimal dilutions) which are serial 1/100 dilutions. One could express concentrations as moles per liter, but rapidly the units have no sense (even though it is frequently used) because molar concentration refers to a number of molecules. One calculates indeed – it is the main polemical point on high dilutions – that there is less than one molecule after un number of dilutions. Let us take for example the case of anti-IgE at high dilutions which was the subject of the article of *Nature* in 1988. Starting from an antiserum that contains 1 mg/mL of anti-IgE, one calculates that after the dilution $1/10^{14}$, there is less than one molecule in the assay.

It is for this reason that one prefers talking about what is obtained (i.e. the dilution) thus referring to an experimental process that does not prejudge the presence or not of molecules. The adjective "Hahnemannian" corresponds to a particular method of preparation: between each dilution, the solutions are vigorously shaken. In practice, we used a vortex mixer that allows a rapid mixing of solutions. This device is widely used in biology laboratories. For homeopaths, this shaking is very important because it is supposed to be a necessary condition to get active homeopathic dilutions.

Notes of end of chapter

[1] F. Beauvais et al. J Allergy Clin Immunol 1991; 87: 1020 ; J Allergy Clin Immunol 1992; 90: 52; Fundam Clin Pharmacol 1992; 6: 153; J Immunol 1992; 148: 149; Fundam Clin Pharmacol 1994; 8 :246 ; Clin Exp Immunol 1994; 95: 191; Immunol Lett 1995; 46: 81.

Appendix 2. Israel results (February-March 1987)

	23 Feb.	**1**	**2**	**3**	**26 Feb.**		**1**	**2**	**3**	**27 Feb.**		**1**	**2**	**3**	**1st Mar.**		**1**	**2**	**3**
Open-label																			
Control		79	82	83			85	95	87			86	79	80			110	106	104
Anti-IgE 1/100		-	-	-			33	45	49			-	-	-			57	63	55
Anti-IgE1/1000		33	38	-			-	-	-			27	29	27			37	42	41
Blind	**Code R**				**Code S**	**Code R**				**Code S**	**Code R**				**Code S**	**Code R**			
Control	B	82	79	84	3	G	88	85	90	5	5	85	82	82	4	A	107	103	105
Control	E	83	79	78	8	H	92	88	84	6	G	79	85	81	8	G	104	107	106
Anti-IgE 1/100		-	-	-			-	-	-			-	-	-	3	H	32	40	39
Anti-IgE $1/10^{32}$	F	78	76	79	4	A	85	88	89	7	7	64	64	71	9	I	96	95	90
Anti-IgE $1/10^{33}$	G	78	76	74	7	B	86	92	88	8	A	75	77	81	7	B	69	78	77
Anti-IgE $1/10^{34}$	D	54	51	56	1	C	55	50	53	3	D	39	37	38	6	D	45	47	53
Anti-IgE $1/10^{35}$	C	44	46	45	2	E	34	34	37	1	1	38	42	44	1	F	51	50	47
Anti-IgE $1/10^{36}$	A	46	49	52	5	E	51	49	51	4	B	52	59	54	2	C	70	78	75
Anti-IgE $1/10^{37}$	H	75	79	83	6	F	84	86	86	2	F	70	75	75	5	E	104	106	106

These results are the first 4 experiments performed by E. Davenas in Israel during her stay in February-March 1987. See Chapter 4 for detail on experiments and Chapter 11 and 12 for additional comments. The figures corresponding to these results are shown in Chapter 5.

Three wells of cells to be counted (numbered 1, 2 and 3) were associated with each dilution (or control). A part of each experiment was "open-label" in order to check that the experimental conditions were correct and the other part was performed "blind". Tubes were blinded with a simple code for the experiment of February 23rd and with a double code with two successive coders for the other ones (Code R = code of B. Robinzon ; code S = code of M. Shinitzky). In the case of a double code, no participant to the experiment was able to identify the tubes. These results were reported in Table 1 of *Nature*'s article 1988, which is also reproduced Chapter 8 (Figure 8.2). (*NB*. there are small differences for rounding of decimal numbers with *Nature*'s article).

Appendix 3. Results obtained during the survey of *Nature* (July 1988)

	ED		FB	
	1	*2*	*1*	*2*
Control 1	45	56	36	24
Control 2	44	56	36	31
Control 3	35	49	39	32
Control 4	32	28	37	20
Control 5	31	31	25	47
Anti-IgE $1/10^2$	11	30	13	14
$1/10^3$	30	37	32	22
$1/10^4$	28	34	39	31
$1/10^5$	41	45	39	36
$1/10^6$	58	59	43	33
$1/10^7$	48	60	20	42
$1/10^8$	31	45	36	29
$1/10^9$	?*	56	28	31
$1/10^{10}$	59	61	30	40
$1/10^{11}$	43	52	37	19
$1/10^{12}$	35	56	40	37
$1/10^{13}$	44	42	35	35
$1/10^{14}$	58	49	29	33

	ED		FB	
	1	*2*	*1*	*2*
$1/10^{14}$	58	49	29	33
$1/10^{15}$	32	54	26	17
$1/10^{16}$	36	56	43	34
$1/10^{17}$	52	30	28	41
$1/10^{18}$	54	36	35	31
$1/10^{19}$	47	42	40	38
$1/10^{20}$	49	54	19	40
$1/10^{21}$	26	33	37	37
$1/10^{22}$	63	45	39	42
$1/10^{23}$	59	44	36	34
$1/10^{24}$	40	32	30	39
$1/10^{25}$	56	36	34	44
$1/10^{26}$	41	40	27	29
$1/10^{27}$	39	60	32	34
$1/10^{28}$	26	54	38	41
$1/10^{29}$	44	65	41	38
$1/10^{30}$	13	65	34	36

* Only one value (error of W. Stewart).

These results correspond to the experiment counted by two experimenters (ED and FB) on Thursday July 7th, 1988 (two counts for each well). These results (67 pairs) were used to calculate the distribution of the difference of the counts of basophils performed in duplicate. For more details, see Figures 9.5 of Chapter 9, Figures 11.3 and 11.4 of Chapter 11 and also Chapters 9 to 12.

Appendix 4 (First part). Results of the article of *Comptes Rendus de l'Académie des Sciences* of 1991

ED

	Exp 1		*Exp 2*		*Exp 3*		*Exp 4*		*Exp 5*		*Exp 6*		*Exp 7*		*Exp 8*		*Exp 9*		*Exp 10*		*Exp 11*		*Exp 12*		*Exp 13*	
Dil.	**E**	**G**	**E**	**G**	**E**	**G**	**E**	**G**	**E**	**G**	**E**	**G**	**E**	**G**	**E**	**G**	**E**	**G**	**E**	**G**	**E**	**G**	**E**	**G**	**E**	**G**
$1/10^{21}$	56	77	56	66	88	76	105	108	93	97	76	85	64	56	74	76	77	75	75	59	33	53	72	58	42	46
$1/10^{22}$	59	94	65	66	86	96	118	106	90	127	64	56	41	61	52	70	45	62	74	56	36	57	70	81	41	60
$1/10^{23}$	80	85	57	69	77	86	97	94	98	107	69	68	62	63	47	78	40	79	84	54	43	66	65	74	53	51
$1/10^{24}$	70	90	42	67	91	86	100	97	82	106	69	68	51	63	70	75	55	71	71	85	41	67	59	77	34	54
$1/10^{25}$	57	91	40	67	67	91	81	86	73	98	57	67	28	56	80	74	79	73	79	74	37	55	50	69	38	57
$1/10^{26}$	56	95	54	58	100	90	63	100	83	105	56	60	55	64	46	88	47	58	68	63	56	58	85	60	43	50
$1/10^{27}$	52	94	47	63	83	95	67	93	80	113	72	76	68	36	73	75	58	70	83	83	52	42	58	87	39	53
$1/10^{28}$	75	84	39	68	85	89	78	95	105	107	61	68	49	63	48	76	48	75	67	74	70	64	74	78	48	57
$1/10^{29}$	51	83	65	62	79	79	79	105	54	113	55	86	37	68	55	81	45	77	74	71	65	65	81	81	41	42
$1/10^{30}$	63	100	61	69	89	85	100	109	121	100	64	72	31	58	62	85	43	80	77	77	64	56	81	92	42	50

These results are for the 18 experiments with "activation" (i.e. experiments aimed for evidencing an effect of anti-IgE at high dilutions).
These results are presented as follows: columns E and G correspond to the counts of basophils in the wells containing anti-IgE and anti-IgG (controls), respectively, from $1/10^{21}$ to $1/10^{30}$.
The results from the two experimenters ED (13 experiments) and SG (5 experiments) are presented separately.
For more explanations see Chapters 16 to 19; see also the original article: 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 [*Agitating highly diluted solutions does not induce specific biological activity*]]. *C R Acad Sci* tome 312 série II n°5, February 28th, 1991 p.461–466.

(Continued on next page)

Appendix 4 (Second part). Results of the article of *Comptes Rendus de l'Académie des Sciences* of 1991

(Continued from previous page)

SG

	Exp 14		***Exp 15***		***Exp 16***		***Exp 17***		***Exp 18***	
Dil.	**E**	**G**	**E**	**G**	**E**	**G**	**E**	**G**	**E**	**G**
$1/10^{21}$	57	78	72	67	89	85	39	50	57	50
$1/10^{22}$	64	83	70	51	98	86	35	40	60	56
$1/10^{23}$	89	63	50	58	79	92	42	54	54	68
$1/10^{24}$	75	83	60	82	75	72	32	42	60	55
$1/10^{25}$	52	46	45	56	77	71	40	37	54	69
$1/10^{26}$	51	57	69	80	69	80	51	28	63	62
$1/10^{27}$	69	71	57	68	91	58	38	39	71	54
$1/10^{28}$	82	45	78	55	85	87	53	51	45	62
$1/10^{29}$	76	64	51	74	103	80	33	32	57	61
$1/10^{30}$	55	73	73	49	88	86	33	35	59	55

Appendix 4 (Third part). Results of the article of *Comptes Rendus de l'Académie des Sciences* of 1991

	ED								***SG***										
	n°1	***n°2***	***n°3***	***n°4***	***n°5***	***n°6***	***n°7***	***n°8***	***n°9***	***n°10***	***n°11***	***n°12***	***n°13***	***n°14***	***n°15***	***n°16***	***n°17***	***n°18***	***n°19***
Control	76	96.5	84.5	70.5	66.5	72	64.5	57.5	130	108.5	197.5	84	94.5	127	101.5	98	90	112	73
Anti-IgE 1/100 + control diluted and agitated ($1/10^{40}$)	34	41.5	35.5	31	36.5	31	30	30	63.5	60	90.5	43.5	48	70	53	44	46	64.5	32.5
Anti-IgE 1/100 + *A. Mel.* $1/10^{30}$	43	62	25	32	45	54	45	40	73	80	124	42	70	114	54	58	35	77	30
Anti-IgE 1/100 + *A. Mel.* $1/10^{32}$	43	42	34	32	55	47	37	44	59	79	95	47	55	70	69	39	36	51	45
Anti-IgE 1/100 + *A. Mel.* $1/10^{34}$	49	48	37	41	39	39	28	34	89	74	100	43	63	76	40	46	56	66	54
Anti-IgE 1/100 + *A. Mel.* $1/10^{36}$	57	62	33	39	28	63	38	29	62	66	80	43	60	77	43	37	46	68	30
Anti-IgE 1/100 + *A. Mel.* $1/10^{38}$	35	58	37	45	33	29	39	40	62	68	74	37	76	124	36	40	35	59	33
Anti-IgE 1/100 + *A. Mel.* $1/10^{40}$	53	67	35	40	43	39	41	43	55	79	103	38	62	74	36	43	59	55	31

These results are for the 19 experiments with "inhibition" (i.e. experiments aimed for evidencing an effect of the homeopathic medicine *Apis mellifica* at high dilutions).
These results are presented as follows: the first line corresponds to the counts for control (maximal number of basophils at resting state), the second line is the counts of basophils in the presence of anti-IgE and control (minimal number of basophils after degranulation induced by anti-IgE) and next lines are the counts of basophils in the presence of *Apis mellifica* and anti-IgE.
Each number of the first ("control") and second line ("Anti-IgE 1/100 + control diluted and agitated ($1/10^{40}$)" is the mean of two counts.
The results from the two experimenters ED (8 experiments) and SG (11 experiments) are presented separately.
For more explanations see Chapters 16 to 19; see also the original article: 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 [*Agitating highly diluted solutions does not induce specific biological activity*]]. *C R Acad Sci* tome 312 série II n°5, February 28th, 1991 p.461–466.

Appendix 5. Results of the article of Hirst *et al* (*Nature*, 1993)

Note that results are given as degranulation percentages in this table.
For more explanations, see Chapters 20 and 21; see also the original article (Hirst SJ, Hayes NA, Burridge J, Pearce FL, Foreman JC. Human basophil degranulation is not triggered by very dilute antiserum against human IgE. *Nature* 1993;366:525-7).

Table 1 out of 3

	Diluted and agitated anti-IgE								
		$1/10^{12}$	**$1/10^{14}$**	**$1/10^{16}$**	**10^{18}**	**10^{20}**	**10^{22}**	**10^{24}**	**10^{26}**
5 sessions with 8 high dilutions at $1/10^{12}$, $1/10^{14}$ … $1/10^{26}$	***1***	-12	-18	-25	-17	-3	-10	-28	-3
	2	-10	-3	-8	-15	1	3	-12	-2
	3	-1	4	-2	-4	8	11	2	9
	4	6	7	7	7	10	12	14	10
	5	10	11	17	25	17	16	25	14
		$1/10^{30}$	**$1/10^{32}$**	**$1/10^{34}$**	**$1/10^{36}$**	**$1/10^{38}$**	**$1/10^{40}$**	**$1/10^{42}$**	**$1/10^{44}$**
5 sessions with 8 high dilutions at $1/10^{30}$, $1/10^{32}$ … $1/10^{44}$	***1***	-16	-14	-12	-4	-22	-13	-13	-30
	2	-14	-13	-8	-3	-2	-6	-12	-16
	3	-2	-11	-7	2	4	-1	-6	1
	4	2	-4	12	9	13	10	-1	14
	5	28	34	13	14	25	28	33	22
		$1/10^{46}$	**$1/10^{48}$**	**$1/10^{50}$**	**$1/10^{52}$**	**$1/10^{54}$**	**$1/10^{56}$**	**$1/10^{58}$**	**$1/10^{60}$**
5 sessions with 8 high dilutions at $1/10^{46}$, $1/10^{48}$ … $1/10^{60}$	***1***	-8	-4	-19	-10	-9	-1	7	-2
	2	4	6	-10	20	1	1	9	-1
	3	5	9	8	21	11	2	17	7
	4	8	13	10	22	26	7	28	32
	5	14	24	16	41	30	29	30	35

Table 2 out of 3

	Diluted anti-IgE without agitation								
4 sessions with 8 high dilutions at $1/10^{12}$, $1/10^{14}$ … $1/10^{26}$		**$1/10^{12}$**	**$1/10^{14}$**	**$1/10^{16}$**	**10^{18}**	**10^{20}**	**10^{22}**	**10^{24}**	**10^{26}**
	1	0	-7	-22	-15	-9	-12	-10	-21
	2	1	1	-6	-6	-2	-6	-6	-9
	3	16	13	3	2	10	-4	0	9
	4	21	15	5	24	11	11	13	10
4 sessions with 8 high dilutions at $1/10^{30}$, $1/10^{32}$ … $1/10^{44}$		**$1/10^{30}$**	**$1/10^{32}$**	**$1/10^{34}$**	**$1/10^{36}$**	**$1/10^{38}$**	**$1/10^{40}$**	**$1/10^{42}$**	**$1/10^{44}$**
	1	-4	-11	9	-15	-11	-4	-12	-8
	2	4	-4	2	2	1	-2	-6	-6
	3	5	-1	4	9	2	13	1	2
	4	7	3	20	14	4	15	13	4
4 sessions with 8 high dilutions at $1/10^{46}$, $1/10^{48}$ … $1/10^{60}$		**$1/10^{46}$**	**$1/10^{48}$**	**$1/10^{50}$**	**$1/10^{52}$**	**$1/10^{54}$**	**$1/10^{56}$**	**$1/10^{58}$**	**$1/10^{60}$**
	1	-4	-9	-14	-1	-11	-7	-11	-12
	2	4	5	-12	2	-4	-3	-1	-3
	3	6	7	5	5	0	4	3	3
	4	11	8	6	7	8	12	13	7

Table 3 out of 3

	Diluted control with agitation								
3 sessions with 8 high dilutions at $1/10^{12}$, $1/10^{14}$ … $1/10^{26}$		**$1/10^{12}$**	**$1/10^{14}$**	**$1/10^{16}$**	**10^{18}**	**10^{20}**	**10^{22}**	**10^{24}**	**10^{26}**
	1	-10	-11	-7	1	-8	-9	-5	-8
	2	-9	-8	-1	2	-4	1	1	-1
	3	21	8	5	15	-3	5	15	11
3 sessions with 8 high dilutions at $1/10^{30}$, $1/10^{32}$ … $1/10^{44}$		**$1/10^{30}$**	**$1/10^{32}$**	**$1/10^{34}$**	**$1/10^{36}$**	**$1/10^{38}$**	**$1/10^{40}$**	**$1/10^{42}$**	**$1/10^{44}$**
	1	-18	-11	-2	-6	-3	-12	-3	-7
	2	-5	1	1	-4	-2	-6	1	-6
	3	4	2	4	14	1	-4	4	3
3 sessions with 8 high dilutions at $1/10^{46}$, $1/10^{48}$ … $1/10^{60}$		**$1/10^{46}$**	**$1/10^{48}$**	**$1/10^{50}$**	**$1/10^{52}$**	**$1/10^{54}$**	**$1/10^{56}$**	**$1/10^{58}$**	**$1/10^{60}$**
	1	-7	-13	-8	-5	-1	-10	-12	-5
	2	-5	-10	0	-2	2	-1	-6	0
	3	-2	1	1	-1	6	3	-3	8

Second part

The game of heart and chance

> *"The encounter with a brutal, unintelligible fact, is a dangerous experience, which puts in jeopardy both the intellectual security and the professional status of the researcher."*
>
> L. Chertok and I. Stengers[1]

[1] L'hypnose, blessure narcissique. *Les Empêcheurs de penser en rond*. 1999.

Chapter 1. A "telephone for molecules"

A scene of science fiction where one teleports "ghosts of molecules"

On July 9th, 1992, at Clamart, there was a public demonstration, which if conclusive would be a strong argument for supporting the new research of J. Benveniste. These new experiments, which J. Benveniste set up a few months ago, generated more incredulity than high-dilution experiments themselves. J. Benveniste indeed claimed that he was now capable of transferring, through an original device, the "activity" of biological molecules to water which thus acquired the "biological properties" of the original molecule.

Four visitors foreign to the laboratory participated to this demonstration.[1] The experiment, called a "transmission experiment", was performed with an electronic device which, to tell the truth, did not look much. It was reminiscent of these devices that handymen who are passionate with electronics build with components bought in specialized stores. Nevertheless, without seeming put off by the rustic character of the equipment, the visitors placed at the "output" of the device a vial of water that was called "naive". At the "input" of the device, a tube containing a solution having a biological effect was also placed. Then the device was switched on. After fifteen minutes, the tube at the "output" of the device was considered to be "impregnated"; water was supposed to have acquired the "biological properties" of the solution contained in the tube placed at the "input".

Irresistibly, we cannot refrain from thinking about the numerous scientists – crazy, of course – who populated the imagination of writers, film-makers or comic strip writers and who, through complex electric equipments, transferred the soul of a human being into a robot. The best-known example is the robot of *Metropolis*. At Clamart, however, one just transferred the "soul" of dissolved molecules… Moreover, the experiment was performed in full light, on a beautiful day of July and the various protagonists had nothing frightening. One was thus far from the nights full of lightning which usually illuminate the mad experiments of these fictional scientists.

Meanwhile, the visitors changed the labels of the water tubes that received various "imprints" during "transmission". Thanks to this coding, the results of the experiment and its interpretation could not be influenced – whatever the reason and the mechanism — by the experimenter. However, these new experiments are not subjective. It is one of the main reasons for which the test of basophil degranulation has been abandoned and replaced by this new method. As a general rule, results obtained after blind process are always more

convincing, if one can exclude of course a complicity between those who code and the experimenter.

When the operation of coding is ended, the tubes were given to Jamal Aïssa and Hédi Litime, two collaborators of J. Benveniste who were in charge of the biological model used for these experiments. Thus let us successively describe the new device for "electromagnetic transmission" and the biological system which was coupled with it.

How did the "telephone for molecules" work?

The device which allowed these unexpected experiments was a radio-electronic device built from a kit sold in specialized shops. This kit allowed building a phone amplifier at little cost with electronic components, a printed circuit board and a few weld points. In 1992, this type of device was used as a sound amplifier for a telephone. The loudspeaker, normally connected to the output of the amplifier, was replaced here by an electric coil (also known as solenoid). The input of the device was connected to another coil (Figure 1.1). The complete device was placed into a plastic box with a switch outside and input and output coils. This is a brief description of this device which was supposed to revolutionize biology. We are far from high technology and from sophisticated equipment. But, after all, important discoveries have been sometimes performed with limited equipment.

A tube containing the solution with "biological activity" to be transmitted was placed on the coil at the input and a tube or a vial containing water that one wished to "imprint" was placed on the coil at the output of the amplifier. The idea behind this device was that the variations of the electromagnetic field supposed to be emitted from the solution containing "real molecules" induced an electric current in the coil at input. This current was thought to be amplified by the low-frequency amplifier and then injected in the coil at the output therefore creating an electromagnetic field in the neighborhood of the latter. The electromagnetic field that was generated by the coil at output was supposed to structure water. Water was thus supposed to behave like a magnetic tape. The technical aspect of this device should not frighten the reader. It is sufficient to consider this electronic device as a simple "black box" with an input and an output.

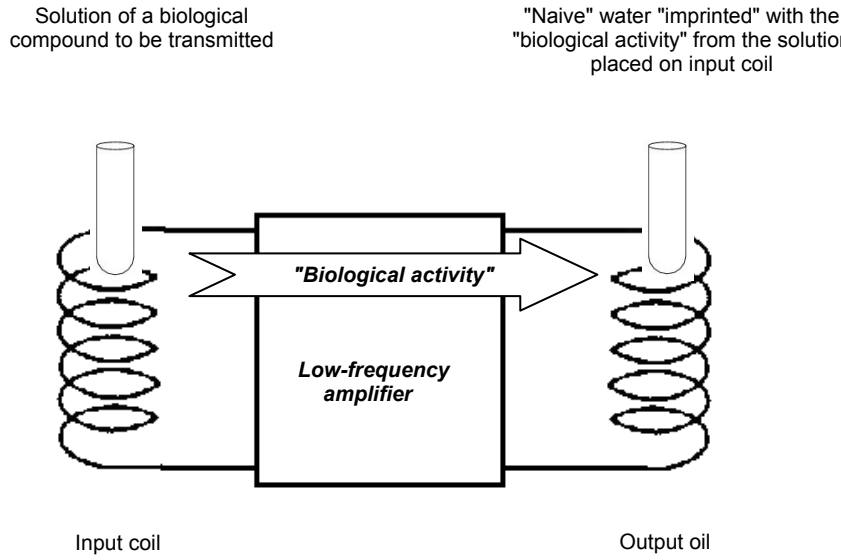


Figure 1.1. First version of the device for "electromagnetic transmission". The first version of the transmission device included an amplifier which was placed between two electric coils (solenoids). On the coil wired at the input of the amplifier, a tube containing the compound with an "activity" to be "transmitted" was placed; on the coil that was wired at the output, one placed a tube or a vial containing "naive" water to be "imprinted" thanks to the electromagnetic field supposed to be emitted from the output coil.

How to listen to information transmitted by the "telephone for molecules"?

In other words, how to know that the "ghosts of molecules" have been transmitted and have correctly "structured" water? For this purpose, a biological model which is known to react in "classical conditions" to the compound to be transmitted is used. The device of physiology used by J. Benveniste for these experiments is called "Langendorff preparation" or isolated infused heart. It allows physiologists to maintain the functions of a heart of rat or guinea pig during several hours. The effects of pharmacological agents on heart functioning can thus be studied.

Here again, we will simplify the technical descriptions so as not to dilute the main subject. The model of Langendorff is a very classic experimental device in heart physiology. It allows measuring various parameters of the heart functioning: frequency, tension of the cardiac muscle or coronary flow. We will talk only about coronary flow because the team of Clamart quickly focused on it.[2] It is indeed with the changes of this parameter that the effects of high dilutions and electromagnetic transmissions were best evidenced.

The understanding of these experiments requires simply remembering that one studies the flow of a liquid which – by construction – goes necessarily through the coronary arteries. The coronary arteries play the role of flow regulator according to their state of contraction. To visualize the coronary flow and it variations, the reader can imagine a flexible rubber pipe enclosed in a fist. As the fist tightens more or less the pipe, the flow of water varies accordingly. When the muscles of the wall of the coronary arteries contract, the flow through the artery decreases. On the contrary, if the muscle fibers of the wall relax, the flow increases. This is what is sketched on Figure 1.2.

How was the coronary flow measured? Simply by using an automatic sampler, which collected the liquid that flowed under the device (one minute per tube) (Figure 1.3).

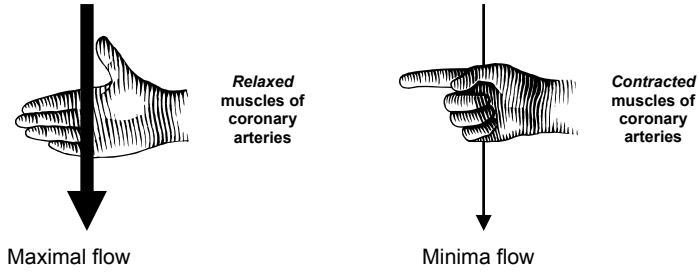


Figure 1.2. Flow changes of coronary arteries. The flow of liquid through coronary arteries is like the flow through a flexible pipe. The flow depends on the state of contraction of the muscle fibers in the wall of the coronary arteries. These muscle fibers are pictured here by a hand. When the muscle fibers are relaxed, the coronary flow increases; on the contrary, when they contract the coronary flow decreases. Various biological or pharmacological substances (mediators of inflammation, acetylcholine, bacterial endotoxins, etc.) modify the contraction state of these muscles. The consequences are variations of coronary flow.

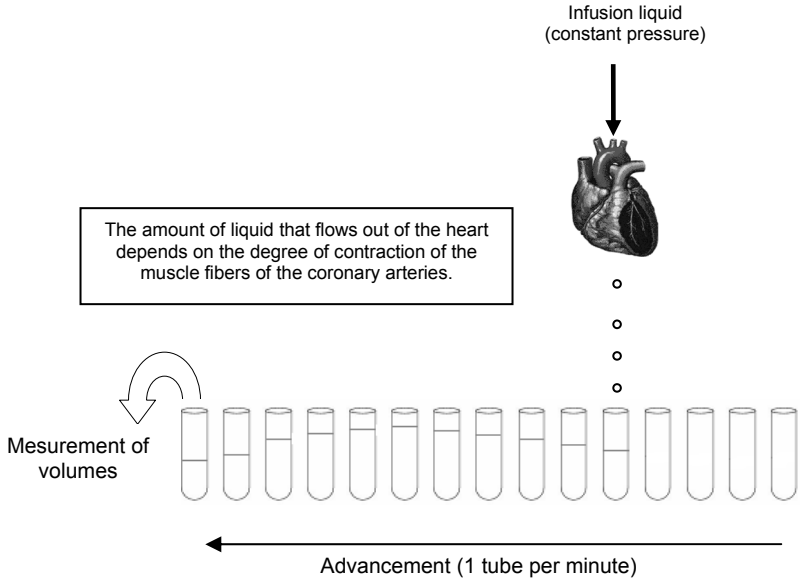


Figure 1.3. Measurement of coronary flow of isolated heart of guinea pig or rat.
The heart is continuously infused by a physiological liquid. The amount of liquid which flows outside the heart varies according to the state of contraction of the muscles in the wall of the coronary arteries. The liquid is collected in tubes which circulate below (one per minute). The volume of liquid in each tube is measured through a graded tube with a precision of 0.1 mL.

To understand how the changes of coronary flow are interpreted, here is how the results appeared for the blind samples n°3 and n°4 of the experiment of July 9th on the worksheet of the experimenter (Figure 1.4). Each minute, the volume collected during this duration is recorded. The injection of the sample is performed when the coronary flow is stable (during at least 3 minutes).

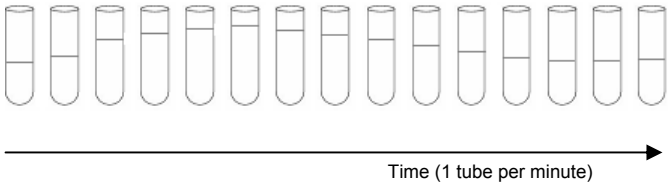
Figure 1.4. Measurement of the coronary flow of the isolated heart of guinea pig or rat. Here is a data sheet in an experiment intended to assess variations of the coronary flow with the Langendorff device. After checking the stability of the flow for 3 minutes, the sample to be tested was injected (arrow). Every minute, the physiological liquid was measured with a precision of 0.1 mL and the result was recorded in the corresponding column and line. On this example we note that the sample n°3 induced a change of the coronary flow ("active" sample) whereas the sample n°4 did not induce significant variations ("inactive" sample).

	Volumes (mL)	
Time (min)	n°3	n°4
-3	4.0	4.1
-2	4.0	4.1
-1	4.0	4.1
1	4.0	4.1
2	4.5	4.0
3	5.8	4.1
4	6.5	4.1
5	6.8	4.0
6	7.0	4.1
7	6.9	4.1
8	6.2	4.0
9	6.0	4.0
10	5.5	4.1
11	5.0	4.1
12	4.5	4.1
13	4.2	4.1
14	4.2	4.1
15	4.2	4.1

With the sample n°3, we observe that the flow which was 4.0 mL/min at the baseline increased from the second minute and reached a maximum of 7.0 mL/min at the 6th minute and then gradually decreased. There were only few changes with the sample n°4: the values oscillated between 4.0 and 4.1 mL/min. Even without cutting-edge knowledge in biology or in statistics, it is easy to understand that these two samples were associated with very different profiles of flow variations with time (Figure 1.5). Let us recall that these two samples were initially the same. The only difference *a priori* could be only in a property acquired during the process of transmission.

Experiment of July 9th, 1992

Effect of sample n°3 on coronary flow (active sample)



Effect of sample n°4 on coronary flow (inactive sample)

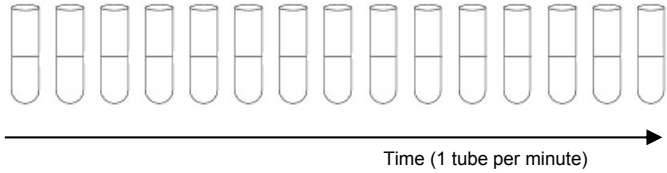


Figure 1.5. Effects of samples n°3 and n°4. This figure illustrates the "direct" demonstration of the effects of high dilutions or electromagnetic transmissions with the Langendorff device. The samples n°3 and n°4 were tested on July 9th, 1992 in a blind experiment (cf. Figure 1.4). One notes on these pictures where the volumes of liquid from the 1st to the 15th minute are represented to scale that the variations of flow for the sample n°3 are immediately visible; on the other hand, concerning the sample n°4, one notes that there was no change of the flow.

On the isolated heart, a pharmacological agent is all the more "active" that the change of coronary flow which it induces is more important. Since the basal value can varies with different preparations, one generally gives the maximal variation of the coronary flow as a percent of the basal value measured during the minutes which preceded the injection:

$$\% \text{ of maximal change of coronary flow} = 100 \times (\text{maximal flow} - \text{minimal flow})/\text{basal flow}$$

Thus for sample n°3, one calculates a maximal change of coronary flow equal to $(7 - 4)/4 = 75\%$. For sample n°4, one finds, $(4.1 - 4)/4.1 = 2\%$.

This calculation always gives positive values. We could distinguish the overall decreases or increases of the coronary flow but we will not do it for reasons of simplification and especially because it has no impact on the understanding and the interpretation of the experiments that we describe here. Unless expressly

indicated, what is reported is always a percentage of absolute change of coronary flow. To put it simply, we try to know if something "moves" but we are not interested in the direction of this change. However, on graphs, we can distinguish the increases and the decreases of the coronary flow with time because in this case the formula applied for every experimental point is:

% of change of coronary flow at time t = 100 × (flow at time t – minimal flow)/basal flow

In practice, one considers that below 10% the change of flow is not significant. We can thus conclude that sample n°3 was "active" and that sample n°4 was "inactive".

Two hearts which beat in unison

The above description allows understanding the interest of J. Benveniste for this experimental device in his quest for the "crucial" experiment which would convince skeptics. On one hand, the effect (or the absence of effect) can be seen first hand within a few minutes after the administration of the content of the "imprinted" vial. On the other hand, "transmission" was made in a sealed vial while the preparation of high dilutions required the decreasing passage of molecules from tube to tube with consequently a non-zero risk of contamination. Even if we reported arguments against contamination as an explanation of the high dilution results in the first part of this book (Chapter 15), the fact that this question was discarded, was obviously more satisfactory.

Furthermore, during several years, from 1992 to 1996, Benveniste used two Langendorff devices that worked in parallel. The purpose was not to increase the pace of the measurements, but rather to consolidate the results with two measurements for the same sample on two different hearts. Besides, a series of samples was sometimes tested in ascending order on device A and in descending order on device B. This allowed making sure that there was no persistence or contamination due to a previous sample. Useless to say that this kind of precaution – that is the use of dual equipment – is rare for "classic" researches.

If we come back to the samples of the experiment of July 9th, we notice that, tested in parallel *on the second device*, the samples n°3 and n°4 confirmed the previous results (Figure 1.6) with 93% of maximal variation for n°3 and only 3% for n°4. We consequently feel more assured for these results. We must admit that we chose these samples for didactic reasons because the change or absence of change was obvious. On average, as we will see, the changes of the coronary flow were rather around 20%.

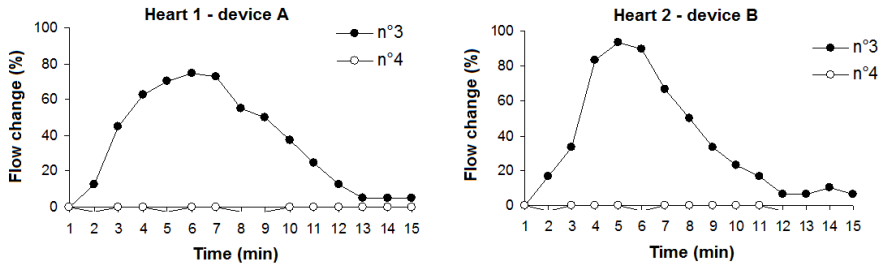


Figure 1.6. At each time point (in minutes), the change of the coronary flow is calculated as a percentage by dividing every change of volume in mL with the basal value of the flow. These percentages are shown on these figures. They correspond to the changes of coronary flow reported for samples n°3 and 4 coming from the experiment of July 9th, 1992. It must be noted that each of the samples was tested on two Langendorff devices which worked in parallel in order to confirm the results.

With some compounds or in some experimental situations, the profiles of the coronary flow over time can be much more complex than in these examples where a simple increase of the coronary flow was observed. Thus, a decrease of the coronary flow, then an increase and finally a return at the basal level were sometimes noticed. This could be due to the large number of mediators released by the heart during this type of reaction. Some substances dilate coronary arteries and consequently increase coronary flow. It is the case for example with nitro vasodilators which are used in patients with coronary insufficiency. Other pharmacological substances such as caffeine contract coronary arteries and thus decrease coronary flow. Rats become allergic to proteins such as ovalbumin (albumin of white egg) after injection of this protein. A few weeks later, the heart of the animal is placed in the device of Langendorff and an allergic reaction is induced by the injection of a small quantity of this protein in the liquid of infusion of the heart. This allergic (or anaphylactic) shock is accompanied with an upheaval of the functioning of the heart. Indeed, diverse mediators of inflammation are then released by heart tissues and various profiles of coronary flow – combining increase and/or decrease – can be observed according to the sequences of release of the mediators.

Generally, after the last "imprinted" sample had been tested during a working session on an isolated heart, a sample of the compound at "classic" concentration" was tested (for example, ovalbumin at 0.1 µmol/L) to assess the reactivity of the heart (calibration) and to demonstrate that the biological preparation had a normal behavior in "classic" conditions.

Another compound – known as lipopolysaccharide (LPS) – was often used in transmission experiments. LPS is an endotoxin, which is a substance from the bacterial wall also inducing a variation of the coronary flow.

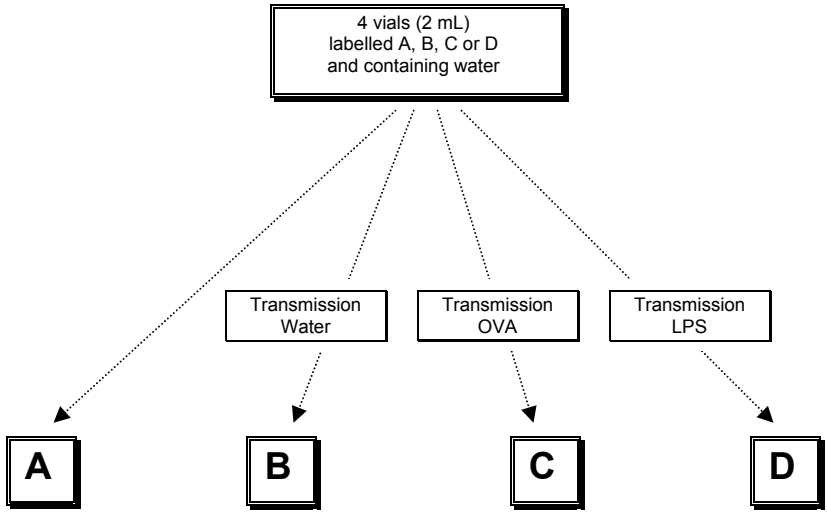
Which "messages" were transmitted on July 9th through the "telephone for molecules"?

As indicated on the technical sheet on the next page, several molecules underwent the process of "transmission" during this experiment of July 9th, 1992. First, ovalbumin (sample C) and LPS (sample D) were transmitted from samples containing solutions of these substances. Then, as a control, a vial of water (without dissolved compound) underwent the same process of transmission (sample B). Finally, a vial of water which did not undergo transmission was also included in the experiment as an additional control (sample A).

Overall, 12 tubes were prepared and one expected to find 5 active samples (4 "ovalbumin-transmitted" samples and 1 "LPS-transmitted" sample) and 7 inactive samples. It is necessary to note that one did not try to discriminate LPS and ovalbumin in this experiment. One "simply" wished to discriminate "active" and "inactive" samples. In order to understand the stake of this experiment, it is necessary to remember that, in the current state of knowledge, there is no physical, chemical or biological means to discriminate these various samples.

Technical sheet of the experiment of July 9th, 1992

Type of experiment: electromagnetic transmission on July 9th, 1992
Place of the experiment: Clamart (for transmission and assessment of samples)
Blinding: on July 9th by 4 participants not belonging to l'U200; unblinding on July 13th.
Number of recordings to be tested: 12 tubes tested on July 10th on 4 hearts (measurements on the two Langendorff devices in parallel).
Additional in-house blinding: no.



Blinding of 12 tubes* numbered from 1 to 12 (*blind tests*):

4 tubes "**A**"; 3 tubes "**B**"; 3 tubes "**C**"; 2 tubes "**D**"

+

3 tubes not blinded (*open-label tests*):

1 tube "**A**"; 1 tube "**B**"; 1 tube "**C**"

*The content of each tube was obtained after 1/1000 dilution of "informed" water in physiological saline for heart infusion.

Consistent results

On July 10th, a small volume of each of the 12 tubes was injected in the infusion circuitry of the two devices of Langendorff. We have already anticipated the results obtained with samples n°3 and n°4. Four hearts of guinea pig allowed the testing of all samples (2 successive hearts for each device). The results are described in Table 1.1.

Test samples	Maximal changes of coronary flow	
	Apparatus A	Apparatus B
Blind tests		
n°1	55%	15%
n°2	58%	24%
n°3	75%	93%
n°4	2%	3%
n°5	93%	53%
n°6	3%	2%
n°7	5%	5%
n°8	8%	8%
n°9	3%	5%
n°10	3%	5%
n°11	13%	14%
n°12	42%	37%
Open-label tests		
Water	2%	3%
Transmitted water	2%	3%
Transmitted ovalbumin	35%	37%
Ova 0.1 µmol/L	55%	45%

Table 1.1. Results of the experiment of July 9th, 1992 before unblinding. One expected to find 5 active tubes (transmitted ovalbumin) and 7 inactive tubes (water or transmitted water). One indeed notices that 5 samples induced large changes of coronary flow: samples 1, 2, 3, 5 and 12 (there was however a doubt on sample 11 which had values superior to 10%). Expected results were obtained with open-label samples.

The results of the experiment therefore seemed consistent. We indeed notice that 5 samples (n°1, 2, 3, 5 and 12) were very active during two independent

measurements.[3] Furthermore, the open-label controls were correct. It would be astonishing if the experiment was not a success. But it is necessary to wait for the unblinding which took place next Monday.

Notes of end of chapter

[1] The participants in this experience were Raphaël Douady (CNRS, Ecole Normale Supérieure, Paris), Alexandre Fiebig (Ecole Normale Supérieure Cachan), Anne Jullien (medical student) and Michel Schiff (CNRS, Paris).

[2] For the interested readers, let us remind that the coronary arteries irrigate the heart muscle. Their entry is situated on the aorta, where the latter leaves the heart. In the Langendorff preparation, the circulation of the liquid is against the normal flow. Indeed the physiological liquid at constant pressure is administered by a cannula introduced into the aorta by taking care of not going too far and to block the entry of the coronary arteries. The valves of the aorta prevent from penetration into the left ventricle. The liquid is then forced into the coronary arteries. Having irrigated the heart, the liquid is collected by the coronary sinus and conducted into the right auricle. The liquid thus goes out of the heart by the right vessels.

[3] One could consider that sample n°11 being above 10% is significant. It was moreover considered inactive but doubtful ("negative?" was reported on the data sheet before unblinding). One could also point out that given the important reactivity of the heart on this day for this series of samples, the background noise could be higher.

Chapter 2. The broadcasting (or not) of "pernicious" information

The Director of Inserm does not like typing errors

The unblinding of the experiment of July 9th, 1992 was experienced as a triumph by Benveniste and his team. The mean changes associated with each tube are presented in Table 2.1. The tubes which were associated with the highest biological activity were samples 1, 2, 3, 5 and 12 that corresponded to ovalbumin or LPS. Other tubes contained either "naive" water or "transmitted water", i.e. controls which were supposed to not modify coronary flow. Especially, in the previous chapter, we followed samples n°3 and n°4 step by step and we observed that n°3 was "active" whereas n°4 was "inactive". We know now that n°3 was "transmitted ovalbumin" and n°4 was "transmitted water".

J. Benveniste exulted. It was – if the experiment was confirmed – the crowning of long-term sustained efforts and J. Benveniste intended to repeat this type of demonstration so that other scientists would be convinced and could witness on the reality of the phenomenon. He immediately drafted a report of the experiment where, in conclusion, he did not hesitate to write in bold type:

> "This experiment eloquently demonstrates the transmission of a biological activity by an electronic circuitry, asserting without any possible objection both the electromagnetic nature of the molecular information and the role of water as a magnetic tape, memory of this information." [1]

Maybe it was jumping the gun. But the results were there and J. Benveniste explained: "There is a probability 1/4000 that this result is due to chance".

To allow an easy reading of the tables of results, even for the reader who is not accustomed to analyze this type of experiments, the following presentation is adopted for all tables: means of biological activity are classified ***in an increasing order*** and samples ***supposed to be active according to the code*** are indicated ***in bold characters*** in the last column. The "aim of the game" is thus to put a maximum of "bold" ***in the box at the bottom of the last column***.

Tested samples	% of maximal changes of coronary flow (means)	Biological activities in increasing order	Unblinding
Blind tests			
n°6	3%	1	Water
n°4	3%	2	Water tr.
n°9	4%	3	Water
n°10	4%	4	Water tr.
n°7	5%	5	Water tr
n°8	8%	6	Water
n°11	14%	7	Water
n°1	35%	8	**LPS tr.**
n°12	40%	9	**Ova tr.**
n°2	41%	10	**LPS tr.**
n°5	73%	11	**Ova tr.**
n°3	84%	12	**Ova tr.**
Open-label tests			
Water	3%	-	-
Water tr.	3%	-	-
Ova tr.	36%	-	-
Ova 0.1 μmol/L	50%	-	-

Table 2.1 Result after unblinding of the experiment of July 9th, 1992. As indicated in the above box (last column of the table), the mean values of the biological activity were ranked in increasing order. After unblinding (right column), one notices that the highest activities correspond to the samples which were supposed to be the most active (LPS tr. and OVA tr. are all in the box at the bottom of the column "unblinding"). It was thus a "success" and it was indeed as if an "electromagnetic transmission" occurred.
tr.: Transmitted.

J. Benveniste sent this report to the participants of the experiment and to the Director of Inserm, P. Lazar, whom he always took care of informing on his work. If J. Benveniste expected to receive warm congratulations and enthusiastic encouragement of his administrative hierarchy, namely P. Lazar, it did not happen. The Director indeed answered him – with delay – by a brief, unkind and almost threatening letter:

> "You sent me a circular letter on July 27th concerning an experimental result that could "hold my attention".
>
> I would like to point out that the attached sheet contains evident typing errors (the indications at the bottom of the table on "H2O") and considering the sensibility, which you are well aware about your activities, there are surprising deficiencies of explanations ("There is a probability of 1/4000 that this result is

> due to chance": *Which* result? Which difference between H2O and H2O tr?).
>
> I would like to seriously draw your attention on the pernicious character of the broadcasting of such "information".
>
> If you had to persist in this type of behavior, I would be obliged to take serious actions." [2]

The "serious consequences" to which P. Lazar alluded were probably related to the next renewal of the laboratory of J. Benveniste that shall be discussed one year later by the scientific committees and the administration of Inserm. J. Benveniste then answered to P. Lazar:

> "The report of experiment which I sent you is not a circular letter. It is a result of an experiment, intended for the dozen scientists who now oversee these experiments at U200. […] The scientific events which take place now at Clamart are indeed of a sufficient importance so that I inform about them step by step, as I always did, a limited number of officials. The purpose is to keep in touch, to look for a support and to allow criticisms and suggestions of the highest number of scientists, as yourself and the President of the Republic himself in a recent letter had constantly encouraged me. I thank you on one hand for your possible personal scientific participation and on the other hand for indicating me very exactly what is now forbidden to me and on what basis?
>
> I send you a modified version of this report. There was effectively *one* omission, H20 tr. I rewrote the comment so that the difference between the active tubes and the controls appears more clearly, because it seems that you did not notice it". [3]

In a letter which he sent on September 1st after the response of P. Lazar to a "colleague and friend" who was close to the management of Inserm, J. Benveniste expressed his anxiety:

> "I send you these elements so that you can judge what motivates this storm (not diluted) in a glass of water. This answer worries me because: either P. Lazar loses his cool, and it is disturbing in itself; either he gives in to outside pressure, which that become very strong after the disclosure of our transmission experiments, and anything and everything, including the most absolute arbitrary power, can arise.
>
> In both cases, the researchers of U.200, who – is it necessary to remind? – and, even if they make a mistake this time, committed no crime, no fault and scientific error, with continuous "classic"

> production in journals of the best level, will need your help and your advices."

"The consequences of these new results will be incalculable."

Despite the veiled threats of P. Lazar related to the "pernicious character of the broadcasting of such "information" ", J. Benveniste sent a circular letter to many scientists and colleagues to inform them about these results and to invite them to participate in these experiments:

> "In the past few weeks, we obtained a scientific result, which was certainly predictable, but which is not less surprising. To put it simply, we transfer an activity […] between two sealed glass vials through a radioelectric device. […] The transmitted activities disappear with heating which leaves the original molecules intact. We just "unblinded" an experiment, in collaboration with a group of scientists not belonging to the laboratory: 12 correct results out of 12, there is a probability 1/4000 that this is obtained by chance […]" [4]

J. Benveniste can then expose his ideas on the conceptual framework of these results:

> "Now one will have simply to accept that a biological molecule, at least in its function of specific signal, is in fact the only support, inert in itself, of fluctuating charges that generate a specific radioelectric activity which is the true vector of the molecular information. The natural role of water around molecules is the role of a liquid magnetic tape capable of storing temporarily, and maybe amplifying, the information between two molecules at a distance of a few angstrom. Only molecules presenting co-resonant fields […] can recognize themselves, even remotely, and then can communicate by exchanging energy. Yet, we know almost nothing at present about mechanisms of recognition and exchange of molecular information […]. Nevertheless, the consequences of these new results will be incalculable …"

Finally, he linked these results with the "memory of water":

> "*[These results]* confirm what was called – we know it now with good reason – "the memory of water". By diluting/shaking we have, it seems, artificially separated the molecules of their natural environment, water, which preserves information, by mechanisms

> still to explore but for which theories are published, and transmits it from molecule to molecule."

Finally, he invited the recipients of the letter to join the group without wasting any time because, he said "U200 being guilty (we confessed it) of innovation outside the allowed limits will soon be closed".

New experiments were already scheduled. Did they confirm this first success?

Notes of end of chapter

[1] Letter of July 27th, 1992 to the participants of the experiment of July 9th, 1992.

[2] Letter of P. Lazar to J. Benveniste of August 18th, 1992.

[3] Letter of J. Benveniste to P. Lazar of August 25th, 1992.

[4] Circular letter of J. Benveniste dated July 1992.

Chapter 3. From "high dilutions" to "electronic transmission"

Back to "high dilutions"

Before speaking about the developments with the "telephone for molecules" in Chapter 4, let us go back a few years and see which thought process J. Benveniste followed in order to set up these outstanding experiments.

The first experiments with the device of Langendorff and high dilutions took place in March 1990. Indeed, a researcher of the laboratory, Lahlou Hadji, then used this experimental model to study the effects of the mediators of inflammation and allergy on heart functioning. Quite naturally, given the context and the "high-dilution" atmosphere which reigned in the laboratory, L. Hadji studied if substances which modified the functioning of heart at "classic" concentrations had also an effect at dilutions where molecules had virtually disappeared. High dilutions of paf-acether – the mediator discovered by J. Benveniste – were thus prepared according to the usual method of dilution and shaking. Positive results were obtained – as well as with high dilutions of histamine – and it appeared that the most reproducible and most marked effects were observed on the coronary flow.

It was thus a major result. It meant that the results obtained with basophils could be generalized to another experimental model. Moreover, this new model possessed a notable advantage. Indeed, it allowed visualizing "in live" the effects of high dilutions without any intermediate. It was thus much more convincing than the previous experiments with basophils.

We remember that high dilutions had an effect on basophils that depended on the place of the dilution in the series and gave the famous "sinusoidal" curves. To avoid testing long series of dilutions, an ingenious method was used. A series of successive dilutions – generally the dilutions from $1/10^{31}$ to $1/10^{41}$ – were mixed. This high dilution was named "pool 31–41" and was often used during these experiments. Figure 3.1 shows the effects obtained with histamine at a high dilution in two experiments as an example of experiments performed in January 1991.

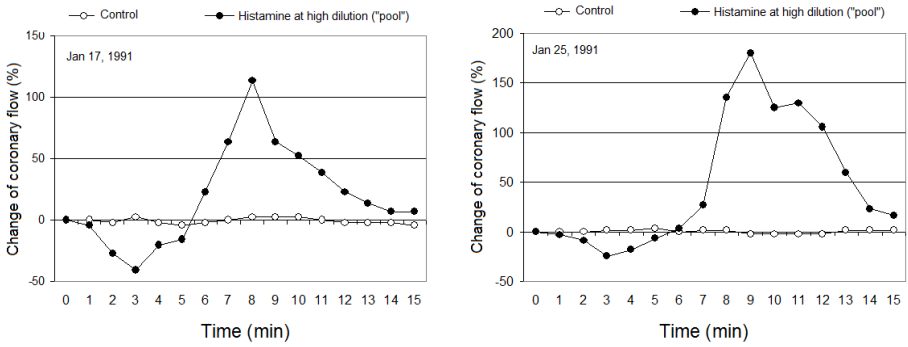


Figure 3.2. This figure shows the effect of histamine at high dilution ("pool 31-41") in 2 out 10 experiments which were performed from January 17th to 25th, 1991. One notes a large change of coronary flow which exceeded 100%. Such large variations were only rarely observed afterward (for the 10 experiments the mean change of coronary flow was 51%).
The high dilution of histamine was obtained by dilution-shaking of histamine at 1 mmol/L up to dilution $1/10^{41}$. The dilutions from $1/10^{31}$ to $1/10^{41}$ were then mixed. Before being injected into the infusion circuitry of the heart, this "pool" of high dilutions of histamine was diluted with shaking at 1/1000 in physiological saline that was used for infusion. During this series of experiments, each injection of histamine at high dilution was preceded and followed by injection of a control prepared in the same conditions, but with solvent alone.

"The high dilutions, we do not know how it works, but it works"

The device of Langendorff offered then a unique opportunity to move forward in the understanding of the physics of high dilutions. This period reminds us of the one which followed the "discovery" of the second peak of basophil degranulation (cf. first part). A wide boulevard seemed to open under the feet of the Clamart team. With the system of Langendorff, the effect of physical means (heat, electromagnetic radiations) could be studied in a relatively easy way. Thus, the effect of heat which had been highlighted with the basophil model was found again: heating at 70°C for 30 minutes "erased the memory". The specificity was also highlighted; an inactive analog of histamine (methyl-histamine) had no effect at high dilutions.

J. Benveniste kept in mind the theory of the Italian physicists, Giuliano Preparata and Emilio Del Giudice, which was published in the same year as the article of *Nature*. This theory could be the support of a possible "memory of water", as J. Benveniste explained:

> "The Italian physicists had developed a theory known as theory of the "coherent domains", which postulates that the molecules of solids and liquids are not connected between them only because they exercise electrostatic forces on their neighbors, as it is usually admitted. According to their theoretical model, these molecules would also exercise long-range *electromagnetic* forces and fields between them." [1]

J. Benveniste thus moved towards an explanation of the "memory of water" where these hypothetical long-range electromagnetic fields would play an important role. It should consequently be possible to modify the effects of the high dilutions by submitting them to electromagnetic fields:

> "To verify this, I got in touch with physicists of the Central Laboratory of magnetism of the CNRS at Meudon. […] We designed together a protocol of experiments: I sent a series of test tubes to this laboratory, containing histamine at usual doses and histamine diluted up to 10^{-41}. On site, the various tubes were submitted to electromagnetic fields with a low frequency. […] About hundred experiments were performed in 1990 and 1991 (in particular with histamine, but also with other active compounds)."

These experiments, performed blind with the cooperation of two CNRS researchers, Marcel Guyot and Vladimir Cagan, allowed J. Benveniste to conclude that the physical support of "memory of water" had an electromagnetic nature:

> "With the hearts of guinea pig infused with various liquids, I notice that magnetic fields inhibit the effect of histamine at high dilution whereas they have no effect on histamine at usual active dose. […] The laboratory of the CNRS in question can testify the reality of the results of these blind experiments. These researchers often repeated to me: "The high dilutions, we do not know how it works, but it works" ". [2]

J. Benveniste did a scientific communication on these results as a "poster" during a congress of the FASEB (*Federation of American Societies of Experimental Biology*) in 1991. [3]

Difficult days

However, dark clouds accumulated in the sky of Clamart. Indeed, after the enthusiasm of the first experiments, the spectacular biological effects which were then observed became scarcer. The exploration of the physical properties of the high dilutions passed in the background. The priority was to find a stable biological system reacting to high dilutions. To explain these difficulties, reasons concerning the sensitivity of animals according to the season and according to the state of immunization were hypothesized by J. Benveniste:

> "These experiments gave impressive results and then relatively irregular results until December 90. However we obtained enough information to be able to present an abstract to the congress of the FASEB [4] in April 91 concerning the first results obtained in autumn 1990 on histamine at high dilution on isolated heart of guinea pig. At this date, we had also collected enough elements with M. Guyot and V. Cagan to show an inhibition by a magnetic field of 50 periods 150 oersteds during 30 min […].
>
> However it appeared that the sensitivity of guinea pigs to histamine, even at usual concentration, was variable, most probably according to the season and, furthermore, according to poorly known experimental variations." [5]

In this uncertain context, the first public demonstration was nevertheless programmed on February 13th, 1991. The results were not convincing as J. Benveniste told in his report:

> "This first session for the demonstration of an effect at high dilution on the heart of guinea pig, in front of people who did not belong to the laboratory, has been instructive. Let us specify that, on this day, the heart did not work as we expected. There is approximately one heart among ten which does not react at all to histamine, but the type of reaction that we saw today is seemingly unique. Indeed, while the heart was generally stable, it began reacting to any injection by a weak but clear and *immediate* increase of the coronary flow, with either histamine or diluted buffer." [6]

These difficulties have nothing unusual in physiology but, for a first demonstration, these trivial problems were particularly inopportune. Other public experiments, on April 3rd and 15th, took place with results which were not more encouraging. [7]

Faced with these technical difficulties, a new protocol was set up. Histamine was discarded and replaced by ovalbumin (white egg albumin), a protein often

used to induce allergy in laboratory animals. Animals were thus prepared a few weeks before with the injection of ovalbumin at "classic" concentration and a reaction of the heart was induced by the same protein at high dilution:

> "As a consequence, during year 1991, we began to increase the sensitivity of guinea pigs by immunizing them against a very sensitizing antigen, ovalbumin, associated with an adjuvant capable of increasing the production of antibodies, the complete Freund's adjuvant. At the end of December 91, we had enough information to be able to send an abstract to the FASEB again […] reporting a reaction of hearts to highly diluted albumin." [8]

But again the experimental results became disappointing:

> "However, the results continued to be erratic, excellent for a few weeks, and then null. Altogether, these variations could not be imputed to the system at high dilution because they also occurred on hearts stimulated with normal concentration. In fact, the practice of the technique was rather unreliable in the laboratory and at that time we had many difficulties obtaining an experimental regularity of the experimenter and of the researcher in responsibility."

J. Benveniste, not succeeding in understanding the source of these variations, was eventually persuaded that the source of these problems was a lack of care and precautions during the experiments led by L. Hadji. A conflict emerged between J. Benveniste and L. Hadji which ended at the departure of the latter from the laboratory. A malaise persisted after the conflict because the reasons of the grievances of J. Benveniste towards his researcher seemed irrational and questionable both scientifically and humanely. In a tense atmosphere, J. Benveniste had nevertheless to resume the experiments with staffers having no experience of this biological system which required some dexterity and long experimental practice. Other difficulties arose and they were then interpreted as water "contamination":

> "From January 1992, we have thus changed the staff and resumed both the process of immunization and the various experimental steps from the beginning, because from this time we were very worried about contaminations by endotoxin, coming for example from water used for infusions." [9]

We will dedicate a complete chapter to the question of the "contaminated serum". But these temporary difficulties with the biological model were forgotten for a while because a major event arose in spring 1992.

The "invention" of the electromagnetic transmission

As we will repeatedly notice, when the experimental system became difficult to master, a cunning improvement of the experiment or a new attractive technique each time allowed "to relaunch the machine" and to find faith in future. In this case, a decisive event opened a new chapter, the advent of "electromagnetic transmission". The idea that the support of the effects of high dilutions was electromagnetic made its way because, as J. Benveniste said:

> "In spring 1992, I speak about these experiments done in association with the CNRS to a friend electronics engineer.
> "If it is an electromagnetic field which is emitted by molecules, he explains to me, you must be able to do it get through an amplifier and to make it circulate"." [10]

The friend of J. Benveniste then built a low-frequency amplifier using a cheap kit which one finds in electronic shops. Two electric coils (solenoids) were connected, one at the input and the other one at the output of the device. Having placed a tube of histamine on the coil at the input and a tube of "naive" water on the coil at the output, the first experiment could be performed:

> "I let the amplifier work during fifteen minutes with maximal volume. For the first testing, the content of the tube at the output, infused in the Langendorff system, induced a response of the heart of isolated guinea pig." [11]

The fact that the experiment was a success as soon as the first attempt remains intriguing for anybody who has some experience about experimental work. It is a permanent feature during this story to see the first attempts almost systematically successful. Thus, the first experiments performed in association with the Laboratory of magnetism of the CNRS to "erase the memory" were performed for practical reasons with fields of low frequency at 50 Hz (the same frequency as mains electricity). In case of failure, higher frequencies would have certainly been tried. But, here again, the first attempt was the good one. Concerning the amplifier, it was far from evident that a cheap amplifier limited to the audible frequencies (20 to 15 000 Hz) would work. Indeed, one would rather expect electromagnetic waves at high frequency if they were the support of the effect of high dilutions as explained by J. Benveniste:

> " […] the physicists consider that molecules taken individually emit vibrations of very high frequency (in the terahertz). Making the hypothesis that they would emit signals in the range of sound waves […], what must be indeed the case since a phone amplifier transmits them, would be thus incompatible with the dominant theory. But this contradiction could be overtaken if we do not consider the vibration (*one* wave), emitted by a given molecule, but wave trains, that are billions of vibrations emitted by a molecule or a set of molecules *every second*. We collect in this case the "beat frequencies" of this train of waves, which is the average of the differences between the frequencies. The beat frequencies summarize the billions of vibrations in a single wave whose the frequency could presumably be in the range of low frequencies." [12]

The explanation of the phenomenon with low-frequency beatings is thus an *ad hoc* explanation which allowed reframing the theory with the experimental facts and therefore to "save the phenomena". Indeed, nothing proved at this stage that this explanation was the good one. Moreover, low-frequency beats between two waves require that they have very close frequencies (less than 1 % of difference).

"The perfect trap"

During the summer of 1992, blind experiments with a public were again performed but now with the system of "electromagnetic transmission". Thus, on June 16th, 1992, a public demonstration was performed in the presence of visitors, in particular M. Schiff who will be soon talked about. But, as J. Benveniste indicated in his report: "the results were not satisfactory".[13] And he added:

> "The "transmitted control" was negative but not the naive vial which induced a slight reaction after a simple dilution. We had not seen a wrongly positive control for several months! On 17th, this vial once again induced a mechanical and vascular reaction. Other vials of distilled water [with brand name] Biosedra also induced a reaction of the coronary arteries. Conclusion: the water in bottle is excellent; this one of the same brand in vial is contaminated! The perfect trap".

We will talk again about this experiment of June 16th because it was the starting point of the "contaminated serum" affair that we will describe in Chapter 5. In the same report, J. Benveniste underscored again the difficulties of these demonstrations with spectators:

"Furthermore, we observed that it is materially difficult to perform complex experiments, implying numerous steps, each of them being crucial, in the middle of five to six people who cannot remain silent and motionless. Demonstrations can be made, but with a simpler protocol: an active vial versus one control. […] Since 16th, five or six transfers were performed with a total success, including a blind experiment and including a heart which definitively stopped having received distilled water imprinted with information from "histamine" log 31–41, that is distilled water."

Unfortunately these last successful experiments mentioned by J. Benveniste were not performed with the participation of outside visitors who could testify. A new demonstration was performed on June 30th, 1992 in front of visitors but, again, it was a failure:

> "The results of the analysis are clear: the two experiments with histamine did not work, with numerous controls giving positive results and, on the contrary, tubes supposed to be active giving no result. On the other hand, we detected 7 ovalbumin tubes (OVA) among 7. […] The results of the samples OVA are particularly clear, in particular when we compare the very positive effect of the sample 15 on the OVA-immunized heart with the heart of a guinea pig having received only the adjuvant (alum) where the same sample gives no result. This indicates that a transfer indeed occurred, that it is completely specific, but that we are still disturbed by very numerous background noises." [14]

He added a postscript on July 2nd before sending this letter to the participants: "the controls in distilled water, saline solution and clean sterile vials are negative. Transfers work […]. All these experiments are open-label. If this is confirmed in blind experiments during several days, […] we could resume our games."

On July 9th, the experiment described in Chapter 1 was performed and satisfactory results were finally obtained. J. Benveniste hoped that this celebrated demonstration was the first one of a series of successes which would allow him to convince the scientific community that his approach was valid.

A participating researcher

During some of these experiments, we saw Michel Schiff's silhouette, researcher at the CNRS, making its appearance. A physicist by training, M. Schiff then turned to human sciences and sociology of sciences. Having ended a thesis of

physics in the United States at Yale University (New Haven, Connecticut), he returned to Paris and entered the CNRS to study nuclear physics in the Leprince-Ringuet laboratory at the Ecole polytechnique. In 1970, he radically changed his area of study and approached experimental psychology. He then studied the role of social background and heredity on the intellectual performances of children who had comparable genetic capital but were adopted by families having different social and occupational levels. This work was published in 1978 by the journal *Science*. He also wrote several books concerning the school system and the place of the experts in the society.

Early 1992, M. Schiff attended J. Benveniste's experiments out of curiosity, but he did not grant much credit at first. The attitude of numerous scientists and the passionate reactions incited him to focus on this affair. He explained his approach in these terms:

> "I have been working since March 1992 to conduct a participating research on the memory of water. From a study of laboratory notebooks on high dilutions, I began to participate in a more recent research in Unit 200 of Inserm, essentially as adviser on some methodological points. In this function, my previous practice of research in physics is useful for me. My current research is however centered on the researchers as knowing subjects, and more exactly on the obstacles to communication and scientific knowledge. [15]

On another occasion, he specified in which state of mind he began this inquiry:

> "It appeared to me that, if I came to see Benveniste and his co-workers with a suspicious state of mind to lead an Inquisition-like inspection (as the investigators of *Nature* who had prompted the affair), I would accomplish nothing and I would miss most of the processes. Even if I avoided being quickly expelled, I would not succeed in acquiring information necessary to real understanding. That is why I decided to try a participating research: in exchange for helping in the current research, I would obtain information about this research." [16]

And he added:

> "During the year 1992–1993 (which covers the main part of my inquiry), I came to Clamart only twice a week on average, generally on Monday and Thursdays. The rest of the time, I examined documents. I also reserved time to think and take some distance

> with regard to the research in which I had decided to get involved." [17]

In spite of his initial skepticism and critical distance, M. Schiff eventually adopted a position similar to that of J. Benveniste – even if it differs on the idea of "crucial experiment" – namely that the explanation of the observed phenomena is in water itself:

> "Instead of raising a problem, which one had to eliminate as quickly as possible, the memory of water would be on the contrary one of the elements of the solution of a scientific puzzle. The memory of water would be thus a detail among others which would include some problems of physics of condensed matter (in particular water), the effects of alternate magnetic fields on some cell processes and also chemical communication inside cells". [18]

As for A. Spira and later Didier Guillonnet, M. Schiff's rigor allowed "channeling" J. Benveniste who had a natural tendency to leapfrog the steps, not hesitating for example to change two parameters at the same time during an experiment. Mr Schiff brought some methodological rigor, more particularly during public demonstrations. After 1993, he participated in some experiments only occasionally.

The year 1992 was therefore fertile in experimental results. J. Benveniste knew that he took a true step forward with "electromagnetic transmission". The arguments with "contamination" as the only explanation of his results did not hold any more, even if at this stage some difficulties persisted during public experiments. These recurring problems were experienced by J. Benveniste and his team as technical obstacles that would be eventually overcome. Moreover, electromagnetic transmission put J. Benveniste's research outside the field of homeopathy. His early works could be considered as a support for homeopathy, but his original scientific contribution should be now recognized.

In the next chapters we will describe experiments performed under the supervision of M. Schiff.

Notes of end of chapter

[1] J. Benveniste. Ma vérité sur la mémoire de l'eau. p. 126.

[2] *Ibid.* p.128.

[3] The results of a series of experiments intended to assess the effect of a magnetic field on high dilutions of histamine were reported in the summary of this communication to a congress: 32.6 ± 4.5% of maximal change of the coronary flow (n=24 experiments; mean ± S.E.M.) before any treatment of high dilution of histamine ("pool 31-41") and 3.7 ± 0.5% (n=20 experiments) after exposition to a magnetic field (50 Hz, 150 oersteds, 15 min) (L. Hadji, B. Arnoux, J. Benveniste. Effect of dilute histamine on coronary flow of guinea-pig isolated heart. Inhibition by a magnetic field. *FASEB Journal* 1991; 5: A1583).

[4] The congresses of the Federation of American Societies for Experimental Biology take place each year in USA.

[5] J. Benveniste. Aspects physique, chimique et biologique des échanges biologiques dans l'eau. Document préparatoire à l'occasion de la réunion du 5-6 mars 93. *[Physical, chemical and biological aspects of the biological exchanges in water. Preparatory document for the meeting of March 5-6, 1993]*

[6] J. Benveniste. Rapport sur la session « cœur-invités » du 13 février 1991 *[Report on the demonstration of February 13th, 1991]*.

[7] Circular letter of J. Benveniste of May 13th, 1991.

[8] J. Benveniste. Aspects physique, chimique et biologique des échanges biologiques dans l'eau. Document préparatoire à l'occasion de la réunion du 5-6 mars 93. *[Physical, chemical and biological aspects of the biological exchanges in water. Preparatory document for the meeting of March 5-6, 1993]*

[9] Ibid.

[10] J. Benveniste. Ma vérité sur la mémoire de l'eau. p. 129.

[11] *Ibid.* p. 130.

[12] *Ibid.* p. 130.

[13] J. Benveniste. Compte-rendu de l'expérience du 16 juin 1992 ; daté du 19 juin 1992. *[Report on the experiment of June 16th, 1992; dated June 19th, 1992]*.

[14] J. Benveniste. Commentaire sur le dépouillement de l'expérience à l'aveugle du 30 juin ; daté du 2 juillet 1992. *[Comment on the analysis of the blind experiment of June 30th; dated July 2nd, 1992]*.

[15] A propos d'une recherche participante sur la mémoire de l'eau, Michel Schiff, octobre 1993. p. 2. *[About a participating reasearch on memory of water, Michel Schiff, October 1993, p. 2]*.

[16] M. Schiff. Un cas de censure dans la science. L'affaire de la mémoire de l'eau, p. 15.

[17] *Ibid.* p.16.

[18] A propos d'une recherche participante sur la mémoire de l'eau, Michel Schiff, octobre 1993. p. 1 *[About a participating reasearch on memory of water, Michel Schiff, October 1993, p. 1]*.

Chapter 4. When hearts get tangled

A blind experiment for all the participants

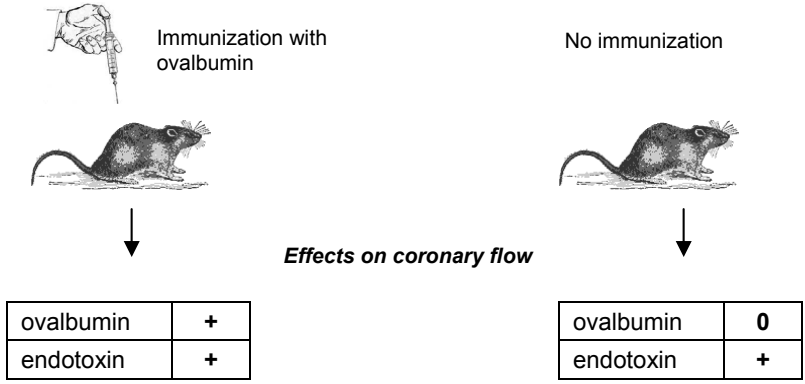
We thus resume the story after the summer 1992 when a successful transmission experiment had been performed on July 9th with visitors. One remembers that this experiment had upset the Director of Inserm. A new experiment was organized on September 28th. The purpose of J. Benveniste was to manage demonstrations with witnesses not belonging to the laboratory before drafting an article. Six new visitors attended this session.[1]

The design of this public experiment looked like the one of July 9th (see technical sheet). It was however a little more complex. Indeed, the design contained 16 tubes "to be guessed" versus only 12 in the experiment of July. Furthermore, an additional refinement was introduced: it was planned to discriminate not only the active tubes from the inactive ones, but also to determine the initial molecule from the active tubes: ovalbumin or endotoxin (LPS). The purpose was to demonstrate that during the transmission the specific activity of the initial molecule was transmitted. For that purpose, samples were tested on hearts of guinea pig immunized or not with ovalbumin. If the activity was ovalbumin-like then the heart of immunized animals shall react; if it was an endotoxin-like activity, the heart had to react whatever the state of immunization of the animal (Figure 4.1).

At first, the transmission experiment was performed. Three types of samples were prepared: samples of transmitted ovalbumin (from a solution containing 10^{-8} mol/L of ovalbumin), transmitted endotoxin (from a solution containing 10^{-8} mol/L of endotoxin) or "control" samples (from a tube of water without biological compound). The transmission experiment was described in these terms by J. Benveniste:

> "On September 28th, the transmission experiment began in the presence of Gérard Chaouat and Pierre Richard. A first vial of 10 ml-distilled water was randomly chosen by P. Richard and given to G. Chouat who distributed it in 10 tubes of 1 ml. Vials having undergone a transmission from vials of distilled water, ovalbumin 10^{-8} M and endotoxin 10^{-8} M, were also chosen at random by Pierre Richard and given to Gérard Chaouat […]. Most of the participants having then arrived, the blinding was performed in the

presence of Gérard Chaouat, Pascale Pacaud, Pierre Richard, Michel Schiff and Jean Staune."[2]



ovalbumin	+
endotoxin	+

ovalbumin	0
endotoxin	+

Figure 4.1. Assessment of the specificity of the "electromagnetic transmission". How to discriminate between samples "transmitted" with an ovalbumin-type or an endotoxin-type activity? Proteins such as ovalbumin have no effect on the heart of "naive" animal. If an animal has been injected with albumin (with specific experimental conditions), its immune system synthesizes allergic-type antibodies which get fixed onto organs, heart in particular. When the heart is in the presence of ovalbumin, it "reacts" (this reaction can be recorded by measuring different cardiac parameters). The heart does not react in the presence of a protein against which the animal has not been immunized. Endotoxin has an effect on the heart whatever the immunization state of the animal.
NB. For the experiment of September 28th, 1992, guinea pigs were immunized.

The random choice of samples and blinding were performed by the six participants according to a method proposed by M. Schiff. This method named "method of the envelopes" allowed blinding so that the initial label was unknown to everyone.

The method of envelopes is simple and cunning. Let us summarize it briefly. Each of the tubes for random blinding is marked with a label that identifies it. One unsticks the label which one sticks *inside* an envelope where the tube now without label is also placed. Envelopes are not sealed and are mixed. Then, for each envelope, an observer takes the tube, without looking inside the envelope, and he writes the same sign (a figure or a letter) *both on the tube and on the outside of the envelope*. He then seals the envelope. The tube can be then given to the experimenter who can test it. All the envelopes are then placed in a big envelope which is then sealed and the participants sign on its flap. For unblinding, each

inside label is placed beside the outside code. Thanks to the method of envelopes, nobody can have the information – consciously or unconsciously – because all participants are not aware of the code *including those who were directly involved in the process of blinding.*

Coherent results

During the days which followed September 28th, the contents of the tubes were tested. But the measurements were done on a slow pace. At first, the isolated hearts poorly reacted to stimuli. Thus, the measurements began late (from October 7th to 14th) and samples were tested as a precaution 10 times (on 7 hearts of immunized animals and on 3 hearts of not immunized animals). In order to inform the participant, J. Benveniste wrote:

> "We took our time to measure the experiment blinded on September 28th. Indeed, animals are currently slower to immunize, with reactions that are not as strong as before summer […] This allows us to have clear effects but not as spectacular as in the past." [3]

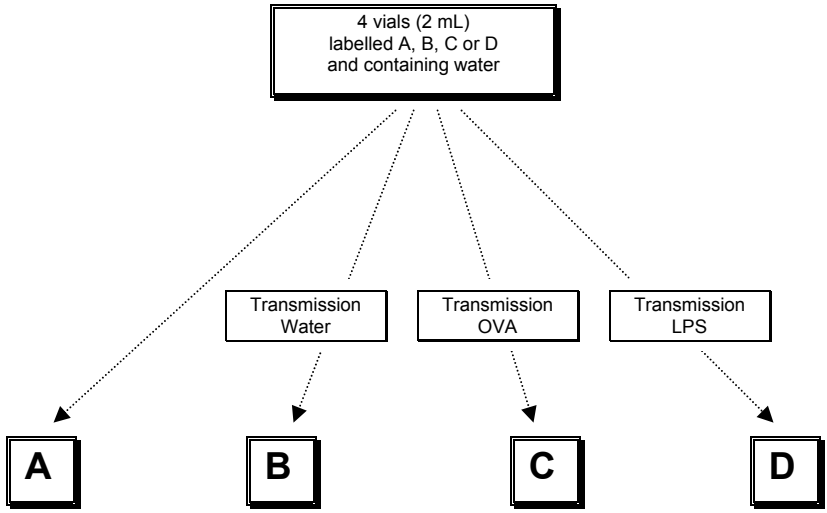
Nevertheless, the results appeared homogeneous and seemed to correspond to what was expected. J. Benveniste could thus announce:

> "Overall the results are coherent and we are particularly impressed by three experiments on hearts from animals having received alum alone, without ovalbumin *[i.e. not immunized]*, which, as expected, reveal only a single active tube and we have to hope it is the endotoxin tube."

Indeed, the open-label tubes gave expected results and, among the blind samples, five of them strongly changed the coronary flow (but had no effect in not immunized animals) and among them, as reported by J. Benveniste, only one was effective on hearts of immunized or non-immunized animals. Taking the coherence of the results into account, one is unable to help but thinking that these results were not accidentally obtained and that this experiment should be a success.

Technical sheet of the experiment of September 28th, 1992

Type of experiment: electromagnetic transmission on September 28th
Place of experiment: Clamart (for transmission and assessment of samples)
Blinding: on September 28th by 6 participants not belonging to U200; unblinding on October 22nd
Number of samples to be tested: 16 tubes tested between October 7th and 14th on 10 hearts (7 from ovalbumin-immunized animals and 3 not immunized); one part of the measurements was performed on the two Langendorff devices in parallel.
Additional in-house blinding: no



Blinding of 16 tubes* numbered from 1 to 16 (*blind tests*):

5 tubes "**A**"; 5 tubes "**B**"; 5 tubes "**C**"; 1 tube "**D**"

+

4 tubes not blinded (*open-label tests*):

1 tube "**A**"; 1 tube "**B**"; 1 tube "**C**"; 1 tube "**D**"

*Dilution at 1/1000 in physiological saline for heart infusion

"There is no crucial experiment"

On October 22nd, the experience was unblinded in the presence of an audience of about ten people.[4] M. Schiff prepared an introductory document in which he reminded some principles of "applied psycho-socio-epistemology":

> "In a chain of reasoning, the skeptic looks for the weakest link, according to the logical idea that a chain has the solidity of its weakest link.
> Thus the game of the critics consists in raising questions such as "Did he calibrate his test of degranulation? Did he perform kinetics? Did he cover his tubes with a silicone film?" etc… The trap for the experimenter consists in adopting one of the two attitudes, which are both indefensible. You begin by considering these arguments, with more or less conviction, then at one point you say "they piss off me, they are dishonest". Even if it is true that some opponents have an irrational attitude, this is not reason enough to be irrational oneself." [5]

M. Schiff then explained his own conception of an approach susceptible to be constructive during a change of scientific theory:

> "I believe that the correct attitude from both an epistemological point of view and from a point of view of balance of power in the context of any change of scientific theory consists in examining the relevance or the absence of relevance in the arguments. From this point of view, the statistical reasoning and the use of blind manipulations can bring solid arguments, without being however sufficient. I am repeating my personal conviction to you that there is no crucial experiment. The change of paradigm occurs following a convergence of presumptions going to the same direction, which eventually achieves general agreement."

Then he explained how the statistical reasoning could bring forceful arguments, particularly in the field of biology where the studied objects are never identical making the application of the experimental method more delicate:

> "Let a biological object O1 to which I apply a treatment T, and which becomes different. To prove that the change is really attributable to the treatment, I have to compare the evolution of the object O1 to that of another biological object O2. The statistical reasoning allows comparing not objects but populations

> of objects. The fact that, individually, objects inside a population are different, both intrinsically and because of errors or fluctuations in the manipulations becomes *not relevant*, or to be more precise, it acts only on the signal to noise ratio".

It is thus an experimental approach totally different from a "horse-race approach" as J. Benveniste was accustomed. M. Schiff specified:

> "In other words, when you use a statistical approach, in which you analyze two populations statistically equivalent by randomization, all the arguments about the lack of reliability of your operations turn against the skeptics: the fact that a result is statistically significant *in spite* of the inevitable fluctuations and the inevitable unknowns show that the physical or biological meaning is *bigger* than the one empirically observed, and not weaker as one often believes."

M. Schiff finally explained the best possible strategy using a statistical approach:

> "To resume the argument of the chain, the strategy consists in concentrating the argumentation and the attempt of proof on a single link, at the same time easy to display and difficult to attack from a logical point of view. The reasoning consists in saying that. Let two samples P1 and P2, which are obtained from the same original population of objects P. I applied the treatment T1 to the population P1 and I applied the treatment T2 to the population P2, with T2 identical to T1, except a part t. I observed a statistically significant difference between P1 and P2. I attribute the difference of the effects to the difference of treatments, which is symbolized by t."

And he concluded:

> "All the difficulty consists in proving, or rather in convincing oneself and then the others, that the treatment T2 actually differs from the treatment T1 only by the part t and not by a hidden part e. In the arguments of the skeptics, this hypothetical hidden difference e (e symbolizes the error) can contain the unconscious biases of the observer, the errors of manipulation such as the accidental contamination of a sample, and even, without being explicitly stated, a fraud.
>
> I think that it is impossible to individually counter each objection, and that it is better to consider the unknown effects as

> black boxes, and it is here that the procedures of randomization and blinding are involved."

Finally, the unblinding …

Then, after the theory, the practice succeeded and the experiment was unblinded. The big envelope was opened and the small envelopes were extracted. The codes and the corresponding transmitted activity were successively announced.

There was some disappointment. Among 16 tubes, 12 fitted with what was expected, but for the 4 other tubes there was some bewilderment (Table 4.1). Indeed, sample n°11 that was supposed to contain endotoxin-like activity turned out to be "naive" water which directly came from the vial and did not even undergo any transmission process.

A discussion began with two dominant attitudes among the participants:

> "After the unblinding […], two points of view expressed themselves. The first one consisted in trying to understand the imperfect character of the results, in particular with the hypothesis of a double inversion of tubes. This first point of view is argued by J. Benveniste who points out that the blind results with tubes 10 and 11 do not concern transmission, because these tubes were supposed to come from the pure water batch. The second point of view, argued by M. Guyot and M. Schiff, consisted in centering the attention on the results of the statistical analysis."[6]

One understands that J. Benveniste who tried "to guess" the "good" tubes preferred this type of explanation. He clanged consequently to the idea of an error when blinding was done. He thus pointed out that a simple inversion of two couples of tubes would allow obtaining the correct results (Figure 4.2). M. Schiff, on the contrary, faithful to the probabilistic approach that he had developed into the introduction, calculated that the odds of success were only 1 on 60 to find 4 of the 5 ovalbumin-type transmitted tubes among 15.

Tested recordings	Maximal changes of coronary flow (%)		Increasing order of biological activities (immunized animals)	Unblinding
	Immunized animals (7 measurements)	Non-immunized animals (3 measurements)		
Blind tests				
n°12	3.0 ± 1.0	6.0 ± 1.7	1	**Ova tr.**
n°6	3.4 ± 1.6	2.7 ± 1.2	2	Water tr.
n°13	3.4 ± 1.9	2.7 ± 1.2	3	Water
n°8	3.4 ± 2.8	4.3 ± 2.5	4	Water tr.
n°2	3.6 ± 1.0	3.7 ± 1.5	5	**LPS tr.**
n°4	4.0 ± 1.6	3.7 ± 1.5	6	Water tr.
n°3	4.1 ± 2.0	4.3 ± 2.5	7	Water tr.
n°16	4.7 ± 2.4	3.7 ± 1.5	8	Water
n°9	4.9 ± 1.7	3.7 ± 1.5	9	Water tr.
n°14	6.4 ± 3.4	3.3 ± 1.2	10	Water
n°11	10.0 ± 2.1	13.7 ± 1.5	11	Water
n°5	15.4 ± 2.9	6.7 ± 1.5	12	**Ova tr.**
n°1	15.4 ± 4.5	2.3 ± 0.6	13	**Ova tr.**
n°10	15.9 ± 4.0	3.3 ± 2.3	14	Water
n°7	16.7 ± 3.6	3.7 ± 1.5	15	**Ova tr.**
n°15	20.0 ± 8.0	4.3 ± 0.6	16	**Ova tr.**
Open-label tests				
Water	2.6 ± 0.8	3.3 ± 2.3	-	-
Water tr.	4.4 ± 2.1	4.0 ± 2.0	-	-
Ova tr.	17.3 ± 3.1	6.3 ± 2.5	-	-
LPS tr.	12.0 ± 2.4	14.3 ± 3.5	-	-
Ova 0.1 µmol/L	24.9 ± 5.0	6.7 ± 4.0	-	-

Means ± standard deviations

Tableau 4.1. Results of the experiment of September 28th, 1992. This table describes the results obtained with the 7 hearts from ovalbumin-sensitized animals (i.e. hearts that were expected to react as well to "ovalbumin activity" as to "endotoxin activity") and with the 3 hearts from non-sensitized animals (i.e. expected to react only to "endotoxin activity".) Open-label samples also included ovalbumin at 0.1 µmol/L. This control was always the last tested sample on a given heart in order to assess the sensitivity of the physiological preparation and to check the immunization state of the animals for albumin.

Open-label samples gave expected results. With blind samples, 6 out of 16 were associated with a change of coronary flow in albumin-sensitized animals and only 1 sample in non-sensitized animals. Before unblinding, observed results were thus consistent with expected results. After unblinding (last column), there were some inconsistencies in the results.

● : transmitted ovalbumin ; ○ water (naive or transmitted) ; ■ : transmitted endotoxin

n° tube	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16
code	●	■	○	○	●	○	●	○	○	○	○	●	○	○	●	○
result	●	○	○	○	●	○	●	○	○	●	■	○	○	○	●	○

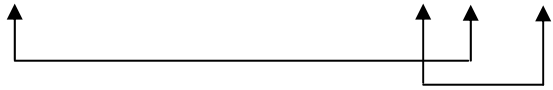


Figure 4.2. In the experiment of September 28th, 12 tubes out of 16 were correctly "guessed". To explain this imperfect result, J. Benveniste suggested that two couples of tubes (2-11 and 10-12) had been inverted by mistake.

For this reason, trying to explain the cause of this partial failure, J. Benveniste again performed during the next days the measurements by using samples which had been prepared on September 28th, but which had not been included in the blinding tests (only a part of the tubes that have been prepared were used after random selection). He asked to Jacques Testart (the "biological father" of the first French "test-tube baby" who worked in the same building) to blind the tubes:

> "On October 23rd, J. Testart blinded 13 remaining tubes, which had not been used for the blind experiment of September 28th: 4 ovalbumin, 4 naive water, 4 transmitted water, 1 endotoxin. We measured them on October 23rd and 26th and J. Testart unblinded them on October 27th. Result: 100% of the measurements are correct. The hypothesis of the inversion of 2 tubes [7] – at which moment? – is strengthened by these experiments."

J. Benveniste suggested for next experiments that two people managed each stage and he concluded:

> "In spite of some errors and uncertainties, which we will try hard to avoid afterward, the experiment of September 28th goes in the same direction as our recent open-label observations and also this one which was performed on July 9th in blind conditions: the hypothesis of a transmission of biochemical information by a magnetic way appears to us at present as the most economic one."

An error of manipulation was indeed always possible, but the precautions and the important number of participants who mutually watched themselves implied that this hypothesis was admitted only by default. The fact that the "good results" were obtained after unblinding of the new experiments made

with the original samples was actually in favor of an error during the blinding process. However, this *a posteriori* argument could satisfy only those who were already convinced as for the reality of the phenomenon supposed to be highlighted.

Notes of end of chapter

[1] P. Richard (Scientific director, Bouygues), G. Chaouat (biologist, CNRS, Hospital Antoine Béclère, Clamart), A. Fiebig (Ecole Normale Supérieure Cachan), J. Staune (European University of Paris), P. Pacaud (SAUR), M. Schiff.

[2] J. Benveniste. Compte rendu du décodage de l'expérience du 22 octobre 1992. *[Report of the unblinding of the experiment of October 22nd, 1992]*.

[3] Letter of of J. Benveniste of October 13th, 1992 "to the participants of the treansfert experiments".

[4] Participants present at the unblinding meeting of October 22nd, in addition to J. Aïssa, J. Benveniste and M. Schiff: Gérard Chaouat (biologist, CNRS, Hospital Antoine Béclère, Clamart), Raphaël Douady (CNRS, Ecole Normale Supérieure, Paris), Alexandre Fiebig (Ecole Normale Supérieure Cachan), Jean-Yves Follézou (physician, Hospital Pitié-Salpétrière, Paris), Marcel Guyot (physicist, CNRS, Meudon-Bellevue), Geneviève Potier de Courcy (ISTNA-CNAM, Paris), Pascale Pacaud (SAUR), M. Reynier (from the laboratory of Henri Laborit, Hospital Boucicaut, Paris), Alfred Spira (epidemiologist, Inserm U 292), Jean Staune (vice-president of the European University of Paris), Jacques Testart (biologist, Inserm U335, Clamart), Yolène Thomas (CNRS, Inserm U200).

[5] M. Schiff. Note de préparation à la séance d'ouverture du code pour l'expérience de transmission du 28 septembre 1992 ; datée du 15 octobre 1992. *[Preparatory note of the unblinding meeting for the experiment of September 28th, 1992]*.

[6] J. Benveniste. Compte rendu de l'expérience du 28 septembre 1992. *[Report on the experiment of September 28th, 1992]*.

[7] In fact, according to this logic, there were two inversions of two tubes.

Chapter 5. An affair of "contaminated serum"?

"Heating! History repeats itself, right?"

Of course, we cannot totally exclude that tubes had been inverted during the demonstration of September 28th. However, as we have already reported, oddities in the results with the isolated heart had already occurred during previous experiments. These anomalies had been related to shortcomings of the method and they were supposed to occur more particularly when multiple tests were performed, therefore increasing the probability of errors or contaminations. Furthermore, given the spectacular aspect that J. Benveniste wished to give to his public demonstrations – with all-or-nothing responses – it was during these meetings that the "inversions" were most often evidenced.

The episode of the "contaminated serum" was reported by J. Benveniste himself.[1] Moreover, M. Schiff gave a detailed chronology.[2] The reader interested by this episode can refer to these texts. M. Schiff attempted more particularly to show why this "affair" illustrated the role of the experts in our society. According to him, this affair was a caricatural example of a common behavior among scientists; he named this the "I do not want to know" syndrome.

Note that in French "physiological saline solution" (or "physiological saline") is named "*serum physiologique*" for historical reasons although, strictly speaking, it is not a "serum". In this text, I prefer to use the literal translation "physiological serum" because one keeps the allusive proximity with blood.

As I differently interpret this episode compared with J. Benveniste and M. Schiff, it seemed important to me to talk about these events because it took up a lot of working hours for the Clamart team. Furthermore, the knowledge of this episode is necessary for the understanding of the next chapter. Indeed, the "contaminated serum" is, according to me, one of the diverse aspects of the strange and destabilizing phenomenon that blocked J. Benveniste for years despite the technical improvements of the experimental system.

For the reader who is not familiar with biology, it is important to point out that what is here commonly named "physiological serum" (or "physiological salt solution") is nothing else than water and salt, that is sodium chloride at a concentration of 9 gram per liter. Strictly speaking, this serum has nothing common[3] with blood serum which is the liquid where blood cells are suspended and free of proteins for blood clotting. The semantic closeness that one could establish between "contaminated serum" and "contaminated blood" is thus

imaginary and misleading. It would be offending the various protagonists of the affair by suggesting that there was some misunderstanding due to unfamiliarity with these technical terms. Nevertheless, playing on the unconscious power of the words, J. Benveniste did not hesitate to bring "contaminated serum" closer with the affair of "contaminated blood". Coincidentally, this scandal was frequently on the front page of the newspapers at this time. Indeed, in June 1992, the first lawsuit of the "contaminated blood" opened in France. Former Prime Minister, Ministers and persons in charge of the French national health service were implicated for their management of batches of blood contaminated by HIV, the AIDS virus.

Of interest, according to J. Benveniste, this so-called "contamination" of physiological serum could be destroyed by heating. It is also by heating that HIV present in plasma extracts can be inactivated. The delay in the implementation of this process was one of the motives, among others, of the trial. J. Benveniste did not miss to underline the parallel: "Heating! History repeats itself, right?" [4]

"With self-confidence, too much self-confidence…"

The origin of the "affair of the contaminated serum" began in June 1992. With the aim of performing public demonstrations of transmission experiments, J. Benveniste then tried to design a convincing protocol, therefore not leaving room for suspicion. A possible solution consisted in asking the participants to bring themselves vials of physiological serum that they had purchased in any pharmacy. Everybody knows these self-breakable vials. Their use discarded any suspicion of having put in "something" before the experiment. For the scientists who wished to perform such electronic transmissions, it could be also convenient. Indeed, the transmission being directly made on sealed vials having undergone rigorous controls because of their usage in medicine, this should allow eliminating any concern of artefact related to contamination.

M. Schiff used explained how the commercial physiological serum was suspected to be contaminated:

> "One afternoon of June 92, I am a member of a group of 3 people to whom Benveniste wants to make a demonstration of the transmission phenomenon which he begins to study. […] To make his demonstration more convincing, Benveniste wants to proceed blind, and he asks us to blind the tubes which he has just prepared in front of us. We go to a small room to change the labels which identified tubes. Then, while Jamal Aïssa tests the first tube by measuring the effect of its contents on the coronary flow of a

> heart of guinea pig, Benveniste watches the cathode-ray screen to try to know if it is an active liquid or a liquid without effect on the heart. With self-confidence, too much self-confidence, he announces: "it is an active tube." In fact there is a problem because, according to its code number, the tube would be a control tube whose the content should be ineffective on the heart." [5]

J. Benveniste himself told this episode in similar terms:

> "During the first experiments, I notice poor results in terms of transmission. What I especially notice was that some hearts of guinea pigs, contrary to what is expected, react to the solution of sodium chloride. The event is all the more significant since it occurs during a blind experiment whose the coding was made by Michel Schiff." [6]

The next days, the team systematically tested various batches of vials and flasks of physiological serum and significant changes of coronary flow were observed for batches from some origins. Thus, batches from Canada and United States did not induce these changes.

Naturally, an extreme care is taken by the manufacturers of these medical products to eliminate any bacterial contamination as well as contamination by bacterial products such as endotoxin. But J. Benveniste did not think about this type of contamination. He suggested that in spite of the elimination of the bacterial products by diverse means, a "magnetic trace" of the molecules of endotoxin could nevertheless be present. This hypothesis was reinforced when he noticed that heating or exposure to intense magnetic fields erased this activity. Curiously, the activity seemed to be able to reappear a few weeks after one of these treatments.

"I had anticipated a long time ago the possibility of such an electromagnetic contamination"

Having orally informed P. Lazar, J. Benveniste wrote to him officially:

> "I would like to inform you officially about the results that I obtained in the past few weeks. By using, at the beginning as a control, injectable physiological salt solution Biosedra distributed in glass bottles of 500 ml from *Assistance Publique* [*i.e. public hospitals of Paris area*], we obtain extremely strong hemodynamic reactions on isolated heart of immunized guinea pig: a decrease in the coronary flow – completely suppressed if the animal is, particularly after immunization, very sensitive to endotoxin – and mechanical

changes, the most striking of which is the strong decrease of contraction leading to heart arrest. These effects are sometimes obtained with undiluted serum, sometimes only after amplification (a dilution of 1/1000 in water, followed or not with a moderate heating). We tested physiological serum coming from USA and from Canada, which have no effect, and we have serums of about ten countries which we are ready to test. We have not tested the serum of the central Pharmacy of hospitals yet." [7]

Then he proposed hypotheses that could explain these results:

"The nature of these reactions suggests an endotoxin-like activity, although we cannot prove it formally. Since the physiological serum Biosedra does not certainly contain molecular endotoxin, because the activity which we detected disappears after heating and under the influence of an oscillating magnetic field (laboratory of magnetism of the CNRS, Meudon-Bellevue), it is plausible that it is something like an electromagnetic transfer, either during the manufacturing of the serum or during the transport by amplification of a residual trace on glass. […] I anticipated the possibility of such an electromagnetic contamination a long time ago, I remind you, in silence and general hostility. […]"

He specified what could be the consequences for public health:

"Such a contamination, probably without danger for normal subjects, could have consequences yet undetermined on subjects who are made sensitive to endotoxin by a concomitant disease."

And he added in a note:

"I draw your attention to the fact that hearts from normal guinea pigs do not react or poorly to endotoxin, even at a classical dose, while immunized animals become very sensitive. This is a classic result in scientific literature as is the depressant effect of endotoxins on cardiac function. My results and the model I use should incite us for example to launch very quickly a research on sudden infant death syndrome where the conjunction of vaccination and Gram-negative infection could play a determining role."

He then described the urgent measures that he judged necessary to take:

"Therefore, it seems urgent to me to take ad hoc measures immediately, the first one would be the immediate creation of a

> committee in charge of the evaluation of these results and, when appropriate, their origin and their consequences.
>
> On this occasion, I remind you that I ask for years for the creation of a committee of experts on the general theme of the electromagnetic transmission of biological information. I strongly wish that the facts which I report here would be not validated or would result from an artefact that the experts can help us to identify. However, if that was not the case, the passivity of the political and scientific authorities which I regularly alerted for several years, and again quite recently, on the reality and the importance of this phenomenon, and who left me battling against this difficult research in the most complete solitude, the blatant absence of means allocated to this research, and even the regular decrease of the budget of my laboratory, could later, and rightly, be blamed to our research organization."

He asked to P. Lazar to reply quickly to his mail; otherwise, after a deadline of one week, he "will directly alert the Health and political authorities". In order to draw the attention of P. Lazar to this problem, he made a clear allusion to the "affair of contaminated blood":

> "You will understand my extreme caution according to tragic events which make the news at present. Besides, I do not insist on the essential confidentiality on a subject that could traumatize the public. But it is necessary that the evaluation and the possible decisions closely follow, and again against the probable opinion of some "experts", the scientific advance."

On February 12th, 1993, the Minister of Health Bernard Kouchner informed J. Benveniste that the National laboratory of health was going to begin a study on "contaminated serum". However J. Benveniste had the feeling to be sidelined from the inquiry. By insisting, he finally obtained a meeting with the director of the National laboratory of health and a detailed protocol was established in common, that one names a standardized operating procedure according to the current terminology. A short time later, the director of the National laboratory of health told to J. Benveniste that a credit of 150,000 francs was attributed to him:

> "The managers of the National laboratory of health come again to my laboratory and after that I did not hear from them. It is only later that I learn that the inquiry was led by Professor Mercadier of the hospital Marie-Lannelongue in Paris area and my friend Alfred Spira who did not even warn me about it. I will never see the grant

> promised in writing by the ministry, and the imminent sending of which was announced to me several times by managers of the "National network of health service". "[8]

While this expertise was performed behind J. Benveniste's back, the experiments continued at Clamart.

"The laboratory would be definitively discredited"

A few months after the experiment which had prompted this new "affair", M. Schiff, confined to bed by flu, wrote to his "colleagues" of Clamart. He had just drafted a report which reviewed the story of the contaminated serum and he sent it for opinion. He explained that the idea to perform blind experiments was certainly important, but that there was some danger in case of failure:

> "I do not mention in this text, and maybe it is an error, what seems to me the only possible explanation other than a contamination of serum: the introduction of a contamination during the manipulation of the serum from *Assistance Publique* (opening of flasks, etc.) The first idea which will come to a reader of the report will be "Why did they not perform blind tests to be sure that the contamination was in the serum from *Assistance Publique* and not in their procedure?" From the point of view of the public health, it would be the "better" solution. But I believe that, if it turned out to be the case, the laboratory would be definitively discredited. Blind tests are not a miraculous solution, but it is the precaution for which one will blame us for not having taken if things go wrong."[9]

And he suggested a protocol for this blind test:

> "In practical terms, I suggest random and blind testing of five tubes of American serum and five tubes of French serum from one or several freshly opened bottles, or better five bottles, if they are identical for both the American and French serum. […] Blinding should be made by a person chosen from outside U200 (me if I am valid, Testart otherwise). Two hearts in parallel should be used and serums will be discriminated after 20-minutes heating. In case of detection of five tubes from *Assistance Publique* without error, the hypothesis of a contamination due to manipulation would be discarded with a risk of error of 1/250."

The experiment is thus performed according to this protocol after blinding by J. Testart. Ten tubes of physiological serum are tested from December 1st to

3rd. Five tubes among 10 were indeed associated with a change of coronary flow. Moreover the results were coherent from day to day and were also coherent on both hearts in parallel. But, besides, a public "classical" experiment of electronic transmission was performed on December 10th. Difficulties to assess the activity of blind tubes appeared (with 5 "active" and 10 "inactive" vials). Therefore, J. Benveniste and M. Schiff wrote to the participants in the experiment:

> "With Michel Schiff we decided to stop the measurement of the transmission experiment of December 10th. […] The main reason is that the animals have been reacting very badly since mid-November to any stimulation […]
>
> We think we will be able to fix these small details in the course of January and we will be asking you to make a last effort in order to finish with a third experiment in the best possible technical conditions." [10]

For that reason, the blind experiment made with physiological serums during the same period was not unblinded. A new attempt of blind experiment with various lots of physiological salt solution was not organized afterward.

Nevertheless, a short article was drafted at the beginning of 1993 for *The Lancet* – an English first-level medical journal – in order to make these results public. The reported experiments were the ones obtained from November 1992 to January 1993. The manuscript specified that heating inhibited the effect (one hour at 70°C).[11] The text was sent to *The Lancet* on February 16th, 1993 and J. Benveniste added to the accompanying letter an experiment obtained on the same day showing a spectacular effect of the physiological serum obtained from a French pharmaceutical company on the coronary flow (Figure 5.2). The manuscript was straightaway refused without being evaluated. It is, and it must be said, the fate of the great majority of articles sent to high-level scientific journals, *The Lancet* in particular. But, curiously, J. Benveniste did not try to submit his text to another journal.

Blind code	Number of measurements	Maximal changes of coronary flow (%)	Biological activities in increasing order
Tube 10	5	3.6 ± 1.3	1
Tube 7	5	3.8 ± 1.6	2
Tube 6	5	5.8 ± 1.9	3
Tube 9	5	6.2 ± 3.7	4
Tube 8	5	8.4 ± 5.5	5
Tube 5	5	14.1 ± 3.0	6
Tube 1	5	14.4 ± 11.4	7
Tube 2	5	14.4 ± 7.5	8
Tube 3	5	16.2 ± 4.5	9
Tube 4	5	19.3 ± 3.6	10

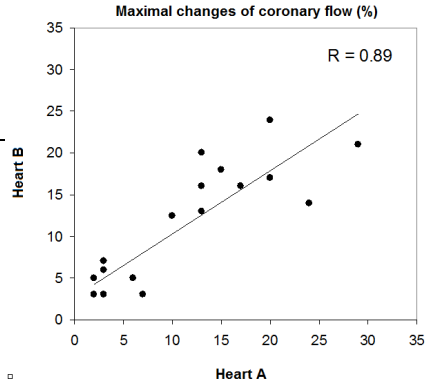


Figure 5.1. Blind experiment intended to show "contamination" of physiological salt solutions. Ten flasks of physiological salt solution (5 from a French and 5 from an American pharmaceutical company) were blinded and tested on rodent isolated heart model (from December 1st to 3rd). Out of 10 flasks, 5 induced a mean change of coronary flow above 10% and were thus considered as "contaminated". Each of the samples was simultaneously tested on both Langendorff systems (A and B) which worked in parallel. The correlation between the results obtained on hearts A and B showed that the results were coherent: the more a sample was efficient on one heart and the more it was effective on the other one.

The results are expressed as means ± standard deviation of the maximal changes of coronary flow (changes had thus always positive values; cf. Chapter 1); for the correlations, only results of the experiments of December 2nd and 3rd, which had been made on the two hearts in parallel, are shown. The couples A-B of 20 measurements are shown; one counts only 17 points on figure because some points are superimposed.

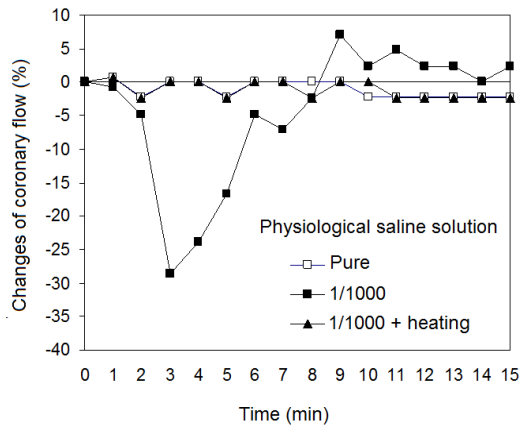


Figure 5.2. Experiment of February 17th, 1993 attached to the text submitted for publication to *The Lancet*. This experiment was performed on the same day the manuscript was sent to the journal in order to show both the current and dramatic aspect of the results. Moreover, this figure shows that dilution 1/1000 (with agitation) increased the effect of the "contaminated serum". One also notices that heating (2 hours) prevents the consequences of the "contamination".

"A small effect of this serum cannot be totally excluded"

It is only during the summer 1995 that J. Benveniste learned about the existence of a report on the survey of the National laboratory of health. The report which is communicated to him upon his request is dated December 1994. Nobody informed him about the existence of the report or about results.

It is on reading the report that J. Benveniste learned that an activity, relatively low, but statistically significant (with $p < 0.001$) was found by the authors of the study for the physiological serum of the brand under investigation. The text indeed reported a mean decrease of the coronary flow of $8.4 \pm 10.4\%$ for 24 experiments. To achieve this result, a preliminary study was first performed from December 1993 to March 1994. Indeed, the experimenters did not use the Langendorff system and the entire equipment had to be acquired.[12] When the experimenters considered that the technique was in perfect running condition, the experiments themselves were performed (from April to June 1994) and the results reported above were obtained. Noticing the large standard deviation (10.4% for a mean effect of 8.4%), the individual results of each experiments being not given in the report, J. Benveniste concluded that some rat hearts had certainly variations of coronary flow largely above 10%.

But, despite this significant variation of the coronary flow, the report concluded:

> "Overall, the physiological serum […] that we studied does not contain contaminant agents inducing a significant change of the contractile performances of the rat heart over the defined period of observation, in an experimental configuration reproducing as faithfully as possible, with the two reservations detailed at the beginning of this report, the standardized operating procedure."

Nevertheless, he added:

> "Considering the small decrease of less than 10% of the coronary flow fifteen minutes after the end of the injection, a small effect of this serum on the coronary flow cannot be totally excluded. New series of experiments would be necessary, in order to confirm or not this effect on longer periods of observation. Nevertheless, in the present state of the experiment, a decrease of the coronary flow lower than 10% cannot be considered *a priori* as presenting a particular character of gravity."

After reading these conclusions, J. Benveniste was stunned:

> "The reading of this report and its conclusions, which are in total contradiction with its contents, are quite astonishing. Certainly, I cannot pronounce on what a 8.4% decrease of the coronary flow of a rat heart implies in terms of public health. However, I consider on the other hand that these results – obtained, I remind, with a methodology which does not correspond to the one that I recommended – are anything but negligible." [13]

He wrote then to Didier Tabuteau, Director of the French drug agency:

> "I thank you for having kindly sent me the report of Professors Mercadier and Spira on the cardiotoxic effect of the physiological serum. I note that this report, dated December 1994, shows significant changes ($p < 0.001$) of the cardiac flow[14] after infusion of 1 ml of commercial physiological serum. I also observe that the protocol was modified on five points […]" [15]

Having detailed the modifications[16] of the method in comparison with the initial common protocol, he concluded:

> 'Finally, it is miraculous that after an accumulation of blunders (which, given the professional character of the experimenters, it will be necessary, in due course, to wonder on what is related to a conscious or an unconscious approach), a significant variation ($p < 0.001$) of the coronary flow was obtained 15 min after injection of only 1 ml of physiological salt solution to infused hearts, a time duration in compliance with our own observations: the effect is relatively late."

J. Benveniste thus took advantage of this report that gave him the possibility to contact the authorities again:

> "I thus report by mail to the presidency of the Republic and eventually to obtain an interview with the Minister of Health Elisabeth Hubert, thanks to the intervention of President Mitterrand's adviser for social affairs, René Lenoir […]. The meeting with the Minister takes place on October 3rd, 1995. Mrs Hubert explains to me in substance that she will act only when the results of my research will be recognized by the international scientific community." [17]

J. Benveniste could thus conclude:

> "In other words the decisions of a Ministry of the Republic which could concern public health depend on the initial maneuver of a trio of "investigators" and can be revised only with the kind authorization of the journal *Nature*."

Now, in hindsight, with all these experiments on the isolated heart in perspective, how could we interpret this episode? It is indeed unquestionable that a change of the biological system occurred and was not trivial. Besides, the National laboratory of health also noticed a significant effect which seemed to support the hypothesis of the "contaminated serum" even if this variation was considered as relatively small. But, was it really due to a "contamination" of the physiological serum? Indeed let us note the circular character of the reasoning. The observed effect and its supposed cause define themselves mutually. It is also the same circular reasoning which presided over the experiments with high dilutions or the experiments of transmission.

Thus let us pursue the examination of the facts by going back in time because, dragged by the action, we anticipated the chronology of the events. Indeed, on early 1993, the question of the "contaminated serum" gave the opportunity of a tense arm-wrestling between J. Benveniste and the Director of Inserm, P. Lazar.

Notes of end of chapter

[1] J. Benveniste. Ma vérité sur la mémoire de l'eau, chap. 7.

[2] M. Schiff. Un cas de censure dans la science, p. 219.

[3] Except a comparable concentration of sodium chloride.

[4] Letter of J. Benveniste to D. Tabuteau, Director of "Agence du Médicament" *[former Frend Drug Agency]*, of July 28th, 1995.

[5] M. Schiff. Un cas de censure dans la science. p. 98

[6] J. Benveniste. Ma vérité sur la mémoire de l'eau. p. 136.

[7] Letter of J. Benveniste to P. Lazar of November 17th, 1992.

[8] J. Benveniste. Ma vérité sur la mémoire de l'eau, p. 143.

[9] Letter of M. Schiff to J. Aïssa, J. Benveniste, Y. Thomas and J. Testart of November 24th, 1992.

[10] Letter of J. Benveniste "to the particpants in the blind experiment of December 10th"; dated January 7th, 1993.

[11] But, oddly, as we have already said, the effect reappeared after approximately three weeks. Other curiosity, the 1/1000 dilution increased the effect and sometimes even revealed it.

[12] Agence du Médicament, Hôpital Marie-Lannelongue. Rapport scientifique (convention du 31 décembre 1993), « Evaluation des risques cardio-toxiques liés à une éventuelle contamination du sérum physiologique Biosedra » *[Scientific report of the former French Drug Agency entitled "Assessment of the cardiotoxic risks related to a possible contamination of physiological saline Biosedra"]*

[13] J. Benveniste. Ma vérité sur la mémoire de l'eau, p. 146.

[14] In fact, strictly speaking, it is coronary flow and not cardiac flow.

[15] Letter of J. Benveniste to D. Tabuteau, Director of *Agence du Médicament* of July 28th, 1995.

[16] The main modifications in comparison with the protocol recommended by J. Benveniste were the following ones: important increase of the infusion pressure which could decrease the sensitivity of the biological system; increase of the distance between the site of injection and the entry of the aorta what increased the dilution of the tested physiological saline; anesthesia of the animals before the sacrifice thus adding variables which had been not tested beforehand; modification of the duration between the immunizing injection and the experiment; introduction of a positive control, cadmium chloride, the effects of which on the heart are very far from the product to be tested. Concerning this last modification, J. Benveniste noted: "The only interest of cadmium is its modest effect, thus demonstrating the low sensitivity of the pharmacological system that has been used, probably related to the increase of the infusion pressure."

[17] J. Benveniste. Ma vérité sur la mémoire de l'eau, p. 143.

Chapter 6. "You'd better … otherwise you are dead"

A lifeline?

As we have seen, a simple method had been found by Benveniste's team to "decontaminate" water: heating the samples of before "imprinting" them. Indeed, this simple process eraser any "electromagnetic memory". Demonstrations on the reality of the "electromagnetic transmissions" were thus again possible without being anxious about possible "contaminated" samples.

The opportunity of a demonstration in front of an elite audience – namely, a commission of Inserm – occurred in the spring of 1993. Indeed, at Inserm, every spring saw the return of the four-year evaluations during which the "production" of a quarter of the teams was closely examined by the scientific commissions. In 1993, it was the turn of the laboratory of J. Benveniste to be in the hot seat.

We saw in the first part how hard the task of the examiners had been in 1989 when they assessed the scientific production of the laboratory of J. Benveniste. Indeed, the examiners had been pulled between the "exotic" experiments on high dilutions and the good general level of the laboratory concerning "classic" research, not to mention diverse pressures and extra scientific considerations that had affected this evaluation performed soon after the "*Nature*gate".

However, the evaluation of year 1993 had an important particularity. The Unit 200 of Inserm then reached the limit of twelve years and the rule at Inserm is to close the laboratory at this age.[1] Nothing prevented however the reopening of the laboratory under a new title with the same staff and a new director chosen among the researchers. The purpose of this twelve-year practice, which had been established by P. Lazar, was to challenge the teams periodically. But, the creation of a new research unit required a sufficient number of researchers present on the organization chart of the new laboratory. However, given the sulfurous reputation of J. Benveniste during the last years, most of the researchers of the laboratory migrated in less agitated areas. The administration of Inserm moreover made nothing to limit these transfers when it did not facilitate them. The technician staff followed suit. As for young researchers recently recruited by Inserm, a not written law dissuaded them from asking for a permanent position in the laboratory of J. Benveniste.

Not having the possibility to ask for the creation of a plain research unit, J. Benveniste thus made a demand of "junior-laboratory contract". More exactly, it was a researcher of the laboratory, Yolène Thomas, who did the

demand. In the official jargon of Inserm, a junior-laboratory contract is a laboratory in formation, a structure which can precede the creation of a plain Inserm unit when other researchers will join it. If Inserm granted the creation of this junior-laboratory contract, J. Benveniste could maintain what remained from the laboratory and thus could keep facilities, staff, equipment and operating budget. J. Benveniste in fact hardly believed in this last possibility, but he wished to put the administration of Inserm in front of its contradictions.

The title for this future structure would be "Cellular and molecular immunotoxicology of the toxic aggressions". Three teams would constitute this future structure and J. Benveniste would not be the director anymore but responsible of a team called "Biophysics of the transmission of the molecular signal". [2]

J. Benveniste irritates P. Lazar (again)

Joël Bockaert, the president of the Scientific specialized commission that was committed to examine the demand of creation of "junior-laboratory contract" wrote to J. Benveniste to get in touch with him about the visit of the laboratory:

> "The documents that you had transmitted to me certainly deserve our attention. If we consider that the observations which you did concerning the effect of the physiological salt solution Biosedra on the heart of immunized guinea pigs are reproducible (and I have no reason to believe the contrary today), there is a good reason to examine the problem."[3]

He thus suggested coming to Clamart with experts:

> "On this occasion I suggested to Mister Philippe Lazar, who agreed, to ask the eminent physicist colleagues (Serge (*sic*) Charpak or Pierre-Gilles de Gennes) to accompany the members of the CSS [*Specialized scientific commission*] n°5 (Donny Strosberg, Claude Jacquemin and myself). We could add a cardiac physiology specialist. We will be able to examine the scientific aspect of this problem, the only one within our remit."

J. Benveniste responded to this proposal very favorably and he suggested that another physicist should be added to the team of visitors:

> "We are very honored that eminent physicists come to visit (at last) the laboratory. However, I tried to correspond several times with De Gennes […] and obtained only superficial answers, thus giving me the feeling that he was hardly interested in these

> biological problems. *Georges* Charpak (you mean the recent Nobel prize-laureate?) seems to me a priori more open to biology. However, the presence of physicists of this level raises a problem. We will be unable to answer because it is not within our competence to solve problems of physics. […] In order to be able to provide an appropriate interlocutor to the visitors, we will ask to Professor G. Preparata, chair holder of Nuclear physics at the University of Milan, or to Professor Del Giudice who works in the same department, to attend this visit."[4]

Indeed, he specified:

> "[…] the weight of a criticism, possibly left without answer, from a Nobel prize laureate would be such that we cannot approach this examination without possibility of contradictory exchanges that, maybe, we will ask to be included in the report. As for the specialist of cardiac physiology, the name that comes to mind is Pr. Coraboeuf, Orsay, one of the most respected in this domain, but I am obviously ready to examine any proposal that you will be willing to submit to me."

But, the director of Inserm, P. Lazar, had a copy of this letter and he was a bit irritated. He thus reminded J. Benveniste that he was not responsible, but Y. Thomas, for the demand of "junior-laboratory contract" and he added:

> "It seems totally abnormal to me that you invited a number of personalities, who are external to the laboratory, to attend this visit that is aimed to supply to the competent authorities of Inserm the direct elements of appreciations about the legitimacy of Mrs. Thomas' demand. I therefore ask you explicitly to give up this invitation.
>
> As regards the name of the other experts, it is obvious that it is out of the question to accept that you would select them yourself or, according your own terms, "examine with the president of the commission any proposal that he would be willing to submit to you"." [5]

J. Benveniste answered that he agreed to separate the demand of "junior-laboratory contract" which was under the responsibility of Y. Thomas. But, for the evaluation of the "magnetic contamination" of physiological salt solution, it seemed normal to him to give an interlocutor of the same level to G. Charpak:

> "It is in this context that, with the aim to "provide an appropriate interlocutor" to Mr. Charpak, in order essentially to facilitate

> scientific communication to which you cannot be opposed, it seems suitable that Professor Preparata, with whom we collaborated for four years, explains the physical bases of the phenomenon which we observe. He can then withdraw during the statutory evaluation of the demand of junior-laboratory contract." [6]

And he reminded that an investigation, launched by the ministry of Health, was in progress (cf. previous chapter):

> "I remind you that an investigation has just been asked to the National laboratory of health by Mr Kouchner. None of the skills will be too much to avoid errors with particularly heavy consequences in either direction."

The fact that this visit could be the occasion to raise the question of the "contaminated serum" and especially to prompt an open scientific discussion about this subject appeared to excessively irritate P. Lazar. Indeed, to be clearly understood, he sent again a letter – a very abrupt one – to J. Benveniste where he specified some points:

> "The object of the visit of Mister Bockaert and a delegation of INSERM in your laboratory is not "an evaluation of physiological salt solution", but exclusively the evaluation of the demand of "junior-laboratory contract" from Mrs. Yolène Thomas.
>
> I thus most strongly maintain my observations that were formulated in my letter of March 5th, 1993. I recommended very precisely to Mr. Bockaert, President of the Specialized scientific commission n°5 of INSERM, not to accept any dialog with other people than those who appear in the demand of Mrs. Thomas. If you try to go beyond this recommendation of common sense, I would be forced to draw the appropriate conclusions as regards the continuation of the examination by INSERM of this demand of contract." [7]

With an exasperated tone, he then adds in postscript: "I would be grateful if you did not force me in writing to you a third and why not a fourth letter on this matter. The indications of the present mail are firm and definitive".

J. Benveniste is not the kind of person to be easily impressed, especially when only administrative and regulatory statements are opposed to scientific arguments. He thus answered to P. Lazar that his letter was in "complete contradiction" with the position of J. Bockaert who suggested "examining the scientific aspect of this problem":

> "I am amazed and worried to see that INSERM remains silent once again in front of a potential problem of public health which is presently investigated by the French drug agency and which, in view of our last results, is about to become an international problem.
>
> […] I note however that you did not answer my question on the existence of texts which would forbid the presence of some of our collaborators who could inform the scientific debate. This means that these texts do not exist and that your decision has no legal basis. I draw your attention on the fact that your position could be easily interpreted, during later confrontations, as a will from your part to avoid a scientific debate which would answer the question. […] I have no means to "oblige" you to answer. You are free to do it or not and to proceed through unfounded "firm and definitive indications", that is to say a ukase. I will naturally be forced to obey, at least for the moment, in other words in the expectation of possible further developments." [8]

He specified that he maintained his position for the following purpose:

> "taking advantage of the presence of Mr. Charpak to fully examine the biological and physical problems put by the contamination of the physiological salt solution, in a *totally independent* way and obviously off the record for the report of the visit for the "junior-laboratory contract" itself. Thank you for indicating to me *on which legal text* is this ban exactly based."

And, again, he insisted:

> "For example, if the visit for the "junior-laboratory contract" was performed in the afternoon, why should scientists who are involved not have the slightest scientific discussion that morning with outside personalities? Given the importance for public health, which you do not appear to completely measure, to achieve a solid scientific dossier on this question as quickly as possible, I am determined to make every effort so that the necessary scientific dialog is established and that, for reasons which escape me, you do not wish to see supervene."

"Where is the trick?"

Finally, it was not a question of "contaminated serum" during the visit even if the visitors could participate in an experiment of "transmission". To answer the

questions of physics, as reported by M. Schiff, "Benveniste could put forward only a scientist who had not done physics for twenty years" [9] and who was M. Schiff himself. During the presentation of the activities of the laboratory, the latter tried to explain the theory of the coherent domains of G. Preparata and E. Del Giudice, as he said in a letter to G. Charpak shortly after:

> "Because the general director of INSERM refused to allow Preparata or Del Giudice to explain their theory of coherent domains, which for the moment seems to me the most promising one to solve the epistemological riddle posed by Benveniste's experiment on the memory of water, I was led to act as a substitute and to formulate in front of you what I thought I had understood of this theory. I sent you a text beforehand and I gave an introductory talk at the beginning of your visit on April 21st, 1993 to which you seemed to answer through an argument from authority by explaining that you had consulted Mr. De Gennes, who himself had referred to Mr. Nozières, who, according to him, had declared that the theory of coherent domains was valueless.
>
> After my talk on April 21st, you made an allusion to the possibility of mystification by presenting an anecdote about your past work with Joliot-Curie: on the occasion of a magician's trick, Joliot would have asked to the present scientists: "where is the trick?" You will agree with me that the balance of power and the circumstances did not favor a serene discussion on this point." [10]

But, even the biologists who participated in this visit did not seem to be willing to commit themselves, for example to envisage a collaboration with the laboratory of J. Benveniste. Indeed, as told by M. Schiff:

> "At the beginning of the visit, the specialist of cardiac physiology expressed his skepticism about the reality of an observable effect of high dilutions with hearts of guinea pigs or rats, by indicating that he had never observed such effects. The institutional situation did not allow me to ask him the obvious question: did he perform the experiments in conditions of sensitivity which could favor such an observation? For example, did he use hearts of animals previously immunized as Benveniste did? I nevertheless suggested that collaboration with Benveniste was possible. My interlocutor answered me that the researchers of his laboratory would probably not agree and, moreover, that INSERM would have at first to attribute to this research dozens thousand francs." [11]

Besides, during the morning, Y. Thomas and G. Charpak exchanged some impressions:

> "You think that this famous experiment of "transmission" will work? the Nobel prize laureate asks her.
> – Yes, I think. Except for an accident, it works very well usually, Yolène answers.
> – You'd better, otherwise you are dead." [12]

Fortunately, the prediction of the Nobel prize laureate was not put to the test and the results of the demonstration did not lead the researchers in front of the executioner!

"Benveniste killed Charpak"

At the end of morning, having heard a part of the presentations of the researchers concerning the demand of junior-laboratory contract, the delegation participated in an experiment of "electromagnetic transmission". For this purpose, four sealed vials were chosen among twenty. By precaution, these vials were warmed at 70°C for 2 hours in order to "erase" a possible "electromagnetic memory". Four vials were numbered from n°1 to n°4. The vial n°1 was "naive", that is it was left intact. Three transfers were performed with water, endotoxin (LPS) and ovalbumin for vials n°2, n°3 and n°4, respectively. Each vial was "informed" during fifteen minutes by placing it on the output coil of the transmission device. Then the vials were coded (A, B, C and D) using the method of envelopes (cf. Chapter 4).

The rats used for the experiment had been immunized in order to be able to discriminate ovalbumin and LPS. The rats of the first lot (hearts n°1 and n°2) were immunized with bacteria (BCG) and 1 µg of albumin. The rats of the second lot (hearts n°3 and n°4) were immunized in the same way, but 30 days earlier with a booster of 10 mg of ovalbumin two days before the experiment. These various protocols of immunization allowed, according to protocols designed by J. Benveniste and his team, to make hearts n°1 and n°2 more reactive to endotoxin than to ovalbumin and hearts n°3 and n°4 more reactive to ovalbumin than to endotoxin.

Nevertheless, J. Benveniste warned the participants that according to the state of immunization of animals, it was possible that one of the "active" transfers (ovalbumin or LPS) could be ineffective. Actually, only one tube, tube A, successively induced a reaction of 4 isolated rat hearts, more particularly hearts n°3 and n°4 (Figure 6.1). According to the immunization protocols, it was most probably ovalbumin. This was confirmed by the close correlation of

the effects of tube A and those of ovalbumin at classical conditions, thus suggesting that tube A contained albumin-type activity.

As some visitors were in a hurry, they had to leave the laboratory before the end of the experiments with heart n°4. The envelope was then opened and the tube A turned out to be "transmitted ovalbumin" as suggested by the results. J. Benveniste observed G. Charpak who took the blow:

> "I feel that Charpak who was haughty and sarcastic up to now, is strongly affected by the results. At the end of the unblinding, his face goes pale and he went out of the building for a few moments. I am even afraid that he might faint and I imagine the headlines of newspapers: "Benveniste killed Charpak". We will see that it is rather the opposite which is going to occur." [13]

"A historic responsibility"

As soon as the visitors had left, J. Benveniste began to draft a report concerning the visit of the commission. He broadcast this text by mail to all participants, asking them to indicate their possible points of disagreement. He began by noticing the absence of scientific criticisms from the members of the commission:

> "No methodological criticism was presented by any member of the delegation. Our results had been sent to them before the visit, allowing a thorough examination. Nevertheless, no element cast the slightest doubt on statistical validity of the results compared with the controls. *No additional control was requested*. Of course, propositions of new experiments were made, in particular by Mr. Charpak, for example to isolate input vials and/or output vials in the transmission experiment to better understand the involved mechanisms. These requests incidentally presuppose the acceptance of the basic phenomenon with the aim of a deepening of the research, but are absolutely not revealing the lack of a *control*, the definition of which is very precise in experimental research. There is however a contradiction between these requests and the progressive reduction of the means granted to U200 by INSERM, both for funding and staff, including the closure without reopening." [14]

He also insisted on the absence of criticism by the specialist of cardiac physiology: "Mr. Coraboeuf did not criticize the experiment on isolated heart

which appears to him in compliance with the rules of experimental cardiac pharmacology." What allowed him to conclude:

> "Overall, no methodological criticism was expressed that allows casting doubt on the validity of the results. None of the members of the delegation even only suggested the possibility of an artefact, often put forward by convenience and/or mind laziness without theoretical or experimental proof. This silence can be considered as tacit approval, in the absence of methodological criticisms."

He then arrived to the experiment performed under the control of the delegation:

> "This experiment was particularly demonstrative because not only we indicated the active vial but we announced it was likely ovalbumin (there was indeed another potentially active vial but, on this day, hearts were not sensitive to endotoxin. A check made on April 22 on other rats belonging to the same group show that there is a lack of sensitivity to endotoxin for the complete series)."

And, he maliciously reminded the "reaction" of G. Charpak at the time of the unblinding:

> "I am not certain that, except Mr. Charpak who seemed to perceive the importance of this result, the members of the delegation realized to what they assisted: an anaphylactic shock induced by an "electromagnetic" signal *without any molecular support*."

And – as usual – J. Benveniste lyrically concluded his letter while putting some pressure on the members of the commission:

> "At the end of the visit, I drew delegation's attention on its responsibility (which could be a historic day if Mr. Charpak's judgment is confirmed)[15] in the report of this day and the decisions which would ensue from it. I evoked the disastrous precedent of the visits of the Commission n°2 and of the Scientific council, the texts of which will remain in the pantheon of the scientific incomprehension (to be kind). […] The Commission n°5 for which competence, the integrity and even the open-mindedness are praised is at the center of an epistemological problem with few precedents. Yet, I perceived on several occasions the temptation to give in to the "common sense" – we know what we must think about this in science – which would require exceptional proofs for results seemingly (that is in the light of the knowledge of moment) "impossible". "

A little while after the visit, on May 3rd, J. Benveniste wrote to the theoretical physicist Philippe Nozières, professor at the *Collège de France*, under the authority of whom G. Charpak had sheltered to discredit the theory of the coherent domains of the Italian physicists, asserting the latter "valueless". In his letter to the theoretical physicist, J. Benveniste asked him the scientific motives which supported his words reported by G. Charpak as a definitive argument. In his answer, P. Nozières appeared to be flabbergasted about exchanges with G. Charpak on a theory he did not seem to know:

> "Before answering you, I wish to contact Georges Charpak, who apparently steered you towards me. I do not know what he has in mind and why he considers me as particularly competent. I will certainly read the theoretical articles that you transmitted to me – at least out of scientific curiosity – but not for the moment." [16]

The argument from authority that G. Charpak brandished during the visit of Inserm commission seemed rather weak. But J. Benveniste could not linger over this point because meanwhile the team of Clamart had knowledge of the report of the commission which decided about its fate.

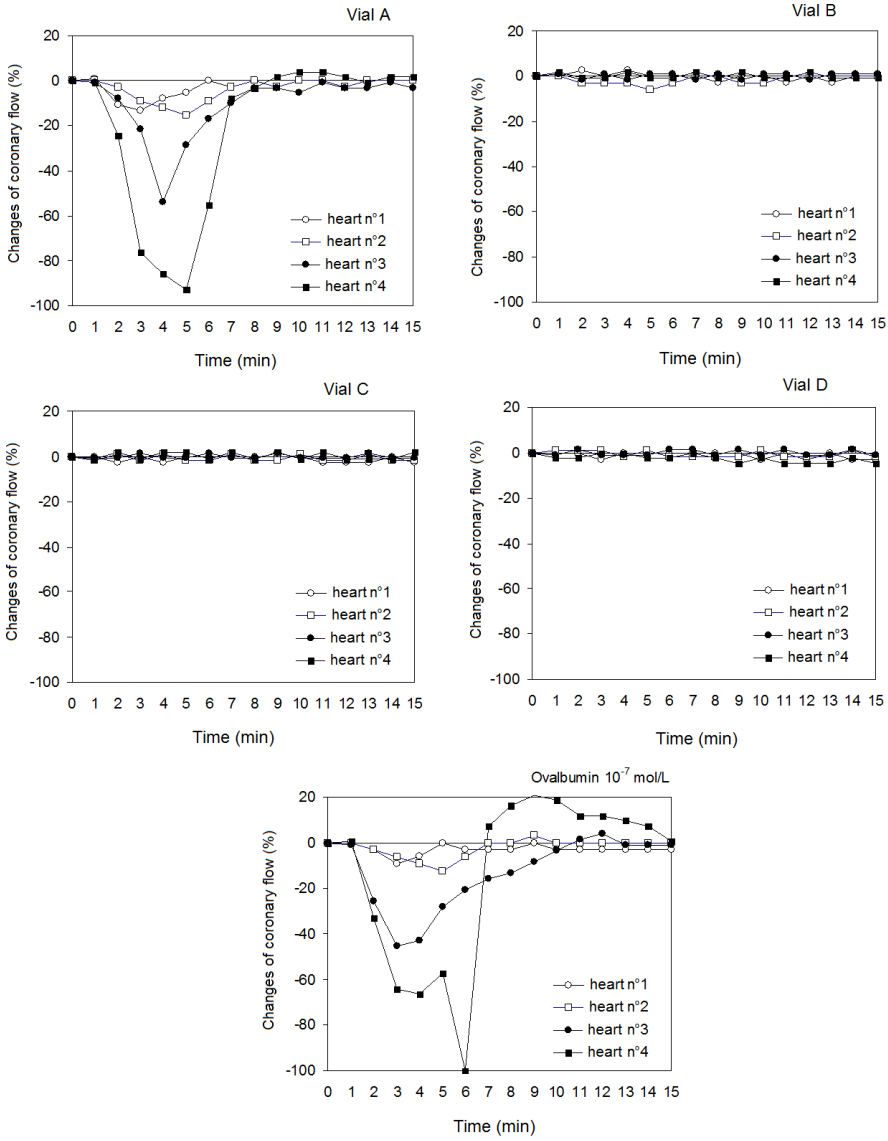


Figure 6.1. Experiment of April 21st, 1993 blinded by G. Charpak and by the members of the Specialized scientific commission n°5. Four sealed vials were numbered from 1 to 4: the vial 1 was kept without any manipulation whereas vials 2, 3 and 4 were "imprinted" for 15 minutes with "information" corresponding to water, LPS and ovalbumin, respectively. Each vial then received a random code (A, B, C or D).

(Followed)
The content of each vial was successively tested on 4 isolated rat hearts. At the end of each series, ovalbumin at usual concentration (0.1 µmol/L) was infused.
One notices that among blind vials only the content of A modified the coronary flow. Hearts n°1 and 2 were not very reactive compared with hearts n°3 and 4 which gave very important variations of flow. It is also important to note that the changes obtained with vial A and with ovalbumin 0.1 µmol/L (the molecule the activity of which had been transferred) were correlated: compare the amplitude of the variations according to hearts on the first and last figures.
It was planned to test vials in the order ABCD for hearts n°1 and 3 and in the order DCBA for hearts n°2 and 4. However, for the heart n°2, one visitor was impatient to see the effect of tube A and the order was in fact DCAB. After unblinding, vial A corresponded to ovalbumin. See text for the reasons concerning the ineffectiveness of LPS transfer.

Notes of end of chapter

[1] The laboratory having been created in 1980, it was in fact 13 years old.

[2] The three teams were entitled "Toxic aggression and lymphocyte activation" (Y. Thomas, CNRS and C. Carelli, CNRS), "Toxic aggression and phagocytic cells" (C. Damais, CNRS and Y. Manuel, CNRS) and "Biophysics of molecular signal transmission" (J. Benveniste, INSERM and M. Schiff, CNRS).

[3] Letter of J. Bockaert to J. Benveniste of February 16th, 1993.

[4] Lettre of J. Benveniste to J. Bockaert of February 19th, 1993.

[5] Lettre of P. Lazar to J. Benveniste of March 5th, 1993.

[6] Lettre of J. Benveniste to P. Lazar of March 17th, 1993.

[7] Lettre of P. Lazar to J. Benveniste of March 30th, 1993.

[8] Lettre of J. Benveniste to P. Lazar of April 5th, 1993.

[9] M. Schiff. Un cas de censure dans la science, p. 101.

[10] Lettre of M. Schiff to G. Charpak of May 16th, 1993.

[11] M. Schiff. Séminaire du 19 octobre 1993 au Centre de recherche en histoire des sciences et des techniques, Cité des Sciences et de l'Industrie. A propos d'une recherche participante sur la mémoire de l'eau, p. 34 [*Text for the meeting of October 19th, 1993. About a participant research on memory of water]*

[12] J. Benveniste. Ma vérité sur la mémoire de l'eau, p. 154.

[13] J. Benveniste. Ma vérité sur la mémoire de l'eau, p. 155.

[14] J. Benveniste, April 23rd, 1993. Commentaires sur la visite de la Commission Scientifique n°5 de l'INSERM le 21 avril 1993 [*Comments on the visit of the Scientific commission n°5 of INSERM on April 21st, 1993].*

[15] Cf. Chapter 10; G. Charpak had said: "If it's true, it is the biggest discovery since Newton".

[16] Lettre of P. Nozières to J. Benveniste of May 17th, 1993.

Chapter 7. "Publish!"

> *"No scientist will admit that voting plays a role in his subject. Facts, logic, and methodology alone decide – this is what the fairy-tale tells us".*
>
> P. Feyerabend. *Against method* (1975).

"Black magic" at Inserm!

A few weeks after the visit of the laboratory, the team of Clamart could read the report of the Specialized scientific commission of Inserm. The authors of this report indicated first of all:

> "The Commission wanted to separate these "classical" activities from HD [*high dilutions*], electromagnetic transfer. Indeed, these experiments cannot be analyzed with our current knowledge and were reproduced in no laboratory until today.."

Then they commented on the experiment they attended and specified their approach:

> "The delegation attended an experiment which does not contradict the results announced by Jacques Benveniste. An experiment having no statistical value, the delegation of visit proposed the following approach, in three points […]:
> 1) Do not include, for the moment, the HD program, transfer, in the demand of junior-laboratory contract, so as to judge this one with criteria comparable to those adopted for the evaluation of the other demands of junior-laboratory contracts.
> 2) To establish in coordination with G. Charpak (for the physics aspect) and E. Coraboeuf, a network of 3 to 4 laboratories committed to analyze the reproducibility of the experiment that we attended (even other experiments) in other laboratories after designing a protocol with J. Benveniste. […]
> 3) Reintegration of the program HD and transfer within the junior-laboratory contract if the conclusions of the network are positive.
>
> We can understand the exceptional character of the approach by the concern to analyze a series of experiments with modesty and honesty which cannot be explained in the present state of our

> knowledge. If a scientific approach is maintained in this affair, this can only help the applicants, INSERM and the scientific community in general." [1]

The report of the Specialized scientific commission was thus rather positive and constructive, even if it remained very careful. This report had the merit to try to maintain the debate on a scientific ground. Maybe it is the consequence that a delegation of this commission went on the ground and participated in an experiment. But, from its Olympe, the Scientific council, the highest scientific authority of Inserm, did not have the same view. It did not retain the proposal "to maintain a scientific approach" and preferred to examine the overall demand without separating the various activities. The result was then the rejection of the demand in spite of the favorable report of the commission:

> "When they presented their report to the commission of specialists, the members of the delegation collided with the skepticism of their colleagues. The conflict achieved its paroxysm at the Scientific council of INSERM, where a mandarin spoke about "black magic" for the transmission experiments.[2] Members of council certainly tried to plead the caution ("and if accidentally he was right? Inserm would not recover from it!"), but the vote was unfavorable to the demand of the researchers." [3]

Indeed in the session report of July 9th, 1993 chaired by Claude Amiel, the Scientific council wrote:

> "The demand of junior-laboratory contract presented by Mrs Yolène Thomas was the object of a favorable report on the immunotoxicologic part. Concerning the part on high dilutions and transfer of pharmacological activities, the general attitude was very reserved not due to some "official science" but, at least for some members of council, while waiting for a possible independent confirmation of the reported effects and/or from the result of the ongoing scientific evaluation."

The vote which followed the debate rejected the demand by 15 votes "against", 9 votes "for" and 3 abstentions. The way the question had been discussed by the Scientific council however left a bitter taste to some participants. So, a member of this council, a "classic" pharmacologist, who voted in favor of the creation of the junior-laboratory contract, wrote shortly after to J. Benveniste to report him his feeling after the evaluation of the team of Clamart. About the scientific discussion which should have taken place, he wrote:

> "Two-third of participants around the table spoke before the vote. In my opinion, there was no debate; only the assertion of convictions for some of them, or a desire to dodge for the others.
>
> With or without quotation marks, does an "official science" exist? The procedures of evaluation being driven by scientists who are judges and defendants, there is some natural tendency that projects and people tend to decline toward an average which does not cause many comments. We evolve towards a posh research. The rules of this research are very suitable for people who pursue a career; they deprive those who are attracted by the playful aspect of the scientific adventure. Everyone is free to choose.
>
> By way of conclusion, I do not have the feeling that Mrs Thomas' dossier, and more generally the dossier of your group, received the enlightened evaluation for which any scientist is entitled to expect from an institution which claims to be professional. The fact that seems more serious for me is that this evaluation was not tolerant." [4]

"Inserm supports a discovery only after its confirmation"

When he received the official decision of rejection, J. Benveniste wrote a long letter to P. Lazar where he pointed out the inconsistencies of this decision. For him the report of the session of the Scientific council and the decision of P. Lazar to close the laboratory by refusing the demand of junior-laboratory contract "show the bankruptcy of a crucial activity of the Institute, the evaluation, and announces the death of INSERM in its current functioning. The overdetermination, which is the subordination of the managers to other factors than scientific objectivity, can partly explain – but does not justify – the inconsistency of their decisions."[5] Evoking the presence of G. Charpak and E. Coraboeuf during the visit of the delegation of the specialized Commission, he specified:

> "These experts did not raise the slightest objection to our protocols and participated in a very positive transmission experiment "which does not contradict the results announced by Jacques Benveniste" […]. G. Charpak proposed cooperation between his team and INSERM on electromagnetic transmission of molecular activities. […]"

Then, concerning the question of the "contaminated serum":

> "This contamination, whose we abundantly showed the *in vitro* spectacular effect, is sufficiently threatening for public health so that an investigation, implemented in this moment by the Drug agency and financed by the National network of public health, is entrusted to the same team that sees disappearing at the same time its resources. How will this decision be interpreted by the opinion, and possibly, by the justice, if not as an obstacle in the demonstration of the truth, an attempt to silence the troublemakers? […]"

As for the decision which means in fact closing the laboratory:

> "The negative decision is taken "while waiting for a possible independent confirmation of the reported effects and/or from the result of the on-going scientific evaluation" (report of session of the Scientific commission). We thus wait for the confirmation (probably abroad), while taking measures of intimidation ("see what will happen to you, if you go beyond the allowed limits") and, while waiting, one removes their resources to the researchers responsible of a discovery which, according to the Nobel prize-winner, would be "the most important since Newton", researchers to whom one asks at the same time to demonstrate their discovery (with what?) INSERM supports a discovery only after confirmation. […] Indeed "the on-going evaluation" for which we wait is the one of G. Charpak who has to experience himself (the 200 experiments that we made are not enough!), that is 2 or 3 working hours. INSERM was not able to organize that for 5 years? A unique example of auto-asserted incapacity.
>
> These inconsistencies and incongruities demonstrate that our research in biology, such as it is managed since several decades, is dedicated to the reproduction of established results or to the "discovery" of predicted facts, but rejects any advance that is disturbing for the certainties and for the dominant pressure groups. They contribute to the failures and to the dysfunctions of our biomedical organization."

"Nobody questions your intelligence, your sincerity, your boldness, your panache"

With the letter that officially announced the closure of the Unit 200 of Inserm, P. Lazar answered to J. Benveniste:

> "I received your letter of last August 5th and I meditated on it. I would want to repeat to you in all simplicity, and without much

> hope to be heard, that INSERM and its director, obviously, respect you and are attached to you. Nobody questions your intelligence, your sincerity, your boldness, your panache. What simply lacks today – what you had not neglected to do for your previous works, those that gave you an international scientific reputation – the endorsement of your peers, materialized by scientific publications in high-level journals (on your current subjects of preoccupation; about the others, I know that you continue publishing!)
>
> *Publish*, and there is no reason that you will not be recognized. for this again. Eighteen months of credit assigned by INSERM beyond 31/dec/93 leave you enough time and the material possibility.
>
> A research institution cannot work on other bases. Allow me, once again, to remind it to you." [6]

About the order to be published, J. Benveniste answered to P. Lazar:

> "After Nature's offensive and the June-1940-like defeat of the French scientific "community", there is at present NO possibility of publishing in a journal with a sufficient level on dilutions/transmission. See the article that I sent to *Lancet* and their answer. *Nature* succeeded to discredit a scientist with an "international reputation" in spite of the absence of scientific criticism and the unworthiness of the methods that have been used. There is no doubt that if I was helped normally by the scientists, in particular from my institute, far below what one expects from a team committed in a usual scientific competition, for example creation of a scientific committee, encouragement of collaborations […], invitations at conferences in the teams and the institutes, etc., my group, INSERM and our country would have materialized this very important scientific advance long ago. […]
>
> Nothing of that is made and you tell me: "Publish". I am unarmed in the arena with the lions, the crowd of the blind and the deaf are on terraces with thumbs down. Yours is horizontal: "Go on, old chap, don't be afraid!" " [7]

Then, on October 18th, J. Benveniste wrote another long letter to P. Lazar where he expressed his disappointment for the lack of sufficient help from him in the past although there were many occasions "even if it meant playing a double game, one of the two being friendship". He reminded him the reflection that P. Lazar would have made to a journalist: "Submitted to a considerable

pressure of the two lobbies who manage French research in biology, I did what I could to leave his chances with Benveniste". [8]

And, shortly after the decision of Inserm, as told by M. Schiff:

> "Ten days later, the person in charge of staff mobility at INSERM came to accelerate the desertification of the laboratory by strongly advising to the personnel to quickly choose another workplace at the risk of being later forced to accept an appointment which would not suit them." [9]

"For the right to "heresy" "

In December 1993, one remembers that the journal *Nature* published an article signed by Hirst *et al* claiming that they did not confirm the results of the article of *Nature* 1988 (cf. first part, Chapter 20). After the decision of Inserm, this publication was a new nasty shot for J. Benveniste. He then drafted a text that he sent to about thirty personalities, indicating in a letter of introduction:

> "Following the publication of the article of *Nature* […], a true attack to scientific integrity, it appears that the time has come to take an initiative. This text aims at favoring the return of the researchers, but also the decision-makers, to normal behavior and procedures.
>
> […] This battle is not only ours. If we win it, it will not be easy anymore to stifle ideas and people who disturb." [10]

The text which appeared in *Le Monde* resumed the main lines of the initial project of J. Benveniste and it was signed by twelve personalities.[11] In fact, the journal *Nature* was no longer mentioned. It is necessary to say that the text was finally published only in March 1994. On the other hand, the emphasis was placed on the Unit 200 of Inserm "[which is] closed, its human and material resources are scattered, in spite of its high level asserted by scientific authorities." [12] The signatories demanded "the establishment of a scientific debate instead of the anathemas and threats on the professional situation and the worthiness of the researchers, which deprive them of any means to defend their work." Finally, they raised the question of the mission of the researcher:

> "Is it not the mission of the researcher to explore different, sometimes risky, ways? Yet, structural rigidity, obedience to the dogmas, deification of reason until nonsense, everything today pushes towards this normative conformity, which is a cause of decline and abandonment, sometimes dramatic, and not only in science."

Acknowledging that they were not competent to judge the scientific merits of the case, the signatories concluded: "We do not want to take part in the scientific debate. We plead for the freedom to search, in other words to think, and for the right for "heresy" ".

Feeling targeted by this text, the direction of Inserm released a communiqué on the same day in which it specified that U200 was not closed due to insufficiency of scientific production and presented the closure of the laboratory as a simple administrative measure "as for all INSERM units after twelve years of mandate of their director". It added that the creation of a new unit at the end of twelve years was possible "provided a sufficient number of researchers, what was no more the case for Doctor Benveniste, several researchers having voluntarily left his laboratory" and that "it is inaccurate to say that "human and material resources have been scattered" because Doctor Benveniste continues to work at his premises, with the same equipment and the same credits as last year until June 30th, 1995."

It concluded by wishing:

> "that the efforts to give Doctor Benveniste all the chances to demonstrate his assertions would be simply recognized. It wished that the legitimate desire to express a moral support for a colleague in trouble would be not translated by a misleading description of his effective situation on this day." [13]

P. Lazar was nevertheless in a good position to know that the question was not simply material, but related with the refusal of high-level journals to publish these experiments. Indeed, as commented by the journalist F. Nouchi in *Le Monde*:

> "The question is actually to know if the scientific community leaves doctor Benveniste with "all chances to demonstrate his assertions". If one considers the virtual impossibility for [Benveniste] to publish his works in high-level international scientific journals, we can regret that the direction of INSERM gives only such an administrative answer. This situation led nevertheless the director of INSERM Mr Lazar to write a letter[14] few weeks ago to the director of the scientific journal *Nature*, asking him to be willing to open his columns to Doctor Benveniste. There is today no response to this letter."

Not being able to count on the support of his administration "to demonstrate his assertions", J. Benveniste once again rushed into the quest for

the "proof" and the "crucial" experiment, with the risk of reproducing the situation of 1988 with *Nature*.

Notes of end of chapter

[1] Inserm report of May 7th, 1993 of the Specialized scientific commission n°5 (President: Joël Bockaert).

[2] A new example of reference to magic (see first part) uttered here by Bertrand Jordan, geneticist.

[3] M. Schiff. Un cas de censure dans la science, p. 124.

[4] Letter of Jean-Louis C. to J. Benveniste of October 5th, 1993.

[5] Letter of J. Benveniste to P. Lazar of August 5th, 1993 (modified on September 3rd).

[6] Letter of P. Lazar to J. Benveniste of September 15th, 1993.

[7] Letter of J. Benveniste to P. Lazar of September 21st, 1993.

[8] Letter of J. Benveniste to P. Lazar of October 18th, 1993.

[9] M. Schiff. Un cas de censure dans la science, p. 126.

[10] Letter of J. Benveniste of December 13th, 1993.

[11] The text was signed by Jean Baudrillard (sociologist and philosopher), Jean-Claude Carrière (writer, scenarist), Roland Castro (architect), Pierre Godeau (professor of internal medicine, Pitié-Salpêtrière hospital), Georges Kiejman (lawyer), Henri Laborit (researcher and writer), René Lenoir (former State secretary), Edgar Morin (sociologist and philosopher), Giuliano Preparata (physicist), Jacques Testart (biologist, Inserm), Haroun Tazieff (vulcanologist), Edouard Zarifian (psychiatrist).

[12] Des personnalités apportent leur soutien au docteur Jacques Benveniste [*Personalities bring their support for doctor Jacques Benveniste*]. *Le Monde* of March 1st, 1994.

[13] L'affaire de la Mémoire de l'eau. L'INSERM affirme avoir laissé à M. Benveniste toutes ses chances de « démontrer ses assertions ». *Le Monde,* March 5th*,* 1994.

[14] This letter of P. Lazar to J. Maddox followed upon a demand of J. Benveniste where he asked for the support of the Director of Inserm to make publish by *Nature* a corrective letter after the article of Hirst *et al* of December 1993 in the same journal (See Chapter 20 First part).

Chapter 8. "The stakes are beyond us, you and me"

The reluctances of G. Charpak

After the visit of the laboratory on April 21st, 1993 by the delegation of the Specialized commission of Inserm, the principle of a collaboration with the laboratory of G. Charpak became obvious. One remembers that this proposal appeared in the report of the commission of Inserm. Moreover, faced with the results of the experience performed on that day, the skepticism of the physicist had seemed shaken – at least for a few minutes. Therefore, J. Benveniste decided to take advantage of the apparent good intentions of the Nobel prize laureate without wasting time. But, before setting up a true scientific collaboration which would take time, J. Benveniste organized a public experiment on May 13th to which G. Charpak was invited.

It was planned that this demonstration – "electromagnetic transmissions" followed by blinding of samples – would take place in a room at the *Institute Cochin of Molecular Biology* (ICGM)[1] put at the disposal of J. Benveniste by its director Jean-Paul Lévy. Indeed, since the experiment of December 10th, 1992 (which had not been completed [2]), the demonstrations of transmission experiments were performed at this place:

> "Even if he is cautious about Jacques Benveniste's studies, Professor Jean-Paul Lévy, specialist of AIDS, gladly lends him a room at Cochin allowing him to lead his experiments: "it is necessary to let him search. He is not the devil. I do not need to exorcise the room when he leaves." [3]

However, G. Charpak, who announced at first that he would personally attend the demonstration, finally delegated two of his collaborators, Claude Hennion and Jacques Lewiner. It was a disappointment, but it was nevertheless a positive sign with the aim of a future collaboration and the hope for J. Benveniste to escape from his scientific isolation.

M. Schiff presided over the organization of this experiment, which we are going to describe step by step. The experiment was indeed performed extremely carefully and, to increase the chances of success, it was simplified as much as possible. This demonstration was constituted in fact by four independent experiments. The purpose of each of these elementary experiments was "to guess" the position of a unique "active" sample among ten. Nine inactive samples contained "naive" water that was water not having undergone transmission. Indeed, in order to be not bothered with a possible background

noise, the transmission was performed only for the "active" samples. Furthermore, ten samples of every series were tested on a single heart. So, if biological activity was detected, it cannot be due to a previous sample which would have contaminated the system or modified the behavior of the heart for the following tests.

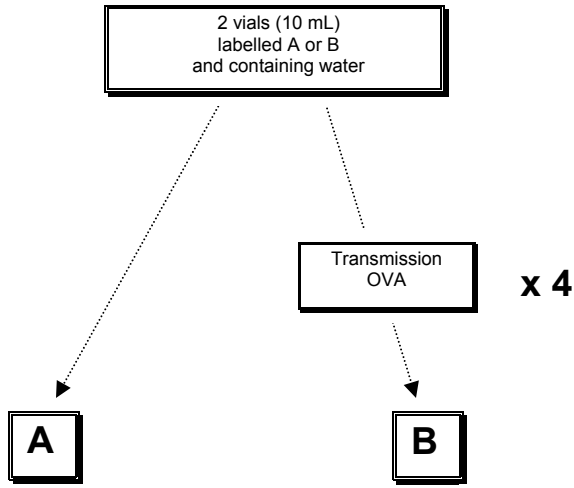
Transmission and blinding of samples were successively performed by eight people not belonging to J. Benveniste's staff and working in pairs.[4] Every pair performed a transmission and then blinded the samples by replacing the initial label with a code. The method of envelopes was used, like in the past. M. Schiff oversaw all the operations but did not participate himself in the process of transmission and blinding.

The manipulations to be carried out were exactly defined in a protocol. Each of the stages was registered on a check list and every stage must be carefully recorded. Within every pair of outside observers, the tasks were distributed in the following way: one of the observers performed the various operations whereas the other one watched him/her and participated in the blinding.

At first, a vial containing ovalbumin at 10^{-8} mol/L was placed on an input coil of the transmission device. Each of the teams successively chose ten tubes of distilled water among a stock and placed them in 10 envelopes. One of the envelopes was chosen and the corresponding tube was placed on the output coil of the machine. Each of the four transmissions lasted 15 minutes. The tube which underwent the transmission was then placed in its envelope and a label with participants' signatures was stuck *inside*. Envelopes were then placed in a box and were mixed. Labels in double were placed at the same time outside of the ten envelopes and on each of ten corresponding tubes, of course without looking inside the envelope. Labels were numbered from 1 to 10 for the first team, from 11 to 20 for the second, from 21 to 30 for the third and from 31 to 40 for the fourth. For every tube, both participants verified the concordance of the numbers of both labels. Envelopes were then placed in a large envelope which was sealed and entrusted to a bailiff until unblinding. Before and after the transmissions on tubes intended for blind tests, a transmission was performed with open-label samples in order to verify that the experimental conditions were correct, both at the beginning and at the end of the session.

Technical sheet of the experiment of May 13th, mai 1993

Type of experiment: transmission on May 13th
Place of the experiment: ICGM (Cochin institute) for transmission on May 13th and Clamart for assessment of samples from May 13th to 17th
Blinding: on May 13th by 8 participants not belonging to U200; unblinding on May 19th
Number of blind tubes to be tested: 4 experiments with 10 tubes each; each experiment was tested on 2 hearts
Additional in-house blinding: yes (between the two hearts)



Blinding of 10 tubes numbered from 1 to 10* (*blind tests*):

9 tubes "**A**"; 1 tube "**B**"

+

2 tubes not blinded (*open-label tests*):

1 tube "**A**"; 1 tube "**B**"

*Experiment 1: labels from 1 to 10; Experiment 2: labels from 11 to 20; Experiment 3: labels from 21 to 30; Experiment 4: labels from 31 to 40.

The tubes were then transported to Clamart where they were tested. Thanks to the method of envelopes, nobody, even those who attributed the codes, could know the codes of the active tubes. The tests were performed from 13 till 17 May on hearts of immunized rats.

Coherent results

The samples of four experiments were successively tested on four hearts of immunized rats on May 13th and 14th. The results (maximal changes of the coronary flow) are presented in the Table 8.1. The results were very encouraging because in each of the series, only one sample induced a change of coronary flow (8, 17, 21, 34).

Exp 1		**Exp 2**		**Exp 3**		**Exp 4**	
N°	Result	N°	Result	N°	Result	N°	Result
Blind tests							
1	3%	11	7%	**21**	**21%**	31	4%
2	3%	12	6%	22	5%	32	2%
3	3%	13	6%	23	5%	33	6%
4	3%	14	3%	24	5%	**34**	**20%**
5	6%	15	3%	25	3%	35	2%
6	3%	16	3%	26	3%	36	2%
7	6%	**17**	**24%**	27	3%	37	6%
8	**46%**	18	3%	28	5%	38	2%
9	10%	19	3%	29	3%	39	2%
10	7%	20	3%	30	3%	40	2%
Open label tests							
Water	5%	Water	3%	Water	4%	Water	4%
OVA tr	21%	OVA tr	18%	OVA tr	20%	OVA tr	15%
OVA 0.1 µmol/L	74%	OVA 0.1 µmol/L	59%	OVA 0.1 µmol/L	56%	OVA 0.1 µmol/L	44%

Tableau 8.1. Results of the first series of measurements (maximal changes of coronary flow) on 4 series of samples (experiments 1–4) of the transmission experiment dated May 13th, 1993. The contents of tubes 8, 17, 21 and 34 (in bold characters) induced changes of coronary flow.
tr.: transmitted.

To confirm these results, a new series of measurements was performed on May 15th and 17th after a new blinding of samples made by M. Schiff in the evening of May 14th. The second series of measurements was thus performed blind for the experimenters who could not link the second series of results with the first one. Thus, the experimenters had to test again four lots of ten samples whose the order had been modified within each series. Besides, the four series were switched around. The results of these second measurements are presented in Table 8.2.

N°	Result	N°	Result	N°	Result	N°	Result
Blind tests (after additional in-house blinding of the first measurements)							
A	-	B	2%	D	2%	C	5%
E	**20%**	F	2%	H	2%	G	5%
O	7%	N	2%	J	2%	I	6%
Q	3%	**P**	**15%**	M	2%	K	3%
U	3%	W	2%	S	2%	L	3%
V	3%	AB	2%	T	2%	R	6%
AA	7%	AG	2%	Z	2%	X	3%
AD	7%	AH	5%	AE	2%	Y	3%
AF	7%	AI	5%	**AK**	**11%**	**AC**	**9%**
AM	5%	AJ	5%	AN	2%	AL	3%
Open-label tests							
Water	3%	Water	4%	Water	4%	Water	3%
OVA tr	13%	OVA tr	10%	OVA tr	15%	OVA tr	13%
OVA 0,1 µmol/L	-	OVA 0,1 µmol/L	25%	OVA 0,1 µmol/L	17%	OVA 0,1 µmol/L	23%

Tableau 8.2. Results of the second series of measurements (maximal changes of coronary flow) on 4 series of samples (experiments 14) of the transmission experiment of May 13th, 1993 after additional in-house blinding by M. Schiff. Note that besides the additional blinding of the 10 samples within every series, the 4 series were switched around. The contents of tubes E, P, AK and AC were those that had the most importing effect on the coronary flow. The hearts of this second series of measurements were less reactive than those of first one.

tr.: transmitted.

For the second measurement of samples, the reactivity of hearts was clearly decreased, including for open-label samples and for ovalbumin at pharmacological concentrations (0.1 µmol/L). Nevertheless, in each series, a sample emerged: E, P, AK, AC. The internal unblinding indicated:

8 = E	**17** = AC	**21** = P	**34** = AK

The results of this second series of measurements were thus coherent with those of the first series. It was thus an extremely important result and apparently the final unblinding should confirm the success of the overall experiment. Were samples 8, 17, 21 and 34 the "first-four winners"?

The experiment is finally unblinded

On May 19th, the large envelope was opened in the presence of the participants and the small envelopes of the four series were opened. The numbers of the envelopes which contained a label indicating the active tubes were the following ones:

Experiment n°1: envelope n°**8** = right
Experiment n°2: envelope n°**18** = false
Experiment n°3: envelope n°**26** = false
Experiment n°4: envelope n°**34** = right.

And, again, the results were half disappointing because only two tubes out of the four, in the experiments n°1 and n°4, were in accordance with the expectations. Once again one did not understand why an activity could be present but not in the exact place where one expected it to be.

M. Schiff tried to understand the origin of these anomalies. But he was faced with two difficulties (that we will systematically find later on): on one hand open-label samples behaved as one could expect and on the other hand there was in-house blinding of these tubes so that the experimenters, J. Aïssa and H. Litime, could not influence the results. Yet, this second series of samples gave results which were coherent with those of the first series. Moreover, M. Schiff himself performed the in-house blinding of these tubes.

In a probabilistic model, M. Schiff tested two hypotheses. In the first one, there was a dysfunction of the measurement system working in an all-or-nothing manner. The second hypothesis supposed a contamination of some tubes with also all-or-nothing reactions that would be coherent for a given tube,

but at random concerning the origin of the tube. In both hypotheses, he obtained extremely low probability and he must reject them. He then concluded:

> "The discordance observed in the blind experiments n°2 and 3 seems to be the consequence from anomalies of numbering which would have occurred between the transport of blind tubes to Clamart and the first series of measurements. It already seems to have occurred in another blind experiment.
>
> In summary, the observed results do not seem to result from a random artefact, an artefact which would be due either to the measurement system or to a contamination of the study tubes. If there was an artifact, it would be much more subtle than the one which would result from such random errors in our modus operandi." [5]

Thus, the conclusion of M. Schiff was close to that of J. Benveniste for the experiment of September 28th, 1992, namely an "anomaly of numbering". And he finished:

> "The situation in which we are after this last series of experiments looks as dangerous as the one that resulted from the visit of three delegates of the journal *Nature* after the publication of the article on the achromasia of basophils. Too confident in the functioning of his experimental device and too confident in the ability of the other scientists to estimate in a rational way experiments that were at the same time difficult and surprising, the person in charge of these experiments was booby-trapped in a problem about fraud, which led to push the experimental device and his operators beyond their possibilities. Besides, the publication of the results of this "expertise" was followed by publications which were only a mockery of reproducibility as we have demonstrated. This past experience must serve as a warning, as well for us as for scientists whom we tempt to interest in the transmission experiments. Clearly, we look for collaborations and help to move forward in a complex research, from both theoretical and experimental standpoints, but we refuse to take the risk of repeating the scenario played in 1988 with *Nature*."

"Act as a scientist, not as a cop"

Even before the unblinding, a dispute began between the two collaborators of G. Charpak and M. Schiff. Indeed, during the session of May 13th, M. Schiff

considered that both representatives of G. Charpak had a nonchalant and unconcerned behavior that irritated him. Besides, when they told the Nobel prize laureate about their visit to Clamart, J. Lewiner and C. Hennion evoked – as a hypothesis it seems – a method which according to them would allow to mark the active tubes, in brief a possibility of fraud. As tinder which needs only a spark to ignite, a brief dispute began. M. Schiff being the organizer of this demonstration, he felt directly targeted by this suspicion. It was painfully ironic for him who tried to understand what was at work in "Benveniste's experiments" by setting up experimental protocols which were flawless. Here he was in his turn in the eye of the cyclone. He could certainly say to himself that it would make another chapter in the book that he intended to write, but the suspicion, even light, was very hurtful. Some correspondences followed.

Thus, M. Schiff wrote to G. Charpak shortly after the experiment:

> "Last Friday, I learned from Mr Benveniste that the report made to you by Mr Lewiner (or Mr Hennion, I do not know which) about the series of 4 demonstrations that I managed on Thursday the 13th of May within the laboratory of Unit 332 of INSERM at Cochin led you to be convinced that this series of demonstrations must have been vitiated by fraud, a fraud of which I was probably the agent. In an affair as complex and as delicate as this one, the fact that of going through intermediaries increases the communication problems. This is why I prefer to communicate with you directly. […]
>
> It seems that you interpreted my temporary irritation and the fact that I objected to your delegates interfering with an ongoing experiment as indicating that a fraud must have occurred. In case your informers did not report it, I mention the fact that I insisted that they should watch at least one of the four experiments; I also insisted that they should accept to play the role of participant-observer and of witness described in the protocol that you should have received. They refused and I insisted that they should at least be present to watch one of the experiments. Actually, they spent only half of the duration of one experiment in the demonstration room. What provoked my irritation was the fact that, instead of watching the ongoing operations, they turned their back to the apparatus and proceeded to argue with Benveniste on fraud and about the "open-mindedness" of the scientific community, which, according to them, is not as narrow-minded as Benveniste claimed. You must admit that I had excuses for loosing my temper!" [6]

J. Benveniste also wrote to the physicist:

> "I am rather worried about the way things have evolved. I think that you are aware of how serious the simple use of the word "fraud" can be. […] I regret your absence during the coded experiments of 13 May. You would have seen that the way it took place showed that every precaution had been taken against the possibility of some system of recognition. The point of the coding was not to combat fraud, but simply to avoid any possible bias of the technicians. Note that they receive numbered syringes that have been prepared by another technician, which means that they never see the original tubes.
>
> When we heard of your coming, we said: "Finally a scientist!" It is therefore quite disappointing to hear that you are taking up again gossip which we thought we had been rid of since 1988. The idea that "someone is cheating behind Benveniste's back" was the way out used by *Nature*'s group with its magician. At the present time, at least 10 people are involved in this research; each of them is thus under trial. Usually, scientists choose their best results once they are convinced that their hypotheses have been demonstrated. We do not act that way, but show everything to everybody, thus taking the risk that misinformation of the worst kind might come out of it. Sir, act as a scientist, not as a cop. What we have found, almost by chance, is indeed enormous. The stakes are beyond us, you and me. Given the issue involved, mediocre attitudes cannot be justified and are intolerable. You do not understand? Neither do I. But it exists. Contribute to the outcome of truth. […]
>
> Concerning the difficulty you have in understanding what is going on with this machine, you are not the only one. As you well know, the argument: "I do not understand, therefore it does not exist" has been used so often in the past that is completely discredited. […]
>
> However, the best way to cut short any suspicion of fraud would be for you to perform the experiment yourself in your laboratory. I remind you of the fact that this is what I had initially suggested (instead of Cochin). The experiment would be performed by two outside observers designated by both of us who would guarantee that the transfers occur according to a protocol that has been defined in advance. […] You are a man of honor: you cannot make remarks that are degrading to a colleague and refuse to perform a verification that would stop the rumor." [7]

In a letter sent from the CERN at Geneva, G. Charpak tried to calm the situation:

> "Please excuse my delay in answering your messages. I was not available because of journeys and conferences.
>
> However, I made certain that two of my co-workers of the School of Physics and Chemistry go to Cochin, because their collaboration is essential for tests in their laboratory. They confirmed to me that the amplifier oscillated in a permanent way. But after thinking about it, I do not intend to draw any conclusion from it for the moment.
>
> The effect which you observe, and you say is easily reproduced, needs only a simple test. The use of about twenty vials of water, some of which have been sensitized according to your method, using a protocol determined by you and without you being be able to know the distribution of the vials, should permit an objective test.
>
> During the visit of my co-workers at Cochin, there was a small discussion with Mr Schiff because they thought that they had noticed a possibility of marking the vials that had been sensitized during the phase of vibration. This certainly does not mean that this possibility was used. But it is clear that no doubt should remain. It will be easy to Mr Spira to define a protocol forbidding any suspicion." [8]

J. Lewiner himself sent a letter to Mr Schiff in order to minimize what he and his colleagues were supposed to have said:

> I received a copy of the letter you sent to Mr Charpak on May 16th, 1993 and it seems important to dissipate the wrong interpretation that seemed to have developed after our visit of 13 May.
>
> Actually, on our return, we communicated to Mr Charpak our feeling about the experimental procedure chosen and we proposed one that differs very slightly and seemed susceptible to us either to convince the scientific community of the interest of your experiments or to show the necessity of additional experiments.
>
> We certainly never claimed that that the series of demonstrations that you conducted was vitiated by fraud, and *a fortiori* fraud perpetrated by you.
>
> Therefore we will propose to Mr Charpak an experimental procedure which, if it seems to him to be of interest, will probably be submitted to you." [9]

For the moment, however, the incident seemed closed. Besides, Mr Schiff discontinued at the end of 1993 his direct implication in the experiments of the laboratory. He explained afterward:

> "As for me, the period when I conscientiously drafted experimental protocols of demonstration for people to whom the transmission experiments of transmission raise existential problems has passed. Tired of speaking with deaf people, I address others." [10]

Then M. Schiff dedicated himself to draft a book on the censorship and the self-censorship in the scientific world based on the affair of the "memory of water" and his experience at Clamart. His methodological rigor was missing when the laboratories of J. Benveniste and G. Charpak collaborated. But before telling this episode, we have to review at first a curious phenomenon.

Notes of end of chapter

[1] Located Street Méchain in the 14th arrondissement on the campus of Cochin hospital.

[2] Cf. Chapter 5.

[3] E. Fottorino. La mémoire de l'eau. Du rêve au soupçon. *Le Monde*, January 21st, 1997.

[4] The four pairs of participants were the followings: experiment n°1, Françoise Russo-Marie and Jean-Claude Salomon; experiment n°2, Isaac Béhar and Jacques Testart; experiment n°3, M. Reynier and P. Pacaud; experiment n°4: J.Y. Follezou and P. Richard.

[5] J. Benveniste and M. Schiff. Compte-rendu des expériences réalisées le 13 mai 1993 pour mettre en évidence la possibilité de dissocier une information moléculaire de son support d'origine. p. 13 [*Report on the experiments performed on May13th, 1993 to evidence the possibility to dissociate a molecular information from its original support*].

[6] Letter of M. Schiff to G. Charpak of May 16th, 1993.

[7] Letter of J. Benveniste to G. Charpak of May 14th, 1993.

[8] Letter of G. Charpak to J. Benveniste of May 19th, 1993.

[9] Letter of J. Lewiner to M. Schiff of May 18th, 1993.

[10] M. Schiff. Un cas de censure dans la science, p. 64.

Chapter 9. Where the existence of a strange phenomenon is confirmed

An oxymoron: the coherent discordance

For J. Benveniste who wished to obtain all-or-nothing biological effects in order to give a spectacular character to his demonstrations, the results of the last experiments were only a half-success. Indeed, even if the results were overall in favor of a "transmission", he could not admit that a sample which was supposed to be "inactive" had nevertheless an effect. The idea that a contamination or a "background noise" could explain this phenomenon was difficult to support because curiously one always obtained the correct number of expected active and inactive samples. Moreover, this wandering activity seemed to be specific: for example, in the case of "transmitted ovalbumin", an effect was observed with hearts from animals immunized with ovalbumin, but not with hearts from naive animals.

But maybe the reader has the feeling that we highlight an anomaly which after all occurred only eight times (four "inversions") among 68 samples tested during these three last demonstrations (July 9th, 1992; September 28th, 1992; May 13th, 1993). At this stage, we could consider that it was bad luck, an unpredictable combination of circumstances or an imperfect technical development. The continuation of the story will show that this explanation is not sufficient, because the phenomenon continued and became even sometimes so obvious that it was not possible then to incriminate an error of manipulation. Furthermore, let us not forget that the idea of a "contamination" of the physiological salt solution was born during a demonstration when J. Benveniste announced with assurance that the content of a tube was "active" while it was only an inactive control. It is even possible that what J. Benveniste considered for months as a "contamination" of physiological salt solutions was only a way to put a name on this unexpected phenomenon. This phenomenon was particularly obvious with the blind samples during public demonstrations.

These activities which appeared to "jump" from one sample to the other one were then nicknamed "wild transfers" by J. Benveniste and his collaborators when it became clear that the explanation of a manipulation error or a "simple" contamination was not satisfactory. We will use the picturesque expression "wild transfer" only with precaution and with quotation marks because this name implies that the activity was localized in the tube or the vial, the content of which was tested. We prefer to talk of *coherent discordance* to underline the discrepancy between the observed effects and the "expected" effects. This name could appear as an oxymoron, but it precisely allows insisting on what causes

the perplexity when one gets the measure of this phenomenon: results are not where one waits for them (*discordance*), nevertheless it is not nonsense because there is still *coherence* between repetitions of the same measurement and with available information. When a coherent discordance is noticed, it is as if the threads that connect the causes and the effects had been tangled.

Finally, it is necessary to insist on the fact that a coherent discordance *is not an absence of effect or a failed experiment* due to poor experimental conditions. In case of discordance, there is nevertheless an effect – it is an essential point – but the cause of this effect seems not to be in its place. To make it clear, we are going to illustrate it by using a metaphor.

Some magic tricks

Let us suppose that a stage magician affirms that he is capable of guessing the color (club, diamond, hearts and spade) of deck of cards the back of which one presents to him. After several hundred trials, one notices that the success rate of the magician is of the order of 25%. We conclude that this magician had neither a gift, nor was it a trick because this result is explained by chance only.

But let us suppose now that another magician presents on stage four empty bird cages (Figure 9.1). He covers each of the cages with a veil and predicts that a parrot will appear in the cage n°2. One removes the veils. There is actually a parrot in a cage, but it is in the cage n°3. It is thus a failure for this first attempt. We do hundred experiments and a parrot appears where predicted by the magician in approximately 25% of the cases.

One can consider that it is a failure, as for the above card trick, because here again the predictions of the magician were not better than chance. Nevertheless, in every attempt, a parrot appeared in a cage, what could be considered as extraordinary. If the magician had been less ambitious, he would have said that he was able to make a parrot appear without specifying the cage. However, if we return to the problem that worries us, the localization of the causes is extremely important in experimental sciences because one must be able to connect them with their effects. The principle of causality is one of the strongest principles that allow us to make a representation of the world. Permanently, scientific and everyday life reasoning calls on this principle.

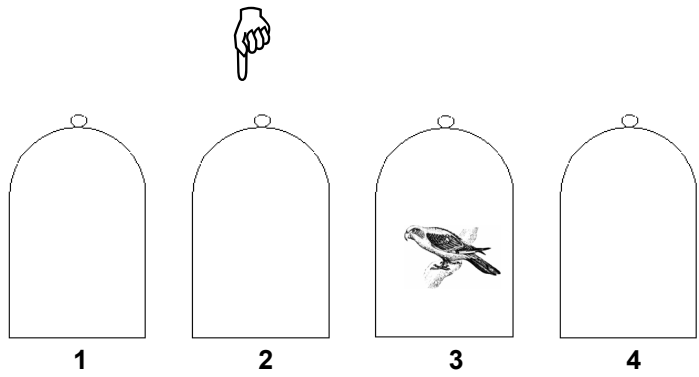


Figure 9.1. A magician claims to make a parrot appear in one of the four cages he previously indicated. First, cages are presented empty to the public; then they are covered with an opaque veil. The magician makes his prediction and when the veils are removed, one notices that a parrot is effectively present in one of the cages. After many experiments, one calculates that predictions were correct in approximately 25% of the cases. His predictions are thus not better than chance. We can consider that the magician failed. But, we can also be amazed by the appearance of a parrot each time.

To explain this disturbing phenomenon, we will see that J. Benveniste always evoked a lack of development of the experimental system or an error of manipulation. Never the basic hypothesis of the experiments was questioned, namely the validity of the underlying concepts concerning the possibility of transmitting biological signals or concerning the reality of the high dilutions. M. Schiff himself, through a statistical and probabilistic approach as we have seen above, strengthened the idea of an error of numbering or a technical problem.

Both J. Benveniste and M. Schiff, however – and one can understand them because of the coherence of the results – considered that there was actually a transmission of a biological activity. But, even though an "expected effect" was present, the supposed "cause" was problematic. We are indeed in a circular reasoning where the cause and the effect define themselves mutually. If there was an effect *A* it was because it existed a cause *a* and the cause *a* defined itself because it was associated with an effect *A*. It has never been possible to go out of this circle by using an element outside the system. The lack of research or the insufficiency of technology were then put forward. For example, when the "digital signal" was recorded on a memory of computer, it would have been useful to be able to discriminate each signal by spectrum analysis. Another possibility was to consider that if nothing was found, maybe it was because

there was nothing to find. However, the "cost" of this last hypothesis would have been too high.

As we will see in the next chapters, the experiments of J. Benveniste and his team became more and more uncluttered to eliminate possible artefacts which could be at the origin of the "jumping of activities". But the irritating problem persisted and did not contribute to the serenity of the debates and demonstrations. It is what we are going to tell with the experiments performed in the laboratory of G. Charpak.

Chapter 10. "If it's true, it is the biggest discovery since Newton"

"The head on the block"

In its report after its visit of April 21st, 1993, the Commission of Inserm called for a collaboration for the respective laboratories of J. Benveniste and G. Charpak. The latter had however canceled an appointment during the demonstration performed a short time later, on May 13th, and had delegated two of his collaborators. Furthermore, one remembers that a certain tension was born between both laboratories with correspondences where fraud had been evoked. This future collaboration which had been suggested by the Specialized commission in the fervor of the moment seemed to weigh more and more upon G. Charpak and one year passed before the first experiments took place. Besides, contributing to the irritation of G. Charpak, J. Benveniste did not hesitate to repeatedly quote that the latter had said during a phone conversation:

> " "If all of this is true, it is the biggest discovery since Newton". He adds even during the same conversation that it would be necessary "to rename Quay Anatole-France [*where the National Center for Scientific Research sits*] as Quay Benveniste" ". [1]

The journalist F. Nouchi who stayed in close contact with J. Benveniste echoed these words in *Le Monde* at the end of 1993.[2] The journalist then wrote that the results of J. Benveniste were:

> "A mystery about which a Nobel prize laureate would have said during a private conversation that "if it were true, it would be the most important discovery since Newton." " [3]

Although his words were anonymous, it was not difficult to recognize G. Charpak behind this "Nobel prize laureate" and he wrote to F. Nouchi and J. Benveniste to replace the conversation in its context so that his words would not be interpreted as an endorsement of the studies on the "electromagnetic transmission". G. Charpak insisted to specify to J. Benveniste about this article in *Le Monde*:

> "An article suggests that I am certain that you are not a victim of an experimental artefact. This is not the case and I do not wish for everyone to believe I support the experiments on the memory of water". [4]

In his letter, the Nobel prize laureate also indicated to J. Benveniste the conditions of their future possible collaboration. In particular, he considered

that J. Benveniste had "an erroneous vision of what must be verification of a scientific fact". He explained that he would collaborate if J. Benveniste granted to make the experiments in conditions of control "satisfactory for a physicist", that is – always according to G. Charpak – by putting "the head on the block". We must admit that this was the beginning of a scientific collaboration in poor conditions if one of the protagonists spontaneously proposes himself for the role of the executioner! Therefore, after his "encouraging" sentence for the success of the experiment during his visit at Clamart ("You'd better, otherwise you are dead")[5], G. Charpak persisted, thus revealing a rather bloody conception of scientific evaluation!

J. Benveniste answered to G. Charpak, first of all for the article of F. Nouchi and the reference to Newton:

> "The article of the latter seemed clear because he reported one of your words without omitting the conditional: "if it *were* true, it would be". It was not question of making you endorse these results, but rather to be surprised that, even it has a chance of one out of one thousand to be true, the scientific "community" is missing "the biggest discovery since Newton". I take this opportunity to tell you directly my regret that our collaboration is not closer. In spite of your independence, you probably are as me under the pressure from the scientists propped up on their certainties. I had hoped that after your visit a more confident, close, steady collaboration would be established between the ESPCI and my laboratory." [6]

He returned then on the question of an experimental error or a possible artefact:

> "I remind you that, during your coming with the delegation of INSERM on April 21st, 1993, no methodological criticism or hypothesis of artefact were emitted by this group on the scientific level and the experience of which one cannot dispute. One cannot thus allude to an artefact, as upon a litany, without proposing credible and experimentally verifiable suggestions. Yet, till date, none resisted the most superficial examination. In particular, I received nothing from you and what I received from De Gennes once again illustrated the fragility of the intelligence in front of dogmatism. If all the French Nobel prize-winners and in addition Baruj Benacerraf[7] did not propose an artifact up to now, can one continue to speak about it, except for separating word and thought? In the absence of this mythical artefact, the immense

> majority of the scientists, including you, refuse in reality to consider these results in the name of: "it is impossible thus it is not" "

J. Benveniste reminded then to G. Charpak – who consulted colleagues about the theory of G. Preparata and of E. Del Guidice – what is sometimes the value of the opinion of "experts":

> "I do not understand your acceptance without discussion of the judgment of *one* French theoretical physicist. The weakness of French theoretical physics throughout the multiple paradigmatic revolutions of the century is a historic fact. From relativity to quantum physics, everything has always been denied by the "experts". A theoretical advance, which would allow to shed some light on the structure of condensed matter and which has already demonstrated its power by the assessment of well-established physical constants, cannot be dismissed out of hand. How about organizing a seminar on this subject?"

He reminded also the experiment of April 21st, 1993 in which participated G. Charpak by coding samples:

> "Before the opening of the code, we designated the tube A, which induced a reaction similar to authentic ovalbumin, as being "transmitted" ovalbumin, what it was. Where can the error be? Afterwards, you asked to redo the experiment in your laboratory, without my presence and "of every person having shaken hands with Benveniste within three months". It was insulting, but I accepted this because the cowardice which prevails among my peers, in particular biologists, leaves me alone – with the only help of Alfred Spira – in front of this choice. Maybe I have an "erroneous vision of what must be the verification of a scientific fact" and, in this case, I would be very happy if you show me what it is, but I would be surprised that you would agree to see your experiments undergoing this kind of checking."

He continued on the methods and conditions of collaboration between both laboratories:

> "Do you really think that "satisfactory conditions of control for a physicist" consist in putting "[my] head on the block"? I did not know that the world of physics was so barbaric… In fact, a verification according to the usual methods would be, as you had proposed, that one of your collaborators comes one or two days a week during one or two months to work in our laboratory

> including, after some developments, in our absence, if that can reassure you."

And he ended by expressing his disappointment in front of what he judged to be a lack of open-mindedness among scientists:

> "In conclusion, I am happy that you still wish to collaborate with us. Certainly I am disappointed that this collaboration is taking place according to unusual scientific rules, on the mode of the "Russian roulette". This atmosphere clearly reflects the one who prevails within French scientific "community" – and not only for my affair – and contrasts with the open-mindedness which you were the only one up to now to express among the great French scientists. However, I have decided to do this experiment with you, as soon as the intensity and the regularity of the responses of the hearts will be as they were during last spring".

J. Benveniste and G. Charpak nevertheless succeeded in agreeing on the technical and experimental conditions. It was decided that the transmission experiments would take place at ESPCI (*Ecole Supérieure de Physique et Chimie Industrielle de la Ville de Paris*) located Street Vauquelin in the 5th arrondissement of Paris and that samples would be then transported to Clamart where they would be tested.

An oppressive atmosphere

As indicated by J. Benveniste, the period itself was rather unfavorable for these demonstrations because hearts reacted weakly to stimuli for poorly understood reasons. The preparatory experiments consequently took time. Thus, a first experiment was performed on March 7th, but was canceled due to technical problems at the time of the measurements. The second experiment took place only on March 30th. Furthermore, as indicated by J. Benveniste:

> "The atmosphere which reigned during this phase of preparation and then during the experiments is extremely painful. The collaborators of Charpak show honesty and benevolence towards us, but the Nobel prize laureate still behaves with a contemptuous attitude. To such a point that at no time I had the opportunity to sit down in his company to discuss the protocol or obtain enlightenments on some questions of physics." [8]

Moreover, the absence of M. Schiff was felt in the methodological organization of the experiments. Thus, results with open-label samples performed in the same conditions as blind samples were only rarely reported.

Yet, these controls would have allowed validating (or not) the experiments before unblinding. In other words, all experiments were taken into account for the analysis even though a simple quality control would have rejected a large number of them. But having promised a lot, J. Benveniste is condemned to a faultiness round.

"Wild transfers" occurred (or at least errors of allocation in the codes were interpreted as such). At the beginning, J. Benveniste incriminated the commercial physiological salt solution and the hearts that poorly reacted. Finally, he suggested that the intensity of the electromagnetic background was higher in the laboratory of physics of G. Charpak than in the laboratory of Clamart:

> "To explain the errors that appear during the unblinding, Doctor Benveniste suggests two phenomena: the hearts of guinea pig would not be very sensitive (the reactions of these animals vary according to the seasons); the radiations blur the data during the transport in car between Street Vauquelin and Clamart. To prevent it, the researcher locks tubes inside big tinplate boxes. He wraps them in aluminum foil and then tries again other armoring methods (mild steel, copper and finally mumetal, an alloy intended to block magnetic fields). "I let him establish his protocol and validate it. But it still did not work", Claude Hennion regrets this." [9]

A paranoid ambiance then developed within the laboratory of Clamart. J. Benveniste who did not succeed in understanding the origin of the "wild transfers" wondered if somebody did not play with him in the laboratory. A scenario similar to the one which had ended with the dismissal of L. Hadji in 1991 was being set up. J. Benveniste even announced his suspicions concerning his own co-workers to C. Hennion. Samples were tested to Clamart in an atmosphere often heavy and suspicious. I. Béhar – a retired engineer and entrepreneur who spent several months in the laboratory of J. Benveniste at this time to participate in this research – testified about this "atmosphere of generalized suspicion which reigned there". He also confirmed the felling of headlong rush:

> "During all the period of the Charpak experiments, Benveniste was effectively obsessed by the problem of water […] and he made trials everyday with new water by changing the details of the experimental protocol also very often." [10]

Nevertheless, Street Vauquelin, C. Hennion was patient and did everything he could so that the experiments were performed at their best. The relations of

J. Benveniste with G. Charpak became evermore tense. Contrary to his commitments of April 1993 during the visit of the laboratory in Clamart, the physicist appeared to take some distance towards these experiments, letting his co-workers manage them, J. Benveniste told:

> "Charpak rarely attended the operations of transmission. During one of the rare occasions where the Nobel prize laureate is present, a statistician, Director of research at Inserm, is also at the premises. I do not know this researcher and had with him only a brief phone contact. It is he who has to perform the operation of coding of tubes. Probably suspecting that the statistician could be in cahoots with me, Charpak intercepts a secretary who passes in the corridor and he made her redo the coding. Another source of confusion." [11]

The experiments continued nevertheless. The laboratory of Clamart appeared entering into a suicidal enterprise. When, in spite of the poor experimental conditions, a forecast was tempted on flimsy results, it was naturally mostly a failure:

> "Benveniste took the blow silently, observes Claude Hennion. But when he was right, he was like a visionary. His behavior was not scientific any more." [12]

The last experiment was performed on late July 1994.

Disappointing experimental conditions and results

The analysis of the results of the experiments performed with the laboratory of G. Charpak is a clear proof of the poor reactivity of the rodent hearts. The samples which were designated as "active" hardly induced changes of coronary flow: 15% on average. We have seen that a change of 10% of the basal flow was the limit which had been empirically defined to discriminate between "active" and "inactive" samples. The experimental conditions were thus mediocre because the intensity of the signal was near the background noise.

After reading Table 10.2 which summarizes these experiments, it is striking to notice that many experiments did not succeed for technical reasons; moreover, experiments without the usual open-label controls were numerous. We are far from the rigor and from the quality control which prevailed for example during the experiments organized by M. Schiff.

Date	Active:inactive samples	"Transmitted" active compound	Number of hearts	Open-label actives samples	Unblinding	N° on figure*
March 7, 1994	1 : 3	Ova	2	Not done	*No results*	-
March 30 and 30 bis	2 : 5	Ova + tet. vac.	3	Not done	False (*in fact non interpretable)*	-
April 21	1 : 4	Ova	2	18-15%	Correct	1
April 21	1 : 2	ACh	Not tested	-	*No results*	-
May 10	1 : 2	ACh	3	Not done	False	2
May 11	1 : 2	ACh	3	Not done	Correct	3
May 13	1 : 2	ACh	3	Not done	*No conclusion*	4
May 17	1 : 4	Ova	3	Not done	False	5
May 18	1 : 4	Ova	2	Not done	False	6
June 1er	1 : 4	Ova	4	18-14-8-11%	False	7
June 3	1 : 4	Ova	Not tested	-	*No result*	-
June 6	1 : 4	Ova	2	25-40%	False	8
June 8	1 : 4	Ova	2	13-21%	False	9
July 7	1 : 4	Ova	Not tested	-	*No result*	-
July 13	2 : 4	Ova	1	12%	1 correct sample	10
July 13 bis	1 : 2	ACh	1	15%	False	11
July 22	1 : 4	Ova	2	Not done	False	12

Tableau 10.1. Summary of the transmission experiments performed in the laboratory of G. Charpak. Among 18 experiments, 13 were considered as exploitable (but with 10 of them the correct code was not found, 2 fitted the code and 1 was intermediate). If we make a selection by defining quality criteria before taking into account the results, only the experiment of June 6th is selected. Unfortunately, the sample which "emerged" in an obvious manner in this experiment was not the correct one (this experience is detailed in Table 10.2).
Tet. vac.: tetanus vaccine; * Figure 11.2 of Chapter 11.

With better experimental conditions, could better results have been obtained? Nothing is less certain. First of all, if we proceed to a selection of the experiments according to quality criteria, a unique experiment of the series combines enough criteria: open-label samples with correct results and change of the coronary flow of 20% or more (experiment of June 6th; Table 10.1). But, even though a biological signal was recorded, thus suggesting that a "transmission" indeed occurred, the biological activity was not where it was supposed to be. It was a typical case of "coherent discordance" with results correlated on both Langendorff's devices which worked in parallel (Table 10.2).

Tested samples	Number of measurements	Maximal changes of coronary flow (%)	Biological activities in increasing order	Unblinding
Blind tests				
G	2	6.0 ± 1.4	1	Water
F	2	7.5 ± 3.5	2	**Ova tr.**
M	2	9.5 ± 0.7	3	Water tr.
B	2	23.5 ± 7.8	4	Water
Open-label tests				
Water tr.	2	4.5 ± 0.7	-	-
Ova tr.	4	32.0 ± 26.5	-	-
Ova 0.1 µmol/L	2	45.0 ± 21.2	-	-

Tableau 10.2. Transmission experiment of June 6th, 1994 performed in the laboratory of G. Charpak. This experiment was one of the rare of the series for which open-label controls were realized and allowed validating the experiment. Both Langendorff devices which worked in parallel gave correlated results. Unfortunately, after unblinding, the most active sample was "naive" water. There was no effect for transmitted ovalbumin which should have modified the coronary flow.

"*You practice a headlong rush which will cut you definitively from scientific circles"*

Not long after the end of the experiments, G. Charpak wrote to J. Benveniste:

> "I consider it necessary to make an assessment of the experiments which you made to the *Ecole Supérieure de Physique et de Chimie.*
>
> It is clear that the results which you obtained are compatible with those for which one could expect with an effect simply due to chance.
>
> In front of negative results, you searched for explanations in interference effects. Apparently, you never wondered if your previous observations were not vitiated by error.
>
> I understood that you wondered, a few months ago, if in your entourage, one of your collaborators did not bias the results systematically because, when these were predictable they were generally confirmed by the experiments.
>
> You seem to have pushed aside this hypothesis, which appeared as the most plausible to me.
>
> Why did it seem to me plausible, you might ask me? Because your experiments challenge the elementary laws of the physics and those of simple common sense.
>
> It is not reasonable to imagine that your amplifier, which is in a state of permanent oscillation, transmits to water electromagnetic

signals that structure this water. The environment in which you are immersed in the laboratory is full of radiations of all wavelengths, having an amplitude whose the value is higher than those of the waves you claim to transmit, by vertiginous factors.

It was obvious from the beginning, but I wanted to give you a possibility of correcting a mistake." [13]

G. Charpak pursued:

"Many famous scientists met artifacts which sometimes excited them because they thought of having fired of the big game. They knew how to, generally, move back in time thanks to a poorly exciting virtue which is a critical mind towards oneself. I really believed that you were manipulated by an unscrupulous circle of acquaintances which found there an interest and that if you could see that your observations were not reproducible magic, you could save your reputation.

You have to your credit, according to your peers, good works in biology and the simple recognition of an error would have been put to your credit.

But you practice a headlong rush which will lead you only to cut you definitively from scientific circles. […]

When cold fusion was announced, dozens of experiences, each more false than the last, confirmed the first observations. I know that some artists as far as extortion of subsidies is concerned continue to become agitated in this domain because one finds an incredible quantity of gullible people even in high positions and I am not surprised that one of these artists gave you the illusion that very learned theories were compatible with your experiments.

I got their articles examined by theoretical physicists of the most eminent. They found them absurd." […]

And G. Charpak ended his letter by distancing himself:

"There is no interest to give the illusion that you undertake rigorous experiments at the *Ecole Supérieure de Physique et de Chimie*. I thus ask you to never mention any collaboration with my team in which I think that Mister Claude Hennion gave a perfect example of patience and rigor".

After one month, J. Benveniste answered to G. Charpak by a long letter:

"I waited a few weeks before answering your letter so that it is not influenced by the sadness which I felt after its reading. I could detail the reasons of this sadness, the two main reasons being your

> contemptuous tone and the distance between your arguments and the scientific stake. But I do not want to be involved in a controversy with you and I prefer to answer you on the content. […]
>
> You have once again mentioned "fraud" and indicate that I considered such a hypothesis myself and that I ruled it out. […]
>
> It would be a fraud because our "experiments challenge the elementary laws of physics and those of simple common sense." Dare I remind you that the "simple common sense", before the development of the theories and the relevant scientific observations, had led to admit that the sun turns around the earth, that the X-rays, the heaviest than the air, the recorded voice, the laser, etc., were hoaxes […] The same "common sense" authorized the most eminent "theorists" to deny the existence of bacteria, that the light can be described at the same time in term of corpuscles confined in a volume and of waves propagating infinitely, that matter is energy, that moving closer two pieces of metal could kill thousands of people in a few seconds? […]
>
> Is development of the sciences not more often made by bringing answers to the contradictions with the prevailing scientific laws than by subscribing to "common sense" and other "elementary laws"? […]"

And once again he reminded G. Charpak about the experiment this latter attended at Clamart:

> "I also remind you the conditions of the experiment in which you participated on April 21st, 1993; you performed, locked into a room with the delegation of INSERM, the transfers of ovalbumin and endotoxin on two tubes of water chosen among twenty identical tubes. We had told you in advance that the one and/or other one of these transferred tubes could work, according to the state of immunization of animals. You blinded four tubes among which two were control tubes (it is necessary to remind that all samples were water which had never left its tube). We then measured the effect of these blind tubes and on four hearts we constantly found an activity for the tube A, an activity that was strictly proportional to the one obtained with ovalbumin at -7 M [*0.1 µmol/L*]. After unblinding, tube A was Ova-TR [*transmitted ovalbumin*]. The results were in the order 13, 15, 32, 93% of change of coronary flow for Ova-TR (that is once again water) and respectively 9, 12.5, 45 and 100% for Ova -7 M. Where can be the

> cheating, the fraud which you then evoked and that you repeat in your letter? […]
>
> I would like to believe that your letter was written in a fit of anger and maybe under the blow of exterior events. I hope with all the involved researchers and technicians that, after examination of the facts summarized above, you will be willing to maintain the collaboration which we think is essential, because only a multidisciplinary research will allow making progress in the understanding of the phenomenon." [14]

The experiments with G. Charpak were a unique opportunity for J. Benveniste. Although he is not a biologist, G. Charpak with his aura of Nobel prize laureate would have been a considerable support if he had been the slightest bit convinced. Without going so far, the neutrality of the physicist in the "debate" would have been preferable in the situation which now prevailed. Indeed, J. Benveniste has now made a new "enemy" in the person of the physicist. Before being committed in the "affair", G. Charpak did not certainly "believe" in it, but it was for theoretical reasons and due to a matter of principle. After the failure of the experiments performed in G. Charpak's laboratory, J. Benveniste thus burned out invaluable ammunition. He could certainly put forward poor experimental conditions, but what would be retained was that "the experiments with Charpak did not work". Moreover, G. Charpak had now concrete reasons for "not believing" in these experiments. He did not hesitate to let it be known by all the authority that conferred him his status and he was furthermore helped by his popularity in the media.

Notes of end of chapter

[1] E. Fottorino. La mémoire de l'eau. Le temps des passions. *Le Monde*, January 22nd, 1997.

[2] The article in *Le Monde* had been written on the occasion of the publication of the article of Hirst *et al* published in December 1993 which, one remembers, tried to reproduce the results of the article in *Nature* of 1988 (see first part).

[3] F. Nouchi. Une équipe de chercheurs anglais n'a pu reproduire les travaux du docteur Benveniste sur la « mémoire de l'eau ». *Le Monde*, December 11th, 1993.

[4] Letter of G. Charpak to J. Benveniste of January 18, 1994.

[5] Cf. Chapter 6.

[6] Letter of J. Benveniste to G. Charpak of January 24th, 1994.

[7] Immunologist, Nobel prize laureate in 1980.

[8] J. Benveniste. Ma vérité sur la mémoire de l'eau, p. 158.

[9] E. Fottorino. La mémoire de l'eau. Le temps des passions. *Le Monde*, January 22nd, 1997.

[10] I. Béhar. Distinguer l'homme du résultat scientifique. *Le Monde*, February 8th, 1997.

[11] J. Benveniste. Ma vérité sur la mémoire de l'eau, p. 159.

[12] E. Fottorino. La mémoire de l'eau. Le temps des passions. *Le Monde*, January 22nd, 1997.

[13] Letter of G. Charpak to J. Benveniste of December 5th, 1994.

[14] Letter of J. Benveniste to G. Charpak of January 9th, 1995.

Chapter 11. "It is a pity to see you unable of appreciating the importance of the stake"

Strategic retreat at Clamart

Just after the series of experiments with the laboratory of G. Charpak were finished, J. Benveniste wanted to redo them, but in experimental conditions that he considered to be more favorable. Indeed, he continued to think that the electromagnetic environment of the physics laboratory of G. Charpak played a role in the anomalies. He also suspected possible interferences during the transport of the tubes between Street Vauquelin and Clamart.

This hypothesis of a "jamming" related to the ambient electromagnetic waves led J. Benveniste to get muffs of mild steel, copper and mumetal. He hoped that these screens would protect the tubes containing "informed water" from disturbing electromagnetic influences. Mumetal is indeed an alloy which possesses excellent performances when one wants to isolate a device from electromagnetic environment. At first, the team of J. Benveniste studied the effect of a muff of mumetal on "electromagnetic transmission". In principle, if the "impregnation" of water actually works via emission of electromagnetic waves, this muff should block or at least strongly decrease the effect of the "electromagnetic transmission". The experiments were blinded by people outside the laboratory of Clamart. In a half-dozen of experiments, an effect was recorded, but "wild transfers" did not allow a clear conclusion on the efficacy of the metal screen. Indeed, in some experiments, the content of the "protected" tube had an effect on the heart… However, rather than to question the underlying concepts of the experiment, namely the transmission of a "biological activity" via an electromagnetic wave, J. Benveniste suggested technical reasons to explain these unexpected results.

"Around ten successful experiments"

Nevertheless, still resolute to show that electromagnetic transmission was possible, the team of J. Benveniste performed from February to July 1995 numerous blind experiments according to a protocol similar to that followed in the laboratory of G. Charpak. These experiments are presented in a synthetic way Table 11.1 and Figure 11.1. They were blinded by about twenty people who did not belong to the laboratory.[1] On May 21st, 1995, J. Benveniste could announce to the "participants in the experiments of transmission" that 10 experiments just succeeded:

> "The blind experiments are working normally: about ten successful experiments. Here is one experiment (18/5) with remarkable vascular and mechanical effects […]. After two years of efforts, we are back in the same experimental conditions as during the famous experiment, with Georges Charpak and the CSS5 [*Specialized commission*] of INSERM of April 21st, 1993." [2]

The "10 experiments" are the experiments of April 26th and from May 3rd to 19th, 1995 in bold characters in Table 11.1 (more exactly, there were 5 experiments made on 10 hearts of guinea pig).

In the same letter, J. Benveniste then evoked the question of the "wild transfer":

> "During the previous months, we looked for many explanations for the troubles which we know for a long time as soon as tubes are walked after the transfer. We remember the large experiment two years ago at Cochin, with 4 groups of 10 tubes among which one received the transfer. We succeeded for 2 groups and for the 2 others one tube induced cardiac effects, but it was not the right one. According to null hypothesis, no tube should move significantly. If the method is poor and the results are "random", all tubes or numerous tubes move at random, but we cannot explain that one tube out of 10, always the same during repeated checks, becomes active after transfer. At this time, we had suggested errors of coding or even, in the sometimes hysteric atmosphere during the experiments, malevolence. The same *jumps of activity* or *wild transfers* occurred on numerous occasions. The most spectacular was the first (*sic*) experiment) ([…] 10/5/94) in the laboratory of G. Charpak […]. Dozens of previous experiments, open-label or blind, had always given the same result: 1 or 2 tubes giving a "flat" effect around 5% and 1 tube an effect with a characteristic bell effect. This experiment gave the same result except that tube "A" associated with a typical effect was water. Yet the same water as the one that infuses the heart, diluted 1000 times and then approximately 10 times, cannot have any effect, unless it underwent a transmission."

The experiment about which J. Benveniste spoke is described in Figure 11.3.

Date	Active:inactive samples	"Transmitted" active compound	Number of hearts	Unblinding	N° on figure
February 10, 1995	1 : 2	ACh	2	Correct	1
February 21	1 : 3	ACh	1	Correct	2
February 22	1 : 4	ACh	1	Correct	3
March 23	1 : 4	ACh	2	Correct	4
April 19	1 : 4	ACh	2	False	5
April 20	1 : 4	ACh	2	False	6
April 26	**1 : 9**	**Ova**	**2**	**Correct**	**7**
April 28	1 : 7	Ova	2	False	8
May 3	**1 : 4**	**Ova**	**2**	**Correct**	**9**
May 17	**1 : 4**	**Ova**	**2**	**Correct**	**10**
May 18	**1 : 4**	**Ova**	**2**	**Correct**	**11**
May 19	**1 : 4**	**Ova**	**1**	**Correct**	**12**
May 24	1 : 4	Ova	1	False	13
June 2	1 : 4	Ova	2	False	14
June 6	1 : 4	Ova	2	Correct	15
June 8	1 : 4	Ova	2	False	16
June 14	1 : 4	Ova	2	Correct	17
June 15	1 : 4	Ova	2	False	18
June 16	1 : 4	Ova	2	False	19
June 19	1 : 4	Ova	2	False	20
June 21	2 : 3	Ova/ACh	2	Correct	21
June 27	1 : 3	Ova	1	False	22
June 29	1 : 4	ACh	2	False	23
June 30	1 : 5	Ova	2	False	24
July 4	1 : 3	Ova	2	False	25
July 5	1 : 3	Ova	2	False	26
July 11	1 : 4	Ova	1	Correct	27
July 12	1 : 4	Ova	1	False	28

Table 11.1. Experiments of February-July 1995. Out of 28 blind experiments, 13 were positive (one should expect only 6 on average if only chance was a work; $p < 0.05$). The first 4 experiments took place with rats and the following ones with guinea pigs; there were no open-label active controls. The "10 successful experiments" mentioned by J. Benveniste in his letter of May 21st, 1995 are indicated in bold characters. .

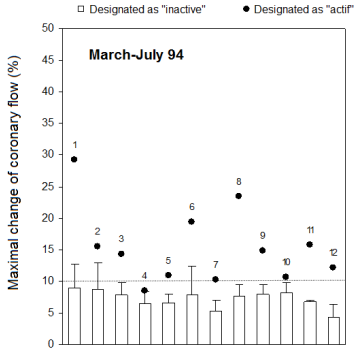


Figure 11.1. These two graphs are intended to summarize and to compare the experiments performed in the laboratory of G. Charpak from March to July 1994 and the experiments performed at Clamart according to the same protocol from February to July 1995. We notice in particular that in the experiments of March-July 1994, the means of the controls were relatively high, close to 10%, making it more difficult the evidence of an effect different from the background noise.
In the experiment 21 of the second graph, two "active" samples were expected.

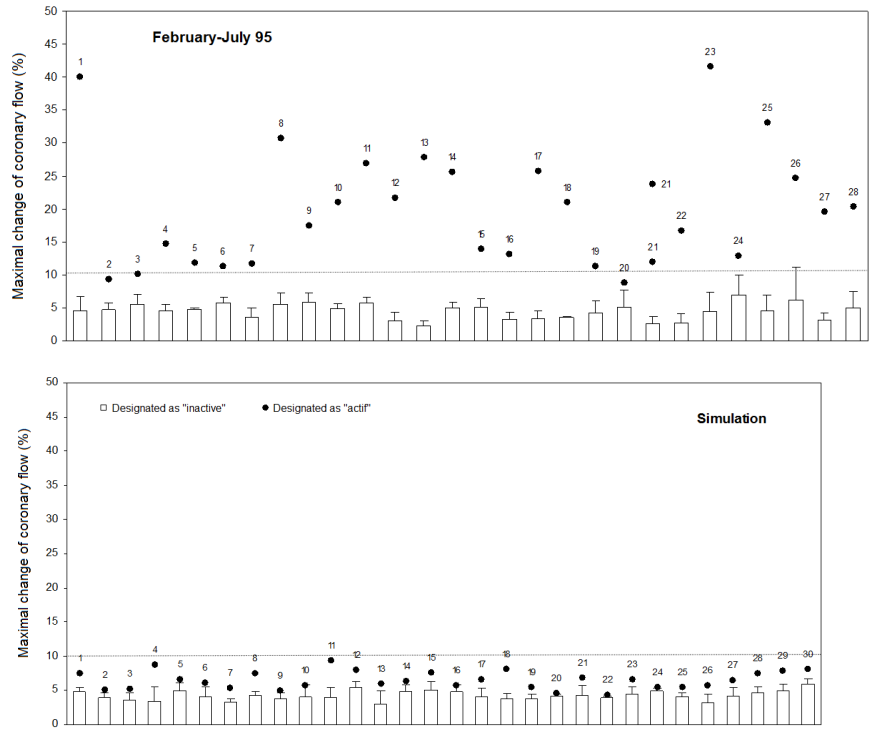


Figure 11.2. In order to explain why the experiments of February-July 1995 are amazing even though the "good tube" was not always correctly designated, a random simulation of this type of experiment has been performed. One could think indeed that, whatever are the results, among the various values obtained in an experiment for the series of tested samples, one of these values is always higher than the others and consequently that the "transmission" results have nothing unexpected and that are simply the consequence of chance.

(To be continued next page.)

(continued from previous page)

For each of the "experiments" numbered from 1 to 30, 5 random values with a mean equal to 4.6, standard deviation at 1.6 (similar parameters than controls of Figure 11.1 from the results of February-July 1995) and Gaussian distribution were generated. The highest value is named "active" and one calculates the mean of the 4 other values which are then named "inactive". One notices that these points move away of the inactive tubes not so much in comparison with the above figure. One can calculate that they are above 10% only in approximately 0.1% of the cases ($z = (10 - 4.6) / 1.6 = 3.37$). Consequently, the fact that some points "emerged" as they did during the "real" experiments is thus an effect that *must be explained* even if the effect is not where it was expected.

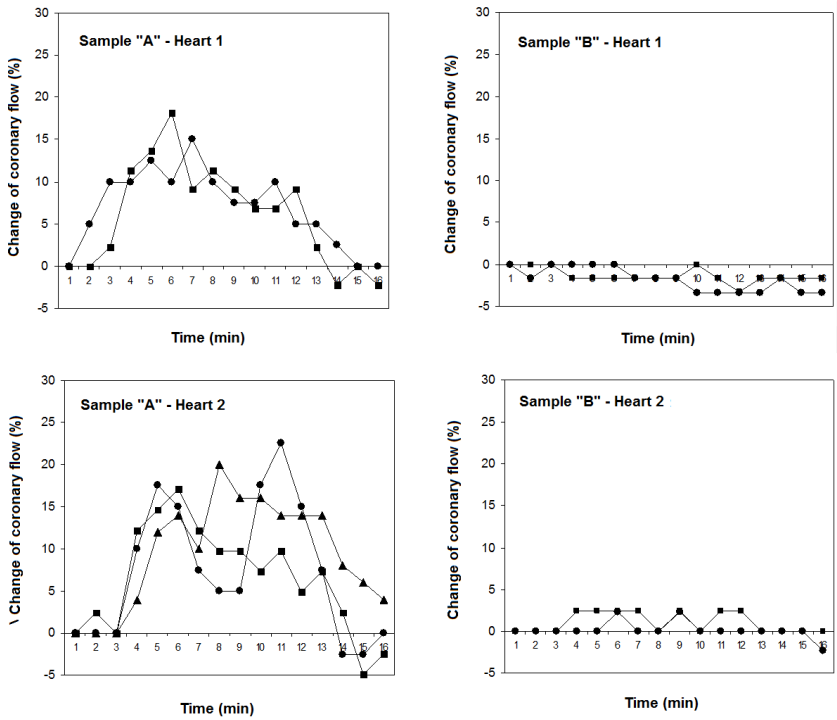


Figure 11.3. Experiment of May 10th, 1994. The transmission of acetylcholine activity was performed in the laboratory of G. Charpak. Samples were tested on two occasions on the device of Langendorff n°1 (Heart 1) and on three occasions on the device of Langendorff n°2 (Heart 2) which worked in parallel. Coherent results were obtained: the sample *A* was "active" whereas the sample *B* was "inactive". Indeed, on both Langendorff devices (heart 1 and heart 2), the sample *A* induced a change of coronary flow during a dozen minutes. Nevertheless, after unblinding, incomprehensibly, *A* was "transmitted" water and *B* was "transmitted" acetylcholine. According to J. Benveniste, it was a typical example of "wild transfer".

This experiment was indeed very demonstrative. It was a typical example of "inversion". The sample *A* supposed to be inactive ("transmitted water") induced large variations of the coronary flow, furthermore on two different hearts. The sample *B*, on the other hand, which should be active ("transmitted acetylcholine") did not induce significant variations. J. Benveniste then gave an example illustrating a possible effect of the environment on the phenomenon of "wild transfer":

> "More recently, after a series of successful transmission experiments performed in the office, relatively dark, of Jacques Testart, the following week we made another series in full light and then transported the tubes in our floor; the tubes had been shaken very close from each other. The result was a magnificent anaphylactic reaction even reproducing the shape of the typical curve obtained with ovalbumin at classical concentration […]. Yet, this active tube was water. It is a typical example of wild transfer. We do not have time to explore all parameters to understand what explains these jumps of information from one tube to another one. The fact remains that this phenomenon, which is perfectly incomprehensible at the moment, is fascinating."

But, he explained, that with the new experimental conditions (the letter was dated May 21st), these "oddities" were not observed anymore. These new experimental conditions consisted in using black cases to protect the tubes from light and to avoid moving tubes too close to one another:

> "Two coders randomly draw 5 tubes of water among 20 tubes (or more) which were previously numbered and then 2 among 5. The 3 tubes that will not undergo transfer (*naive water*) are immediately placed, each in a black case, at distance from each other on a rack in the same room. A tube undergoes *water* transfer, the other one *ovalbumin* transfer and the 2 tubes are placed on the rack, each in a black case. The coders keep the code. The heart operator comes to get, one by one or two by two, the tubes which are never mobilized or shaken together."

He also insisted on the specificity of the transferred biological activity because atropine, an antagonist of acetylcholine blocked the effect of "transmitted" acetylcholine:

> "However, since we did the experiments in the conditions described above, we did not observe such oddities anymore. On May 17th, Jacques Testart being the coder, the blind tube Ova TR

> gave after 4 measurements, 21% of change on average (1 ml on 5 ml) versus 4.9% for water after 16 measurements (0.1 ml on 5 ml). Moreover, on the same day, in an open-label experiment, atropine at classical concentration totally inhibited acetylcholine (ACh) - 7 M, as expected, *but also ACh TR* (ACh TR without atropine: 56.4%; with: 7%). We have approximately ten experiments of inhibition of ACh TR by atropine, which sign the specificity of the transmitted signal."

The experiments of May 17th described by J. Benveniste thus suggested that the new precautions allowed the realization of blind experiments. At the same time, this experiment illustrated the specificity of the transmitted signal because atropine – a "poison" of acetylcholine – inhibited not only the effect of "classic" acetylcholine but also "transmitted" acetylcholine. Here again, these spectacular results appear to confirm that "acetylcholine information" which was "imprinted" into water had the same pharmacological characteristics as "molecular" acetylcholine. Finally, J. Benveniste explained where, according to him, the experimental problems originated:

> "In fact the necessity to transport the tubes introduced, we now know, an experimental bias which explains the irregularity of the results obtained outside. Georges Charpak concludes that our results outside are unpredictable *and* that we cheat at home, what, respectively, does not stand up to an examination of the facts and is a slander. It is simply unusual experimental conditions that have been met with a still embryonic system and all physical bases of which we do not understand."

To avoid any transport of tubes, he logically suggests performing the entire experiment in G. Charpak's laboratory!:

> " […] we have three operational devices and we are ready, if it is absolutely necessary to do the experiments elsewhere, to place an isolated heart device in another laboratory, for example by Georges Charpak. We will install the heart and will let the local staff operates for the transfer and for the injection of the solutions to the heart."

And, being perked up by the last "ten experiments" which correctly identified the active sample, he lyrically ended and not without bombast:

> "[*Your help*] will be furthermore, I believe it, recognized by History because, without any false or true modesty, what we do together at this moment could indeed be History."

If this explanation of "wild transfer" from tube to tube which would be facilitated by light waves could be possibly retained for some experiments, it did not take into account other observations. More particularly, this hypothesis does not explain why "wild transfers" are exceptionally observed with open-label samples.

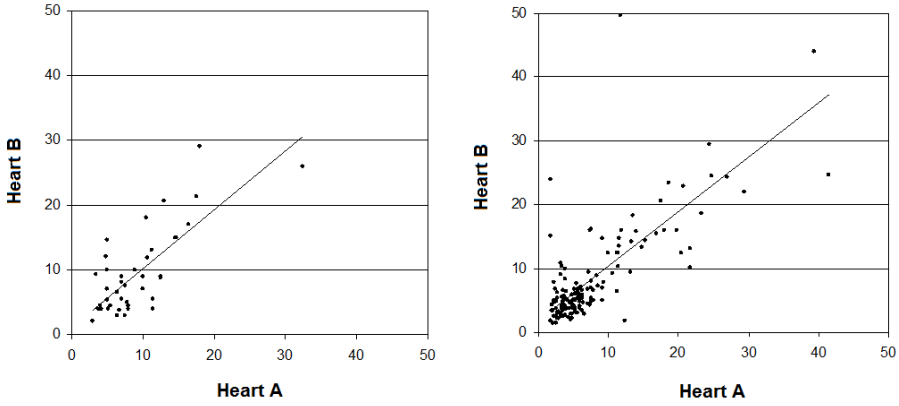


Figure 11.4. Correlations between both devices of Langendorff. These figures illustrate the internal coherence of the experiments performed during the collaboration with the laboratory of G. Charpak (left figure) and the blind experiments of February-July 1995 (right figure). Without taking into account the "success" or not of the experience according to the fitting with the blind code, one notices that the results obtained for the same sample on a device of Langendorff (heart *A*) are correlated with those obtained on the other device of Langendorff (heart *B*) which worked in parallel. This correlation indicates that "something" occurred that could not be reduced to random only.
NB. All the experiments done with Charpak laboratory or those of February-July 1995 were not systematically measured on both devices of Langendorff.

The series of "10 successful experiments" was however only an island of success within the usual "failures". Nevertheless, the background noise which was high during the experiments with G. Charpak decreased. This background noise was indeed closer to 5% than to 10% for "inactive" samples. But in spite of these better experimental conditions, the experiments that followed the "10 successful experiments" contained numerous "wild transfers" once again. Nevertheless, and it is a important point on which it is necessary to insist once again, when samples were assessed on the two Langendorff devices working in parallel, the results were correlated (Figure 11.4). We are thus always in a configuration of "coherent discordance".

"*A craziness without limit*"

With a slight delay, the letter with the "10 positive experiments" triggered a reaction from G. Charpak and C. Hennion. These latter, summarizing the arguments of their last letter of December, wrote to J. Benveniste:

> "We have your letter in our hands dated May 21st, 1995, in which you announce us the success of about ten blind experiments similar to those that one of us – Georges Charpak – could see in your laboratory in 1993.
>
> It seemed very likely to us that the operation of transport of the properties of an encapsulated chemical towards pure water by virtue of an amplifier which oscillates permanently was either an artefact, or trickery. Because of your titles, of your position in an important scientific community, and in front of your enthusiasm and your good faith, we thought of doing it as a service to you by suggesting that you do the operations of transfer at the *Ecole de Physique et de Chimie* under the supervision of one of us, Claude Hennion.
>
> All in all, 20 experiments[3] clearly showed a totally random effect. The table below summarizes the observations made with you." [4]

The authors of the letter presented a table of synthesis (similar to Table 10.1 of Chapter 10) and then they came back one the question of the fraud which obviously concerned them:

> "During a control made by you, where you knew the result beforehand, you had observed that when the result was known, you or your co-workers found the right answer. You then wondered if you were not betrayed in your laboratory.
>
> You rejected this hypothesis, but you invented reasons that explained why the experiment did not work at the *Ecole de Physique et de Chimie* in an obvious headlong rush, where you took into account only the experiments confirming your hypothesis.
>
> It is interesting to also note that you gave credence to publications which are in your favor and that you use the most outlandish reasons to explain the failures. […]
>
> You also gave us the texts of an Italian theorist, a professor of university. We gave his text to be analyzed to the best French theorists. They said that it was stuffed with clumsy false hypotheses. But as it is written in an opaque language for 99% of the physicists, we understand that he can deceive you by his friendly encouragements."

And, on the same day, G. Charpak wrote to P. Lazar that J. Benveniste was affected by "a craziness without limit". [5] The wish of J. Benveniste of wanting to repeat the entire experiments (transmission, blinding, test of samples, unblinding) in the laboratory of G. Charpak did not thus find an echo in Street Vauquelin:

> "I no longer believe it, explains Claude Hennion. He did the trick fifteen times, I did not want to try a sixteenth. I had invested a lot of time, including at home. As long as he was not controlled, it worked (...). Georges Charpak never believed it possible. He was curious. But one does not have the right to let oneself be fooled." [6]

The collaboration between the two laboratories stops right then. In front of the refusal to collaborate in new experiments, J. Benveniste confirmed the break by answering to G. Charpak:

> "My feelings towards you are in fact rather close to pity. I have on my desk a floppy disk of a computer containing, for the first time in the history of mankind, a biological activity. It is indeed pity to see you unable to appreciate the importance of the stake." [7]

In the next chapter we will see to what J. Benveniste alluded about this floppy disk, supposedly nothing but an important milestone in "the history of mankind". Before that, let us examine what makes the protagonists' viewpoints irreconcilable.

The two faces of Janus

In terms of formal logic, we must admit that G. Charpak was right: a hypothesis was formulated and was apparently refuted by the experiment. One thus had to reject it. Yes, but what was the hypothesis? Although it remained implicit, we could formulate it in the following terms: some device allowed transmitting a "biological activity" to water which was then capable of making a biological system react.

The hypothesis having been "falsified" with this logic, was it indispensable to reject it as a whole and move on to other activities? It is indeed necessary to recognize that one was a little reductive when one designed the protocol of the experiment intended to test this hypothesis. One went from the proposal "transmission of a biological activity" to the proposal "if it is true, then one must be able to discriminate more often than chance the supposed active samples among other supposed inactive samples". In the conditions of the experiments done with G. Charpak, the "divination" was not better than

chance. Nevertheless, if one had knowledge of the experiment in general, one could not be satisfied by this conclusion. Indeed, the biological system reacted differently and in a coherent way – it was particularly striking for the measurements with the two parallel Langendorff devices – while it should not have reacted! (See Figure 11.5). One must also admit that the experimental conditions were not very satisfactory. The reactivity of hearts – whatever the reason might be – remained low and the biological effect emerged with difficulties due to the background noise. Nevertheless, even in the experiments with acceptable quality, "wild transfer" was present.

However the observers of these experiments were as the god Janus who has two faces: one of the faces had eyes fixed on the blinding whereas the other face observed the experimental system. The absence of communication between both faces was a source of mutual incomprehension. Indeed G. Charpak tested the hypothesis without worrying about what the other face saw. He considered the experiments of J. Benveniste as a black box under the responsibility of the latter. And if for one of the faces chance indeed seemed to prevail in these experiments, the other face could notice that a modification of the coronary flow had occurred. This change of a parameter of the biological system was not trivial and was not a simple artifact of handling. In fact – and J. Benveniste had the greatest difficulties to get this point understood – what was surprising was not to guess correctly which ones were the active samples. The surprising fact was that "something had moved" and had moved in a coherent way, in particular when two hearts worked in parallel and gave correlated results.

One could nevertheless suggest reformulating the hypothesis but it would be probably expensive in supplementary hypotheses, probably more than the "simple" hypothesis about a structuring of water. For diverse reasons, J. Benveniste preferred to try "to improve" the experimental conditions and the "reproducibility".

Making science takes time

Even though G. Charpak was right to assert that "the experiments clearly showed a totally random effect", he did not try however to be "in sympathy" – it is a euphemism – with J. Benveniste and his experiments. Consequently, he did not try to know what noticed the other "face" or to listen it. Yet every researcher knows that a minimum of benevolence and empathy is needed towards the object under scrutiny. This is all the more true as the discoveries – it is almost a definition – are usually done on the edge of the performances of the technical means of the moment. And J. Benveniste was not wrong when he

asserted that G. Charpak would not have bet on the future of aviation if he had attended the debut of the *Antoinette* of the French aviator Blériot.

If G. Charpak (or one of his collaborators) participated in the life of the laboratory, from the sacrifice of the animal and the removal of its heart, if it attended the injection of the various samples in the system of Langendorff, noticing with excitement that actually some samples gave an answer, then probably his attitude would be different. He would then wonder why some samples had an effect. And his perplexity would be great when he would experience the discordances after unblinding while everything seemed coherent just a moment before. All those who had this approach, even though they were skeptical at first, "got into" (as M. Schiff, for example) or have – at least – suspended their judgment. But making science takes time.

The will to do all experiments Street Vauquelin as proposed then by J. Benveniste was coherent with this approach. The purpose was to take into account the entire experiment and not to focus only on the bet: "If it is true then…" Indeed – and it is the idea which is supported here – what J. Benveniste asserted is "true", but only up to a certain limit. All the difficulty is to highlight the crossing point between "it works" and "it is no longer working". But for that, it is necessary to take the experiment in its entirety (with the eyes of both faces) and not to be satisfied to play the role of a bailiff. Moving forward in the understanding of the experiment requires to realize what is the amazing fact, namely a biological system that reacts differently – repetitively and consistently – to a sample n°1 and to a sample n°2 although these samples are, in the current state of the knowledge, identical because they come from the same bottle.

The working hypothesis of J. Benveniste was thus maybe erroneous or badly formulated. It did not explain however what was daily observed in the laboratory of Clamart. But how to explain these rather subtle arguments when at the same time some people asserted that: "as long as he was not controlled, it worked", as did C. Hennion to the journalist E. Fottorino.[8] This sentence obviously suggested either fraud or incompetence. Since all those who were supposed to control these experiments did it at a distance (without trying to merge the observations of both faces), J. Benveniste could not make them put the finger on the problem that literally undermined him. It was this blind spot in the eyes of those who were supposed to oversee his experiments that logically led G. Charpak to conclude on the "craziness without limit" of J. Benveniste.

Notes of end of chapter

[1] The most important help came from J.C. Salomon, F. Russo-Marie and J. Testart.

[2] Letter of J. Benveniste "to the participants in the transmission experiments of May 21st, 1995".

[3] Overall, there were in fact only 18 experiments; moreover, this is this number that is reported in the summary table included in the letter of G. Charpak and C. Hennion.

[4] Letter of G. Charpak and G. Hennion to J. Benveniste of July 18th, 1995.

[5] E. Fottorino. La mémoire de l'eau. Le temps des passions. *Le Monde*, January 22nd, 1997.

[6] Ibid.

[7] Ibid.

[8] Ibid.

Chapter 12. A "computer for molecules"

The "wild transfer" finally unmasked and defeated?

Early July 1995, J. Benveniste thought that he had understood the reasons of the troublesome inversions of results. In a letter to the "participants in the experiments of transmission", he explained what he thought to be the cause of the "wild transfer":

> "Here is the end of three years of hell and in addition an important advance in the field of electromagnetic transmission and the certainty to succeed now to achieve our experiments within the next weeks.
>
> As you know, what has been stopping us for three years is that the effect, which we are able to detect after transmission, is often attributed, after opening of the codes, to naive water or Tr *[transmitted]* water (water having received information "water"). Yet, in several open-label experiments, water induced no effect to the isolated heart, what is normal because it is the same water which already infuses heart. Recently, by using an anticholinergic, atropine, we were able to show that these "wild transfers" were indeed acetylcholine-Tr. To explain this extraordinary phenomenon, we proposed many causes among which the transport in car, the effect of light, the non-specific magnetic fields, etc. We did not imagine that this "wild" transfer could appear *just at the moment of injection*. It occurs indeed between the two syringes placed side by side which are intended to be injected into an isolated heart and which stay on the electric injector sometimes more than half an hour when two successive injections are made. This "wild" transfer occurs when one of the syringes contains water and the other one water having received active information (ovalbumin, acetylcholine). From this point, everything gets clearer: these transfers rarely arise in open-label experiments or in internal blinding where we use either a single heart, or tubes in the same order on both hearts. It is during "extraordinary" precautions, in particular for the outside experiments that we cross the injections (1, 2, 3, 4, 5 for a heart and 5, 4, 3, 2, 1 for the other one)." [1]

He then explained which experiments allowed confirming this idea:

> "Two decisive experiments recently took place demonstrating this phenomenon: 1) When a syringe, for example n°9, gave a considerable effect on the heart after extended contact with another syringe (n°11) that contained the active transfer, then the corresponding tube n°9, left on the lab bench and injected directly, had no effect (experiment of 5/7). There is therefore a property that has been acquired at the time of contact with the other syringe. 2) We voluntarily placed naive water during 30 minutes in a syringe next to a syringe containing a transferred activity: naive water then demonstrated a very strong acetylcholine-type activity (experiment of 6/7). Naturally this phenomenon cannot arise in the "normal" experimental conditions where one immediately tests a transfer after having made it."

Then J. Benveniste explained that this activity "passively" transferred (by opposition to "active" transfer by the amplifier) is indeed an acetylcholine-type activity because atropine inhibited its effect on the heart. Then he added: "we ignore the origin of the passive transfer, the metallic mass or the electromagnetic fields of the machine".

Even if this explanation seemed to be confirmed by an experiment – like the previous ones – it nevertheless appeared to be *post hoc*. Furthermore, hardly expressed, the interpretation of the anomalies by "exchanges" between syringes risked to become rapidly obsolete because J. Benveniste had just made a new technological improvement by jumping from the "telephone for molecules" to the "computer for molecules".

The early days of "digital biology"

Indeed, because the current in the output coil reproduced after amplification the current of the input coil, moreover in a frequency range close to those of the human ear, it was logical in wanting to record the electromagnetic variations of the input coil as one would make for a conversation or a song. This recording could be then returned to the output coil which would "imprint" water in a tube (Figure 12.1). The interest would be to store diverse recordings that could be "played" as needed.

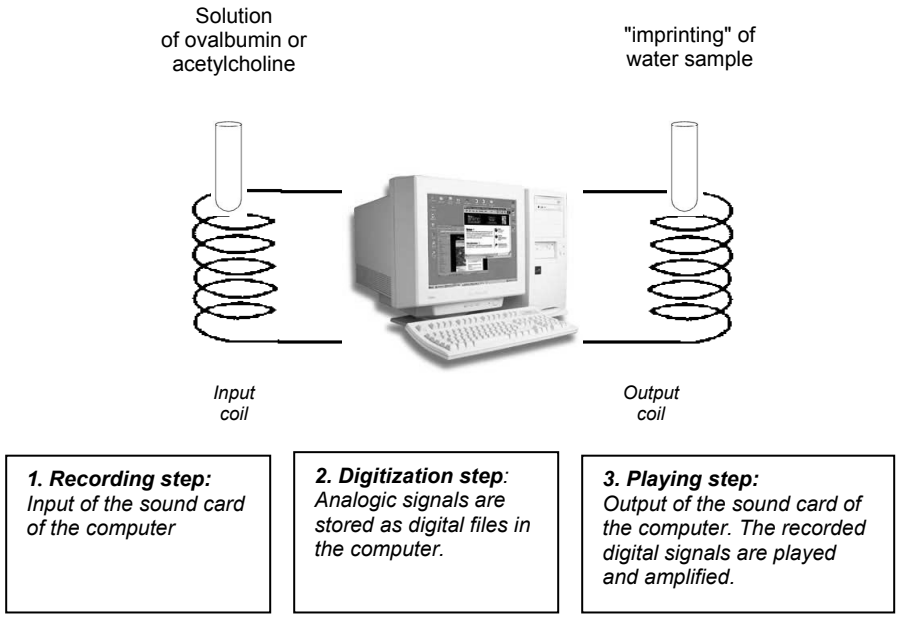


Figure 12.1. Compare this new version of the transmission device with the first version (Figure 1.1 of Chapter 1 of second part). In this new "digital" version, the input coil was wired to the sound card of a computer and the "signals" were recorded as digital files. These recordings were then "played" after amplification and "imprinted" to naive water placed near the output coil thanks to the electromagnetic field generated by the coil. The essential contribution of this new prototype was the possibility of "storing" information in a magnetic device.

J. Benveniste told how he succeeded in developing this device:

> "[…] I found out that Austrian researchers working in the field of homeopathy managed, in association with a firm of electronics, to record the electromagnetic properties of thyroxine (an hormone secreted by the thyroid gland which has an essential role in growth) on a CD. Afterward, by "playing" this recording on tadpoles, these researchers managed to modify the course of their metamorphosis. Their system had the merit to demonstrate the possible digitization of the electromagnetic signals emitted by molecules in the range of radio frequencies. Moreover, there is nothing inconceivable for someone with an open mind: the sound waves perceived by human ear, which are situated in the same

> frequency ranges, are usually digitized and recorded on commercial CD." [2]

I. Béhar spoke about the reaction of J. Benveniste when he learnt that he had been outstripped by the Austrian team:

> "Benveniste was not the first one in "to record" an "activity" on hard disk; I was in his laboratory when he received by fax the summary of the communication that Austrian researchers planned to present to Faseb 95 entitled: "Hormone effects by CD record/replay" [3]. Benveniste was furious of having thus been "overtaken", regretting not having had the means to successfully complete this research." [4]

The interest of this method compared with the former one is obvious. One could hope in particular that the problems of "inversion of activities" which were supposed to occur during the transport of the "imprinted" tubes would not take place any more. Indeed, when the biological activity is "recorded" on a floppy disk or hard disk, it cannot be modified. One can at will "transmit" to naive water an activity which was "canned". J. Benveniste already imagined the possible developments: recording biological activities of molecules and medicines on a magnetic memory and broadcasting them easily across the world. Moreover Internet was available to the general public for hardly one year and the possibilities offered by the "network of networks" began to appear. As soon as information was digitized, its almost immediate routing was child's play and the immense possibilities offered by the combination of the "digitization of the biological signal" and this new means of communication made him dream.

"For the first time in History"

During the summer of 1995, J. Benveniste bought a computer with a sound card and he could then consider making the first experiment of "digitization-transmission". This experiment was performed on July 10th and a significant biological effect was observed on the coronary flow (Figure 12.2). This effect was inhibited by atropine, thus showing the specificity of the biological activity which was "recorded" and then "reproduced" to water.

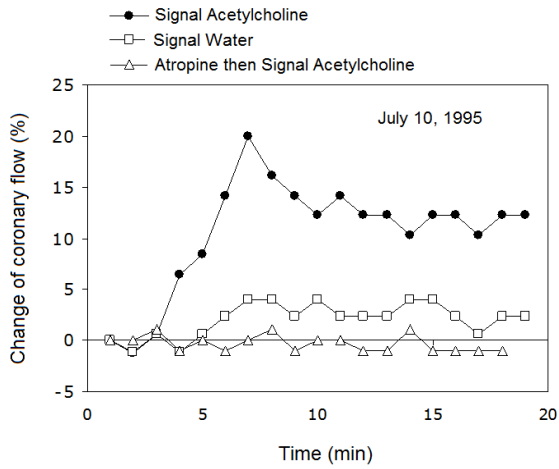


Figure 12.2. This figure shows the first attempt of "digitization-transmission" of a biological activity by J. Benveniste, an "historical" first according to him. The device described in the previous figure allowed to record two computer files which respectively corresponded to acetylcholine and to water (inactive control). We notice that the "signal acetylcholine" had actually an effect on the coronary flow but that the control "signal water" remained without effect. The specificity of the "signal acetylcholine" was highlighted by atropine (at "classic" concentration), an antagonist of acetylcholine that inhibited the effect of the signal. It is important to understand that the only difference between the curves corresponding to "signal acetylcholine" and "signal water" rested *a priori* on the "noise" recorded with an electric coil near a solution of acetylcholine or water only.

Similar experiments were performed during the next days with comparable results. No without some bombast, once again evoking History with a big H, J. Benveniste announced in this terms this new technological breakthrough (forgetting incidentally the contribution of the Austrian researchers) in the bulletin of the association *Science Innovante* that supported his researches:

> "For the first time in History, on July 10th, 1995, we recorded a biological activity on a computer. […] When one transmits this recording to water and when this water is applied to a sensitive organ, the latter reacts as if it had received the molecule itself. This will not surprise our readers who know that molecules communicate by electromagnetic frequencies. The new element is that we know now that these frequencies are between 0 and 22 kHz. On the other hand, the fact that they are digitized opens immense scientific and industrial perspectives in chemistry, biology and medicine." [5]

From this moment, J. Benveniste gave up the devices of transmission from tube to tube by means of an electronic amplifier. He wholeheartedly launched into what he named then "digital biology". Thanks to this device, a new energy was given to his researches and public demonstrations were again possible. The hope was naturally that the "inversions of codes" and other "wild transfers" would be forgotten and considered as trials and errors inherent to any development. The "biological activity" being now frozen in the bits of a computer memory, one could only hope that this "memory" would be much more reliable than an "imprint" in water samples.

Notes of end of chapter

[1] Letter of J. Benveniste "to the participants in transmission experiments of July 10th, 1995".

[2] J. Benveniste. Ma vérité sur la mémoire de l'eau, p. 173.

[3] The reference of this scientific communication was: "F. Senekowitsch, P.C. Endler, W. Pongratz, C.W. Smith. Hormone effects by CD record/replay. *FASEB J* 1995 ; 9 : A392."

[4] I. Béhar. Distinguer l'homme du résultat scientifique. *Le Monde*, February 8th, 1997.

[5] La lettre de Science Innovante. N°6, April 1996.

Chapter 13. Remarkable… but disappointing results

Back to the Cochin institute

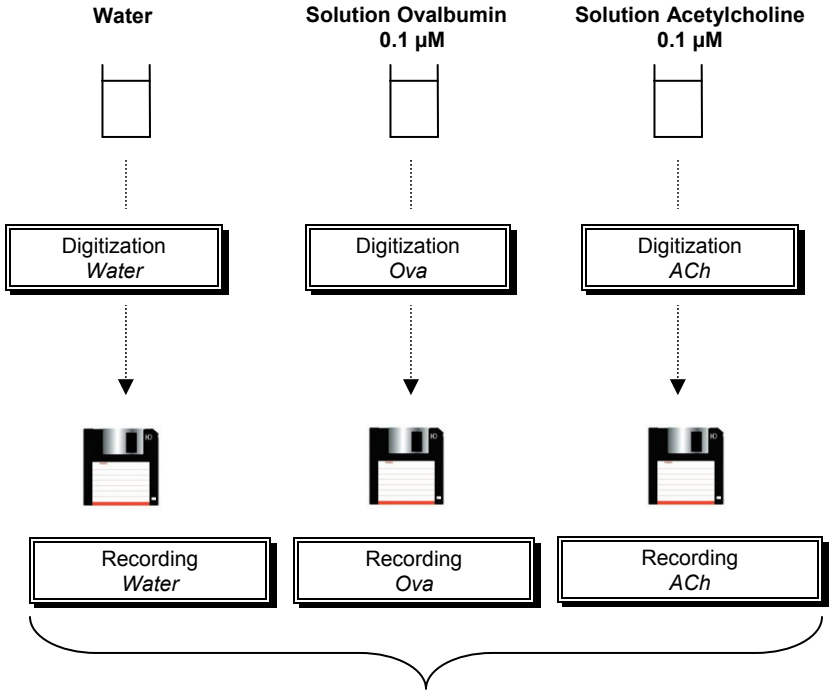
After this "progress" obtained with digitization, the year 1996 was very rich in experiments and public demonstrations. On this occasion, J. Benveniste, in his quest of the "crucial experiment", renewed the "Cochin experiments". He indeed considered that these experiments were of great strategic importance because they were made outside the laboratory of Clamart. According to him, it was necessary to design a device that could be performed in any laboratory, at least for the first part of the experiment, which is the step of recording. With digitization, the problem of the "imprinted" samples, which sometimes mysteriously "exchange" their respective biological activities, should not *a priori* arise any more because the biological activity was recorded at the Cochin institute on a computer's hard disk. At Clamart the recordings were "played" to naive water. The question concerning the transport of the samples of water between the two places that appeared to be a source of trouble was thus resolved.

The public demonstration performed at the Cochin institute on February 27th, 1996 needs to be described in detail. Indeed, probably thinking that he finally had the solution to his problems thanks to the new method involving computer files, J. Benveniste did not hesitate to launch a complex and ambitious experiment.

During this experiment, the experimenters had to determine the activities corresponding to 18 recordings: 6 acetylcholine, 6 ovalbumin and 6 water (inactive controls). For the first step, the 12 active recordings and the 6 inactive recordings were identified. For the second step, the samples with ovalbumin-type activity or acetylcholine-type activity were identified among the 12 active recordings. Indeed, ovalbumin-type activity could be evidenced only on the heart of ovalbumin-sensitized animals; acetylcholine-activity could be evidenced regardless the immunological status of the animal. This second stage was intended to show that the specificity of the original molecule was preserved through transfer and digitization.

Technical sheet of the experiment of February 27th, 1996

Type of experiment: transmission-digitization
Place of experiment: Cochin institute for digitization on May 12th and at Clamart for transmission and assessment of samples from July 4th to May 23rd
Place of experiment: Cochin institute for digitization on February 27th and at Clamart for transmission and test of samples from February 28th to March 8th
Blinding: On February 27th by participants not belonging to Benveniste's laboratory
Number of recordings to be tested: 18 (6 ovalbumin, 6 acetylcholine and 6 water)
Additional in-house blinding: yes



Blinding of 18 recordings numbered from 1 à 18 :
6 recordings "**Water**"; 6 enregistrements "**Ova**";
6 recordings "**ACh**"

(*tested after **transmission** to water sample)*

First step: identification of the active samples

At first, the recordings were "played" to naive water which was administered to hearts (from guinea pigs immunized with ovalbumin) reacting both to ovalbumin and acetylcholine. Twelve recordings which were active on the coronary flow could be identified (they were expected to correspond to ovalbumin or to acetylcholine).

Tested recordings	Number of measurements	Maximal changes of coronary flow (%)	Biological activities in increasing order
n°6	3	3.1 ± 0.6	1
n°9	4	4.7 ± 2.8	2
n°15	4	5.1 ± 2.4	3
n°2	6	5.8 ± 3.6	4
n°18	8	5.8 ± 3.9	5
n°12	4	6.1 ± 2.9	6
n°4	3	16.7 ± 4.6	7
n°5	3	18.7 ± 5.4	8
n°13	4	19.3 ± 3.7	9
n°8	4	21.0 ± 8.3	10
n°10	6	24.8 ± 15.0	11
n°14	4	25.6 ± 10.8	12
n°1	4	26.9 ± 12.2	13
n°17	4	28.0 ± 11.4	14
n°16	4	28.4 ± 13.7	15
n°11	4	29.1 ± 9.1	16
n°7	3	29.4 ± 18.8	17
n°3	4	31.6 ± 16.6	18

6 inactive (< 10%)

12 active samples (> 10%)

Means ± standard deviation

Table 13.1. The experiment of February 27th, 1996 contained 18 recordings: 6 for ovalbumin, 6 for acetylcholine and 6 for water (control). If the experiment confirmed the hypothesis of a transmission of the biologic activity, one should observe changes of coronary flow for 12 recordings. Hearts were obtained from guinea pigs immunized with ovalbumin. The modifications of the coronary flow measured with two devices of Langendorff gave coherent results. Finally an in-house blinding was performed for 8 recordings to confirm the first measurements; for this purpose, the "imprinted" samples were given to the experimenter under a different name to verify the first measurements.

A change of the biological parameter (change of coronary flow) was indeed observed for 12 out of 18 recordings: n°1, 3, 4, 5, 7, 8, 10, 11, 13, 14, 16 and 17. The following stage would allow discriminating among the ovalbumin recordings and the acetylcholine recordings.

Second step: identification of the specific activities of the active samples

The distinction of the recordings of ovalbumin and acetylcholine was made during the second step by taking advantage of the characteristics of the initial molecules. Indeed, on one hand, the effect of acetylcholine is inhibited by atropine and on the other hand ovalbumin has an effect only on hearts coming from animals that had been previously sensitized to ovalbumin.

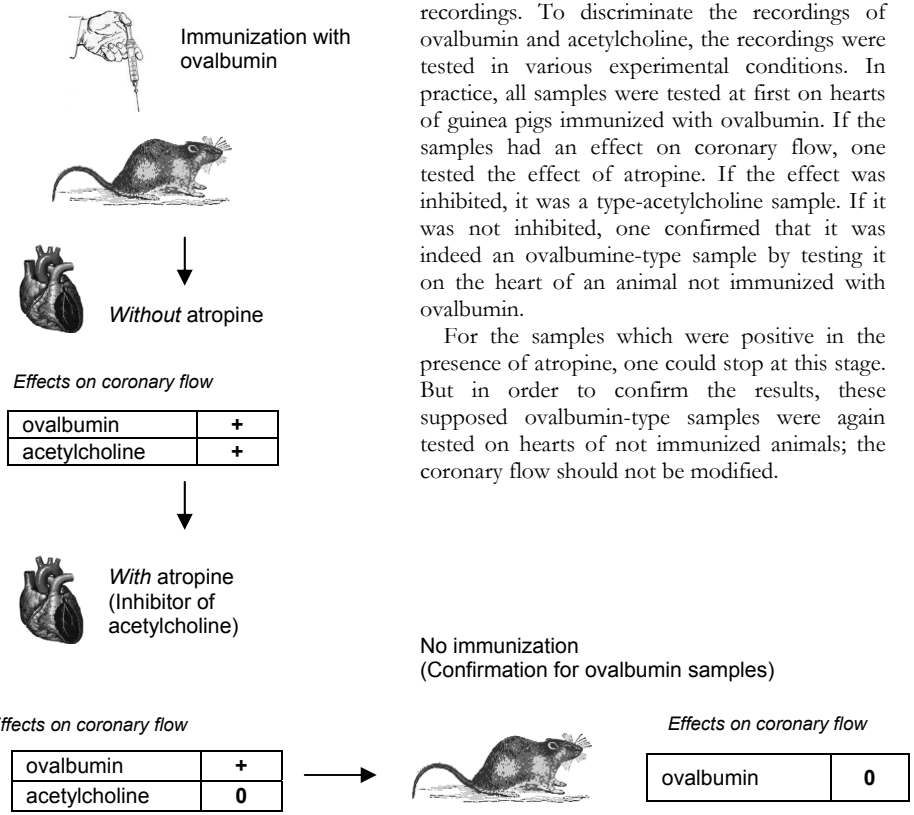


Figure 13.1. Demonstrating the specificity of the recordings. To discriminate the recordings of ovalbumin and acetylcholine, the recordings were tested in various experimental conditions. In practice, all samples were tested at first on hearts of guinea pigs immunized with ovalbumin. If the samples had an effect on coronary flow, one tested the effect of atropine. If the effect was inhibited, it was a type-acetylcholine sample. If it was not inhibited, one confirmed that it was indeed an ovalbumine-type sample by testing it on the heart of an animal not immunized with ovalbumin.

For the samples which were positive in the presence of atropine, one could stop at this stage. But in order to confirm the results, these supposed ovalbumin-type samples were again tested on hearts of not immunized animals; the coronary flow should not be modified.

The biological activities of 6 recordings appeared to correspond with acetylcholine because they were inhibited by atropine and 6 appeared to correspond to ovalbumin because they were not inhibited by atropine and were active only on hearts from immunized animals.

	Type-acetylcholine activity (Maximal % of coronary flow change)			***Type-ovalbumine activity*** (Maximal %. of coronary flow change)		
	Animals immunized with ovalbumin			Animals immunized with ovalbumin		Animals not immunized with ovalbumin
Rec. n°	Without atropine	With atropine	**Rec. n°**	Without atropine	With atropine	
1	25.6	5.7	**4**	17.7	20.3	8.3
3	28.9	4.5	**5**	29.1	45.8	6.2
7	34.5	8.0	**8**	19.6	21.9	3.7
10	27.2	6.7	**13**	18.4	19.6	6.9
14	24.8	6.8	**16**	28.8	26.8	Non fait
11	27.5	19.4*	**17**	37.0	26.9	7.6

* For the sample n°11, the inhibition was only partial; since this sample was active with not immunized animals (42%), this suggested that it was indeed an acetylcholine-type activity. Furthermore, acetylcholine in "classic" conditions was not inhibited by atropine in this experiment. It was thus decided to classify this recording in the acetylcholine group .
Rec.: recording.

Furthermore, three samples (6, 9 and 12), which were considered as inactive during the first step were tested once again and indeed seemed to correspond to "water" activity because they were again found inactive in this second step of the experiment.

Recording n°	Without atropine	With Atropine
6	3.9	3.8
9	4.8	7.1
12	5	2.6

"The results do not fit with the codes"

Everything thus seemed to match and it would be most surprising if the observed biological activities did not correspond to the code. But, again, after unblinding, there was disappointment mixed with incomprehension.

Experimental result	Inactive (***Water-type*** activity)					
N° of recording	2	6	9	12	18	15
Unblinding	Ova	Water	Ach	Ach	Water	Ova

Experimental result	Active with ***Ach-type*** activity					
N° of recording	1	3	7	10	11	14
Unblinding	Water	Ova	Ova	Water	Ova	Ach

Experimental result	Active with ***Ova-type*** activity					
N° of recording	4	5	8	13	16	17
Unblinding	Water	Ach	Water	Ova	Ach	Ach

J. Benveniste then commented on this experiment in these terms:

> "Here are thus the results of this experiment. They are at the same time remarkable and disappointing. Remarkable because, as you can see in the enclosed tables, these experiments work perfectly, in all the compartments of the game. Disappointing because the results do not fit the codes." [1]

In spite of the "technological jump" on which so many hopes had been based, it was once again the same situation as in the past when, on numerous occasions, the code did not fit with the results. As long as one did not unblind the experiment, everything was fine! Before unblinding there was indeed coherence between available information on the "expected" results and the observed results. If one considered the experiments from the outside, the most obvious conclusion was that the attitude of J. Benveniste who hanged on to these experiments was totally irrational.

Furthermore, the interferences which had been suggested as the possible explanation of the previous failures during the transport of tubes until Clamart did not hold any more. It was indeed computer memories which were

transported. It was difficult to imagine a similar mechanism which would arise during the transport. Nevertheless, once again, J. Benveniste tried to find an explanation for these disturbing oddities. He had the hard disk of the laptop computer examined and – for a while – he could thus hold onto an explanation:

> "As demonstrated in the enclosed document, a breakdown of FAT (File Allocation Table), obviously unpredictable, arose on our hard disk which must be replaced. According to the IT specialists this breakdown produces random distributions of files. One notices that the inactive tubes which we detected were replaced according to a particular algorithm: after the initial 2, these files follow one another on the hard disk 3 by 3, what is little compatible with an allocation of random numbers."

Then J. Benveniste explained that the recordings made on the hard disk were compared with their copies on floppy disks which had been kept by the bailiff. Computer files being similar, he deducted that the "anomaly" occurred at the time of the recording of computer files on the hard disk and not at the time of their "reading" to water.

And he concluded:

> "We can thus consider that, without this computer incident which is probably the cause of the disorder of the codes, we would have demonstrated the possibility of recording specific molecular activities on a hard disk, replaying them and recognizing them specifically".

M. Schiff who received the report of the experiment noticed that J. Benveniste himself dug deeper in his quest of the "crucial experiment". He wrote to him in these terms:

> "At first a general comment that I have already expressed several times, but that I repeat because I think it is fundamental. It seems to me that you are trapped by the desire, hopeless in my opinion, to fight the suspicion of fraud. This brings you to present your results as a bet on horse races, in which the objective would be "to guess" the identity of tubes or recordings instead of underlining the internal coherence of the results. […]
>
> The most rigorous statistical analysis in my opinion is based on the analysis of the ranks of files. The least "active" 6 files of the first series are files 9, 6, 2, 12, 15 and 18. The least active six files of the second series of measurements are the same ($p= 6! \times 12!/18! = 1/18500 = 0.5 \times 10^{-5}$). In the third series, you tested

> only three of the least active 6 files. They still find themselves among the 3 least active among the 15 tested ($p=3! \times 12!/15! = 1/455 = 2 \times 10^{-3}$)" [2]

In other words, M. Schiff thus insisted on the internal coherence of the experiment which, from a statistical point of view, cannot be due to random. To verify that this failure is indeed related to simple computer problems, J. Benveniste suggested redoing other experiments, but less ambitious ones to begin with.

Notes of end of chapter

[1] Letter of J. Benveniste of March 26th, 1996 to the participants in the experiment of February 27th, 1996.

[2] Lettre of M. Schiff to J. Benveniste of March 31st, 1996.

Chapter 14. "It could well be that we hold the explanation of the mystery"

"We are now very close to the conclusion"

After having fixed the computer "problems", namely the supposed cause of the "mixing" of the recordings of the experiment of February 17th, 1996, a new public experiment was organized on May 7th, 1996. As already said, this experiment was more limited than the previous one. The objective of the experiment was to identify five active recordings (recordings of ovalbumin) and five inactive recordings. Discriminating the specificity of various "active" recordings was not the purpose of the experiments. The recordings took place as usual at the Cochin institute (see technical sheet).

When the evaluation of the recordings was ended and when the unblinding was done, J. Benveniste as usual sent a report to the participants:

> "Here is the result of the experiment recorded on May 7th at Cochin Hospital. Exceptionally, we also send these results to all participants of February to allow those who wish coming on board again. We are now very close to the conclusion of this series of experiments." [1]

After this quite optimistic sentence, J. Benveniste tackled the results (Table 14.1):

> "As you can see in the enclosed table, we inverted the results of the first 4 recordings and correctly identified 6 others. […]
>
> This experiment allowed us to understand where the anomaly is located: it does not arise at the time of the recording (it is largely confirmed that we are capable of recording and of digitizing biological activities), nor at the time of the reading. It is in the order of the recordings such as they are administered to the heart that these anomalies occur. I cannot go into experimental details here, but the result of these anomalies is that the heart reacts in fact to the *previous* injection. This anomaly is completely induced by the blind procedure: when a tube is not active in first intention (heart with low sensitivity, recording with low intensity), even if it is a tube "Ova" we think that it is water and we do not change, for reasons of economy, the catheter of injection. During the next injection, if the tube is "Ova" it will work and we will be correct,

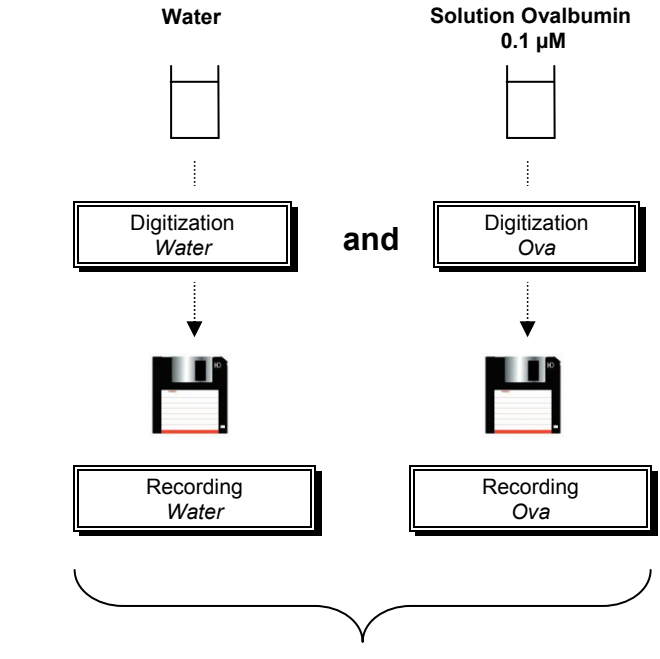
if the tube is "Water", the infusion liquid will gain information in contact with the pipe and we will confuse it with Ova."

Tested recordings	Number of measurements	Maximal changes of coronary flow (%)	Biological activity in increasing order	Unblinding
Blind tests				
n°7	7	4.6 ± 1.7	1	Digital water
n°5	3	4.9 ± 2.7	2	Digital water
n°3	6	6.2 ± 3.5	3	**Digital ova**
n°9	5	6.7 ± 2.8	4	Digital water
n°1	8	7.7 ± 5.1	5	**Digital ova**
n°10	6	13.1 ± 8.6	6	**Digital ova**
n°8	5	16.3 ± 7.0	7	**Digital ova**
n°2	4	18.9 ± 8.0	8	Digital water
n°6	5	20.2 ± 8.2	9	**Digital ova**
n°4	3	20.5 ± 4.9	10	Digital water
Open-label tests				
Digital water	9	4.6 ± 3.7	-	-
Digital ova	11	21.9 ± 27.4	-	-
Ova 0,1 µmol/L	12	24.0 ± 3.9	-	-

Table 14.1. Public experiment of May 7th, 1996. As expected, 5 recordings induced a change of the coronary flow (2, 4, 6, 8, 10) above 10% and the 5 others were considered as inactive (1, 3, 5, 7, 9). One could think that the first ones corresponded to the recordings of ovalbumin (ova) and the following ones to the recordings of water. After the unblinding, the activities of the first 4 recordings were "inverted" whereas the activities of the 6 next ones were correctly identified. The results with open-label recordings were as "expected" as well as ovalbumin at classical concentration (0.1 µmol/L) tested systematically at the end of each experiment to verify the reactivity of the heart.
In this table and the next ones, results are given as mean ± standard deviation.

Technical sheet of the experiment of May 7th, 1996

Type of experiment: transmission-digitization
Place of experiment: Cochin institute for digitization on May 7th and at Clamart for transmission and assessment of samples from May 9th to May 15th
Blinding: On May 7th by participants not belonging to U200
Number of recordings to be tested: 10 (5 ovalbumin and 5 water)
Additional in-house blinding: yes



Blinding of 10 recordings numbered from 1 to 10:
5 recordings "**Water**"; 5 recordings "**Ova**"

(*tested after **transmission** to water sample)*

+

4 open-label recordings
2 recordings "**Water**"; 2 recordings "**Ova**"

(*tested after **transmission** to water sample)*

J. Benveniste thus suggested for the future experiment to systematically change the fine flexible pipe which drove "informed" water to the heart and to test twice in row every sample. This procedure was however more expensive and more time-consuming. But, with this method, J. Benveniste thought he could now succeed, because by testing again some of the samples of the previous experiment again and by applying this method, he obtained the "expected" results:

> "After unblinding, we experimented this method in blind experiments on tubes 1 till 4 and identified them this time in the correct order: Ova/Water/Ova/Water. We are thus going to hold a public meeting again during which we will record a series Water/Ova and a series Water/ACh (acetylcholine). We will introduce a further difficulty: for each series, there will be 20 labels of the couple Water/Ova or Water/ACh from which only 10 will be randomly selected, therefore we will not even know the respective number of recordings Water and Ova or ACh. That should work but it is research and we are not shielded from another unexpected difficulty."

J. Benveniste addressed two important points here. On one hand, the number of active/inactive samples was known until now. Only their distribution must be determined. On the other hand, he indicated that on a small series, he found correctly the expected effects at the good places. The tubes from 1 to 4 which were inverted were then correct (compare Tables 14.1 and 14.2).

Tested recordings	Number of measurements	Maximal changes of coronary flow (%)	Biological activity in increasing order	Unblinding
Blind tests (in-house)				
n°2 of May 7th	4	4.5 ± 1.7	1	Digital water
n°4 of May 7th	2	7.4 ± 0.4	2	Digital water
n°1 of May 7th	4	15.4 ± 4.3	3	**Digital ova**
n°3 of May 7th	4	19.2 ± 7.0	4	**Digital ova**
Open-label tests				
Ova 0.1 µmol/L	3	34.5 ± 12.0	-	-

Table 14.2. After the unblinding of the experiment of May 7th, J. Benveniste tested again 4 recordings (from n°1 to 4) which gave "abnormal" results. These recordings thus served again to "imprint" samples of naive water (experiments performed on May 21st and 23rd). The samples of "informed" water were then given blind to the experimenter for tests on the Langendorff device. "Expected" results were then obtained (compare with Table 14.1).

"Explaining the mystery"

As planned, the public experiment of June 12th was performed in two parts. Two series of 8 recordings were performed, each series containing an unknown number of recordings supposed to have a biological activity. After the unblinding of the experiment on July 24th, in a well-oiled ritual, J. Benveniste announced the results of the experiment to the participants (Table 14.3:

> "The experiment) of June 12th is a failure (see however the appendix). We are in the usual situation: very clean results where tubes are repeatedly measured under different numbers give coherent results… which however have nothing to do with the code. One notices the same phenomenon as during the experiments of February 27th and May 7th: the results are distributed according a regular algorithm: here a positive tube is always followed by two negative tubes. The contrast with real random distribution shows that there is indeed something abnormal." [2]

Beginning to be short of *ad hoc* hypotheses, J. Benveniste suggested nevertheless possible problems related to the computer, but apparently without much conviction:

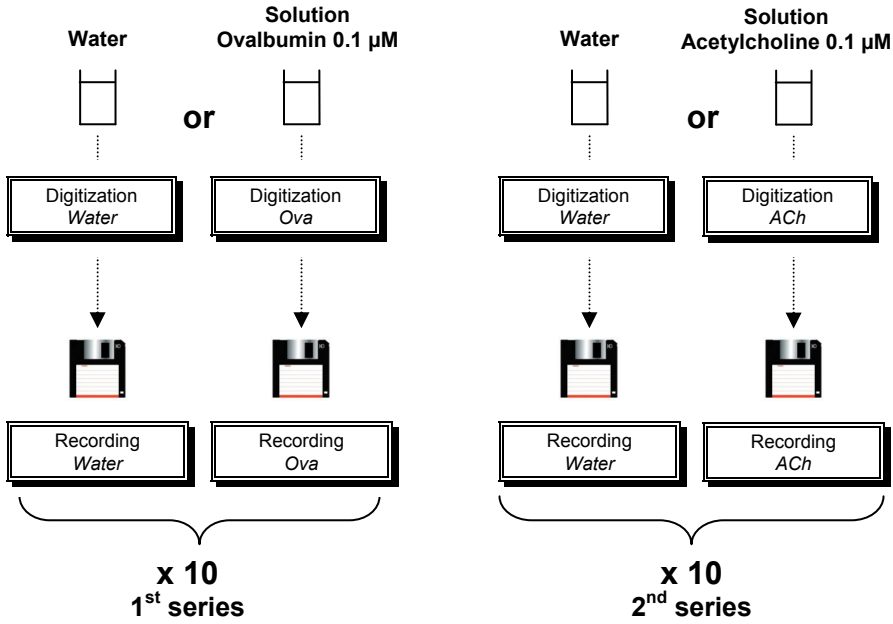
> "I remind you that the recordings were made with one floppy disk for each file. However, maybe I made the error to group them together on the hard disk of the computer because, probably according to the lack of RAM, this one reads directly on the floppy disk what induces an important wow. […] Having said that, there is no valid hypothesis that allows explaining a "mixture", a reorganization of the activities."

He thus concluded:

> "We are incapable to know if the abnormalities arise in large series during the recording on the computer or during the measurement, the heart being submitted to multiple stimulations would thus give any answer. None of the elements mentioned above allows choosing one of these hypotheses and explains this history of *bizarre algorithm observed three times in a consecutive manner*."

Technical sheet of the experiment of May 12th, 1996

Type of experiment: transmission-digitization
Place of experiment: Cochin institute for digitization on May 12th and at Clamart for transmission and assessment of samples from July 4th to May 23rd
Blinding: On June 12th by participants not belonging to U200
Number of recordings to be tested: 2 series of 8 recordings (water or ovalbumin; water or acetylcholine); unlike previous experiments, the number of active samples was not known for this experiment.
Additional in-house blinding: yes



Blinding of 16 recordings:

1st series: 8 recordings "**Water**" or "**Ova**"
(numbered from **1 to 8**)

2nd series: 8 recordings "**Water**" or "**ACh**"
(numbered from **11 to 18**)

(*tested after **transmission** to water samples)*

Tested recordings	Number of measurements	Maximal changes of coronary flow (%)	Biological activity in increasing order	Unblinding
First series				
Blind tests				
n°3	4	4.3 ± 1.2	1	**Digital ova**
n°4	4	5.3 ± 3.0	2	Digital water
n°1	4	5.6 ± 2.7	3	Digital water
n°6	4	6.0 ± 0.5	4	**Digital ova**
n°7	4	6.7 ± 2.9	5	**Digital ova**
n°5	4	15.6 ± 2.5	6	**Digital ova**
n°8	9	19.8 ± 5.7	7	**Digital ova**
n°2	4	23.8 ± 5.5	8	Digital water
Open-label tests				
Digital ova	10	21.0 ± 8.9	-	-
Ova 0.1 µmol/L	9	26.4 ± 11.1	-	-
Second series				
Blind tests				
n°15	2	4.2 ± 0.1	1	**Digital ACh**
n°18	2	4.3 ± 0.0	2	Digital water
n°13	2	5.5 ± 1.7	3	**Digital ACh**
n°12	3	6.3 ± 3.7	4	Digital water
n°16	2	6.5 ± 0.3	5	**Digital ACh**
n°17	9	10.9 ± 4.2	6	Digital water
n°14	3	14.7 ± 1.6	7	**Digital ACh**
n°11	8	17.7 ± 8.4	8	**Digital ACh**
Open-label tests				
Water digit.	1	4.3	-	-
Digital ACh.	2	13.8 ± 2.5	-	-
ACh 0.1 µmol/L	9	17.6 ± 3.4	-	-

Table 14.3. Experiment of June 12th, 1996. This experiment included two series with an unknown number of active and inactive recordings. The active recordings corresponded to ovalbumine (ova) in the first series (recordings from n°1 to 8) and acetylcholine (ACh) in the second series (recordings from n°11 to 18). As one can notice, there were 5 active recordings in each series, but only 3 were found in each one. Furthermore, the results did not fit the code. Thus, a recording supposed to have no effect (control) could be accompanied with a spectacular biological effect (see for example sample 2). Only chance seemed to be responsible of the distribution.

However, J. Benveniste did not mention another very disturbing fact. One remembers that the number of active and inactive samples was not known in this experiment. Yet, it was a failure also on this issue. In the previous experiments, this number was known and one could thus speak about "inversion of activities". It was not the case anymore for this experiment. Everything consequently happened as if the results were obtained according to the available information on the expected results. When there was an internal blinding in the laboratory, the results were consistent.

But, on July 27th, J. Benveniste added a postscript to his letter:

> "It could be quite possible that we hold the explanation of the mystery. To sum up the experiments of February, May and June at Cochin, two major facts emerge:
> 1) The results are consistent with each other but they are very often attributed by the code to tubes not corresponding to the observed activities. The fact that the recording of Ova or ACh could be inactive can be understandable due to a failure of the experiments. But the fact that recording of water is specifically active, meaning that it behaves as Ova or ACh, is obviously impossible.
> 2) The arrangement of the activities according to algorithms for three experiences cannot result from random draws."

This "algorithm" mentioned by J. Benveniste corresponds to the distribution of the active/inactive measurements. If one resumes the results of the experiments of February 27th, May 7th and June 12th according to the order of the numbering of the recordings (summarized in a more visual way in Figure 14.1, one indeed notices that the order of the active/non active measurements appears to be much more regular than expected by chance.

Experiment of February 27th, 1996:	●-○-●-●-●-○-●-●-○-●-●-○-●-●-○-●-●-○
Experiment of May 7th, 1996:	○-●-○-●-○-●-○-●-○-●-○-●
Experiment of June 12th, 1996 (1st series):	○-●-○-○-●-○-○-●
Experiment of June 12th, 1996 (2nd series):	●-○-○-●-○-○-●-○

Figure 14.1. The "algorithm" mentioned by J. Benveniste is schematized here. The black circles correspond to "active" samples and the white circles to "inactive" samples in the increasing order of the numbering of the blinding. Actually, one notices that, except for the 3 black circles at the beginning of the experiment of February 27th, "beads" alternate according to very regular motives.[3]

Returning on the possible anomaly related to the hard disk, J. Benveniste summarized the previous events and proposed a new explanation for these anomalies:

> "These observations led us to question the distribution of files on the hard disk. For this purpose, we recorded on floppy disks on June 12th at Cochin, with one floppy disk for one recording. However, when we replayed these floppy disks on an external hard disk I made an error of strategy: wanting to use a computer more powerful than the laptop to "imprint" the tubes of water, I copied all the floppy disks on an external hard disk which I then transferred to the office computer. We then replayed the activities contained on this hard disk. My error can partially be understandable by the fact that I believed that the anomalies of file allocation on the hard disk occurred at the time of the recording. Moreover the office computer cannot play floppy disks without distortion (wow)."

Although this umpteenth *a posteriori* interpretation of the results was hardly convincing, the next information given by J. Benveniste was nevertheless surprising:

> "Given the catastrophic results of the unblinding of July 24th, I decided to play one by one the floppy disks recorded at Cochin on June 12th directly on the laptop, without any recording whatsoever on the hard disk. The results speak for themselves: *the activities measured with internal blinding were attributed to the good tubes according to the code (see table).*"

Indeed, on July 25th and 26th, new measurements were made with some recordings of June 12th. The results are described in Table 14.4.

In other words, as for the experiment of May 7th, when somebody of the team knew the code (J. Benveniste in this specific case), the code fitted the results. The experimenter, J. Aïssa, who performed the experiments, was blinded. Moreover, this "phenomenon" did not appear to be specific to the experiments of "digital biology". The reader remembers the transmission experiment of May 13th, 1993 (cf. Chapter 8) where M. Schiff did in-house code; consistent results had been obtained.

Tested recordings	Number of measurements	Maximal changes of coronary flow (%)	Biological activity in increasing order	Unblinding
Blind (in-house) tests				
n°1 of June12	2	4.3 ± 1.4	1	Digital water
n°4 of June12	2	4.3 ± 3.5	2	Digital water
n°2 of June12	4	6.3 ± 1.7	3	Digital water
n°3 of June12	3	13.4 ± 0.8	4	**Digital ova**
n°13 of June12	3	13.4 ± 4.8	5	**Digital Ach**
n°6 of June12	3	20.3 ± 5.5	6	**Digital ova**
n°7 of June12	1	33.9	7	**Digital ova**
Open-label tests				
Ova 0.1 µmol/L	4	22.5 ± 6.5	-	-
ACh 0.1 µmol/L	2	18.1 ± 3.3	-	-

Table 14.4. After the unblinding of the experiment of June 12th, 1996, J. Benveniste tested again 7 recordings of this experiment and "imprinted" samples of water (measurements performed on July 25th and 26th). He gave then these samples blind to the experimenter. "Good" results were obtained. Compare with Table 14.3.

The idea that "in-house" knowledge of the code allowed to get "expected" results was of course a concept – if there was actually a concept – difficult to convey because, on one hand, it was very difficult to give an explanation and, on the other hand, this left the door open to all the suspicions. J. Benveniste knew however that his collaborator who handled the experimental devices had no knowledge of what he "must" obtain. All this remained incomprehensible. J. Benveniste readily admitted and he expressed his perplexity:

> "I have obviously no explanation for these anomalies of ranking of activities on a hard disk which, on the standpoint of IT logic, makes no sense. It would however be necessary to ask to a specialist of IT processing of sounds if such phenomena do not occur for example with music files. […]".

And, nevertheless, he optimistically concluded:

> "Taking into account this advance of what appears to be now a control of the recordings of biological activities, we think we can complete the experiments in the first two weeks of September, plus a second experiment by transfer (on floppy disks!) from Chicago. An article in a top-notch journal could be sent by end-September or mid-October."

Before telling the "Cochin experiments" performed during the autumn of 1996, let us describe these "experiments of Chicago" to which J. Benveniste alluded.

Notes of end of chapter

[1] Letter of J. Benveniste of May 24th, 1996 "to the participants in the experiments of February 27th and May 7th, 1996".

[2] Letter of J. Benveniste of July 24th, 1996 "to the participants in transmission experiments".

[3] I have no explanation about this regularity of the distribution between "inactive" and "active" samples. Maybe it corresponded to the (wrong) idea of what "random" distribution should be…

Chapter 15. Transatlantic dreams

The shadow of Lindbergh

In February 1997, J. Benveniste presented a communication to a congress in San Francisco in the form of a "poster" describing his last results. The title of the communication was "*Transatlantic transfer of digitized antigen signal by telephone link*".[1]

Except the reference to "digital biology", this title was unusual. Why was such a geographical parameter specified in an experiment about biology? If needed, one could have spoken about the "long-distance" transfers to further emphasize on future possible applications. Even in this case, billions of computer files permanently go around the world and nobody is upset. Indeed, as soon as information is digitized, the material medium (compact disk, floppy disk, magnetic tape, hard disk or file transferred by Internet) does not matter. To finish, the files are transmitted through Internet by "packets" that are not necessarily in keeping with the geographical logic of the shortest path.

Maybe the answer is cultural, not to say generational. J. Benveniste was indeed an admirer of the pioneers of aviation and particularly the airmail service pioneers such as Henri Guillaumet ("What I have done, no animal would have done.") It is thus possible that this insistence to talk about "transatlantic transfer" in the title of a communication at a scientific congress was related to the dream which always accompanied any victory on this ocean in those days. The crossings of the first "transatlantic" liners, the installation of the first submarine telegraphy or telephony cables, the first flights above the Atlantic Ocean, all first scientific or technical successes concerning this ocean were always human adventures. The passion of J. Benveniste for car racing, engines, sailing and exploits accomplished with panache, is the likely explanation for this curious precision on which he insisted on many occasions. In support of this idea, one can evoke his letter to the French President when he tried to draw the attention on his discoveries: "A phenomenon of which he warns the president of the Republic, on June 13th, 1996, by presenting it as an issue which was more important than the flight of Lindbergh over the Atlantic Ocean…" [2]

A "Masked Researcher" comes on stage

These "transatlantic transfers" were performed in collaboration with a scientist of Chicago. But, up to February 1997, which is the date of the congress of San Francisco, J. Benveniste refused to reveal the identity of the American

researcher not to damage the latter. Who was this "Masked Researcher" on whom J. Benveniste cast a shade of mystery for a while? Without revealing any name, E. Fottorino portrayed this scientist early 1997:

> "Contrary to what Georges Charpak suggests, "the masked professor of Chicago" is not at all an eccentric. The numerous publications of this professor (more than eighty) in high-level journals (European Journal of Pharmacology, Journal of Immunology and even... Nature) demonstrate his professional qualities. As a renowned pathologist, he manages at once, as it is common in this domain in the United States, practitioner's activity (diagnosis before surgery) in a hospital and in a research program regularly renewed by NIH (National Institute of Health). His studies on PAF-Acether brought him, for twenty years, into contact with Jacques Benveniste. But, as he admits himself, he does not understand anything "neither about water nor physics"."

The journalist explained the role of the scientist of Chicago in the experiments) of "digital biology":

> "His role is at the same time modest but essential for the French researcher. Modest, because he simply records the frequencies of ovalbumin and water on a floppy disk on his computer and then transfers them by Internet to the computer of Benveniste, after having coded them. Why go to Chicago while a transfer from Paris would be enough? This is where the role of the masked researcher becomes essential: the latter asserts that no fraud is possible; Benveniste has one chance out two to guess (or to make a mistake). Among twenty nine shipments, he recognized "naive water" or ovalbumin each time by "playing" messages recorded in Chicago on isolated hearts of guinea pigs in Clamart. "I strictly respect his protocol, the American professor explains. He sends me his results. He cannot falsify them. His data are right. But I cannot interpret them nor evaluate their impact. In fact, I am not the right person to help him, because it is not my area of expertise. His problem is to meet a physicist of water." "

Let us see in which circumstances these "29 experiments", which are presented as a success, have been performed. If this success was so certain it was of course extremely important because, at the same moment, the "public experiments" took place at the Cochin institute and J. Benveniste as we saw in the previous chapter the same irritating problem is always an obstacle.

The Chicago-Clamart connection

The "masked researcher" was Dr Wei Hsueh, Professor of Pathology in Children Memorial Hospital at the Norwestern University Medical School of Chicago. She is the opposite of G. Charpak because – except the fact that she is a woman – she considered the experiments of J. Benveniste with benevolence and friendship. As she was acquainted with J. Benveniste for a long time, she knew his qualities, both good and bad. *Le Monde* – which spoke about her using the masculine gender to respect her temporary anonymity – reported her words about J. Benveniste and his studies:

> "According to this researcher, it is premature to judge the work of Benveniste. "He is himself too much in a hurry. He should have better controlled his system before showing it to Charpak. If it is an artefact, it is consistent. If it is the truth, it is consistent." He adds: "The main problem of these experiments is that they come from Benveniste. I sometimes meet honorable researchers treating him of scientific swindler. I ask them if they know him. They answer no. Benveniste is sometimes a little bit megalomaniac, as many are in this milieu, persuaded that they are themselves the truth. Maybe it is the key to success. Before this affair, Benveniste was on the way towards the success. His contribution on PAF-Acether is indisputable." While admitting that his provocative attitude (and his impatience) is detrimental to him, the professor of Chicago wonders about the "excessive" reaction of the milieu. "It is not worthy of a scientific community to condemn what is unexpected. Benveniste does not deserve that type of treatment. He needs means and one should leave him with a real opportunity to prove what he claims. If he is lucky, he will find the practical verification and the therapeutic application of the phenomenon before the theory. In science, it is often the opposite. Such a stake could justify investments." [3]

For the first experiments, the recordings performed by W. Hsueh were sent through Internet to the laboratory of Clamart. It is important to note that W. Hsueh performed the recordings by pairs that systematically contained an "active" recording and an "inactive" one. The "aim of the game" was thus to "guess" their respective places. Thus, each time one had one chance out of two to find the expected result. But again one has to repeat that this is not a simple exercise of divination because one observes a modification of a biological parameter, namely coronary flow. In other words, something "moves" although

the biological system should remain stable because what is administered to the heart is not different from the fluid that permanently infuses it.

In order to perform these "transatlantic" experiments, J. Benveniste supplied all the necessary equipment to W. Hsueh, in particular the sensor which was connected to the soundcard of the computer for the recording of "activitiy". He even went to Chicago to explain its functioning. The first experiment took place on April 10th, 1996. It was a success, but the experiment was open-label in order to verify that everything correctly worked (Table 15.1). Five other pairs were tested until April 19th. Each recording was "played" to naive water which was then tested on both devices of Langendorff which worked in parallel for the consistency of the results. Among these 6 experiments containing each a pair of recordings, the correct answer was obtained for 2 pairs (for the pair n°3, one could not conclude). This was thus the same configuration as the experiments of Cochin with frequent "inversions" of activity.

J. Benveniste and W. Hsueh then decided to change the method. The recordings would be copied to floppy disks which would be sent to Clamart by surface mail. The rationality of this decision is difficult to understand because a digital recording is the same whatever the medium. One remembers however that during the experiments performed at the Cochin institute, J. Benveniste suspected that the results could differ if files were recorded on floppy disk or on hard disk. On May 24th, that is one month later, two new pairs of recordings arrived by surface mail were tested and gave correct results (pairs n°7 and 8 of table).

A new series of 3 pairs of recordings (from n°9 to 11 of Table 15.1) was then realized by W. Hsueh each containing a recording of "acetylcholine" and a recording of "water". The recordings were sent by Internet, but J. Benveniste took care, as soon as he received them on his computer, to save them on floppy disk and not on the hard disk. Once again, this procedure could seem totally irrational. Three pairs of recordings were tested from June 3rd to 19th. But the effects observed on isolated hearts until June 10th had low amplitude and were unconvincing. Only the answers obtained from June 10th to 19th were taken into account.

N° of experiment *Test date*	Names of recordings	Number of measurements	Maximal changes of coronary flow (%)	Blinding and sending (Mail or Internet)	Success
n°1	D	3	4.7 ± 2.0	Digital water (I)	Yes
April 10	F	6	17.8 ± 9.0	Digital ova (I)	*(open-label)*
n°2	A	2	18.8 ± 15.1	Digital water (I)	No
April 16	C	3	5.6 ± 2.9	Digital ova (I)	
n°3	G	2	19.0 ± 11.2	Digital water (I)	?
April 16	I	2	14.4 ± 8.6	Digital ova (I)	
n°4	J	2	14.2 ± 3.5	Digital water (I)	No
April 17	L	2	4.5 ± 0.7	Digital ova (I)	
n°5	M	4	31.5 ± 18.4	Digital water (I)	No
April 17	N	4	5.3 ± 1.8	Digital ova (I)	
N°6	O	2	4.4 ± 2.5	Digital water (I)	Yes
April 19	P	2	25.1 ± 10.5	Digital ova (I)	
n°7	**Q**	2	7.0 ± 1.9	Digital water (M)	**Yes**
May 24	**S**	1	17.1	Digital ova (M)	
n°8	**W**	2	16.8 ± 15.6	Digital water (M)	**Yes**
May 24	**X**	2	4.7 ± 2.2	Digital ova (M)	
n°9	**21**	10	4.9 ± 0.5	Digital water (I)	**Yes**
June 10-19	**22**	6	20.9 ± 2.8	Digital ACh (I)	
n°10	**23**	6	22.4 ± 1.8	Digital ACh (I)	**Yes**
June 10-19	**24**	8	9.8 ± 3.9	Digital water (I)	
n°11	**25**	9	10.2 ± 2.2	Digital water (I)	**Yes**
June 10-19	**26**	5	26.7 ± 7.1	Digital ACh (I)	
n°12	AA	4	20.4 ± 3.7	Digital water (I)	No
June 17-26	AB	8	4.7 ± 0.8	Digital ACh (I)	
n°13	AC	6	3.7 ± 2.1	Digital water (I)	Yes
June 17-26	AD	9	13.8 ± 9.0	Digital ACh (I)	
n°14	AE	6	10.2 ± 2.9	Digital ACh (I)	No
June 17-26	AF	4	30.9 ± 6.1	Digital water (I)	
n°15	AL	7	9.8 ± 6.6	Digital water (I)	Yes
June 17-26	AM	7	16.3 ± 10.2	Digital ACh (I)	

Tableau 15.1. "Chicago experiments" of April-June 1996.
During this series of experiments performed with recordings which were sent either by Internet (I) or by surface mail (M), thirteen blind experiments were interpretable. A success was obtained for 8 of them (chance only would allow 6.5 successes on average).
The results are given as mean ± standard deviation.
The experiments which were included in the communication at the congress of San Francisco (see text) are in bold characters.

The last recordings having given the activities which fitted the code, J. Benveniste asked W. Hsueh to send an official letter describing the results of these experiments (that is experiments from n°7 to 11) and guaranteeing that files were sent blind to Clamart. W. Hsueh thus sent a letter on headed paper of her hospital department where she specified that she "guarantees that she herself recorded the files and that she was the only one to know the code before Dr Benveniste sent her the results." [4] J. Benveniste transmitted this letter to his usual correspondents, but he specified that "for the sake of discretion" he masked the author of the letter. [5]

The third series of recordings which included 4 pairs (from n°12 to 15 in Table 15.1) was then launched. The purpose of J. Benveniste was to achieve a sufficient number of experiments to present them to the congress of immunology of San Francisco which would take place in February 1997. The recordings were tested from June 17th to 26th. But, for this series, the results did not fit the codes. Other experiments were performed in order to understand the source of these discrepancies, but the different and contradictory results according to the transportation of the computer files were obtained and the highest confusion settled down between Chicago and Clamart.

"In thirty years, I have never been treated in such a manner"

J. Benveniste incriminated the computer of W. Hsueh and he remained persuaded that the same recording gave correct results when it stayed on the original floppy disk but that the problems arose when it passed through the hard disk of the computer. He evoked even the possibility of persistence at the level of the computer memory. He also persuaded himself that a single recording with one floppy disk was "safer" than several recordings on the same medium. For an IT specialist it is complete nonsense. Indeed, any computer record is a series of 1 and 0. It is the only "reality" of IT. Nevertheless, J. Benveniste submitted the computer which he used to a strict "cleaning"; he asked to W. Hsueh to do the same cleaning for her computer and to eliminate all the former recordings in order to start fresh again.

At the end of August, W. Hsueh finally performed new recordings by pairs (one "active" and one "inactive") or by triplets (one "active" and two "inactive"). J. Benveniste asked the latter to buy new preformatted floppy disks of a brand which was different from the previous one and to do each recording on a single floppy disk. Once again, from an IT point of view, it makes no sense, especially because W. Hsueh sent the recordings on floppy disks *via* Internet; she gave the code after having received the results of each pair or triplet. It is also necessary to note that the files were repeatedly tested by the experimenter, J. Aïssa, under different new codes so that he could not link,

consciously or unconsciously, the successive results. The results are summarized in Table 15.2. But, towards the end of the series, J. Benveniste realized that W. Hsueh coded the recordings always in the same order, with the active recording in first position. She was thus invited for the following recordings to pay attention on this point which could be criticized (in fact there was only one additional recording).

Besides, "technical problems" with experiments n°2 and n°4 made that J. Benveniste knew the code. In reality, an "inversion" had been straightaway obtained for these experiments. The supposed "technical problems" having been fixed, J. Benveniste performed new transfers and gave blind samples to the experimenter. The "expected" results were then obtained.

I do not specify these points by obsessional passion for detail or in order to suggest that J. Benveniste sometimes "adjusted" the results. Moreover, the fact that for two pairs of recordings the code was known has not been hidden and has been clearly indicated in the communication to the congress of San Francisco. My purpose is to show what bench research is, with trials and errors, hesitations, periods of enthusiasm or disappointment. Especially, one can see in these experiments that J. Benveniste himself had the attitude he blamed his "opponents" for: he is prisoner of his own prejudice on what results should be. In his defense, we could add that obtaining consistent results while the only differences live apparently in a series of 1 and 0 on a computer memory is already totally perplexing. The fact that the results do not fit the code is another question which, at this stage, remains incomprehensible.

N° of experiment	Names of recordings	Number of measurements	Maximal changes of coronary flow (%)	Blinding and sending (Mail or Internet)	Success
n°1	**C2**	3	29.2 ± 16.3	Digital ova (I)	**Yes**
	C5	2	2.4 ± 1.1	Digital water (I)	
n°2	**C4**	2	25.2 ± 0.8	Digital ova (I)	**Yes**
	C6	2	2.1 ± 0.0	Digital water (I)	*(Open-label)*
n°3	**C7**	4	22.1 ± 12.3	Digital ova (I)	**Yes**
	C9	5	3.3 ± 1.6	Digital water (I)	
n°4	**C8**	3	16.4 ± 0.9	Digital ova (I)	**Yes**
	C10	2	3.6 ± 1.7	Digital water (I)	*(Open-label)*
n°5	**C1**	4	24.1 ± 5.8	Digital ova (I)	**Yes**
	C3	6	3.4 ± 1.8	Digital water (I)	
n°6	**C11**	2	35.3 ± 0.6	Digital ova (I)	**Yes**
	C16	2	4.4 ± 1.1	Digital water (I)	
	C25	2	6.1 ± 0.9	Digital empty tube (I)	
n°7	**C21**	6	18.1 ± 10.5	Digital ova (I)	**Yes**
	C22	4	4.8 ± 2.7	Digital water (I)	
	C23	4	4.8 ± 3.3	Digital water (I)	
n°8	**C18**	8	4.4 ± 1.1	Digital water (I)	**Yes**
	C19	3	18.3 ± 6.3	Digital ova (I)	
	C20	7	4.4 ± 1.8	Digital water (I)	

Table 15.2. "Chicago experiments" of August-September 1996.
These experiments were performed by sending the recordings via Internet. The effects of the recordings were assessed from August 27th to September 17th, 1996. For the recordings C2-C5 and C4-C6, the codes were known: in a first time, "unexpected" results had been noticed; after new open-label tests, "expected" results had then been obtained. Out of 6 blind experiments, 6 active recordings were successful (chance only would have allowed finding approximately 2.5 active recordings on average). If we consider all Chicago experiments (results of this table and those of Table 15.2), we find 14 successes out of 19 blind experiments whereas chance only would allow guessing 9. The difference is not statistically significant (moreover re-test of samples after "unexpected" results introduced an important bias. But – and it is what remains incomprehensible – whether or not the "correct" codes was found, consistent changes of the coronary flow occurred.
As for the previous table, the experiments which were included in the communication at the congress of San Francisco (see text) are in bold characters.

Anyway, J. Benveniste had now a series of "correct" experiments that would allow him communicating on "digital biology". He did not then hesitate to speak about 29 out of 29 successful experiments, forgetting incidentally the failures (even if *a posteriori* explanations were proposed) and the delivery with forceps of some results. Indeed, here is how he presented these results afterward:

> "In a few months, during summer 1996, we performed twenty seven of these blind experiments. Twenty seven times, I succeeded in determining if the signal was coming from a tube informed by ovalbumin or acetylcholine or from a tube of deionized water". [6]

As we saw, the reality was less obvious (apart from the error on "27" experiments). It is necessary to note furthermore that there was not about 29 independent successes because the computer files were recorded and tested as pairs (or triplets) always containing a single recording supposed to be active. Therefore it would be more exact to speak about 13 blind experiments including 29 measurements of activities (experiments in bold characters in Tables 15.1 and 15.2). Furthermore, if we consider all the experiments performed from April to September, the "correct" answer was thus found for 14 experiments among 19 analyzable blind experiments. Chance only could allow finding approximately a mean of 9 correct results. Overall, the calculation shows that the number of "successes" is included in chance fluctuations. Nevertheless, these results remain out of the ordinary and inexplicable since, "informed" or not, it was always the same water which irrigated the heart.

The fact that J. Benveniste persisted in not giving the identity of this American co-worker before the congress of San Francisco irritated some scientists because it was not in accordance with current practice in scientific and university milieu and because this attitude allowed all kinds of suppositions:

> "When they received the summary of a paper which will be presented next February to the congress of immunology of San Francisco, the statistician Alfred Spira and the physicist Claude Hennion reacted in a bad mood. Benveniste masked the name of the professor of Chicago associated to this transmission of electromagnetic signals via the Internet network. "In thirty years, I have never been treated in such a manner, Alfred Spira admits, hurt. How to believe what he asserts if he hides a signatory of the text?" Claude Hennion sees there a confirmation: "Benveniste demonstrates that he puts himself outside science." Benveniste is overwhelmed: "why would I expose to the knocks anybody honorable who agrees to participate in my research?" " [7]

The anonymity of the "Masked Researcher" was finally lifted during the congress of San Francisco at the end of February 1997, but this revelation and the communication made by J. Benveniste at the congress in the form of a "poster" were done in an almost complete indifference.

Notes of end of chapter

[1] J. Benveniste, P. Jurgens, W. Hsueh, J. Aïssa. Transatlantic transfer of digitized antigen signal by telephone link. *Journal of Allergy and Clinical Immunology* 1997; 99: S175.

[2] E. Fottorino. La mémoire de l'eau. Le temps des passions, *Le Monde*, January 22nd, 1997.

[3] E. Fottorino. La mémoire de l'eau. Une vérité hautement diluée. *Le Monde*, January 23rd, 1997.

[4] Letter of W. Hsueh to J. Benveniste on June 21st, 1996.

[5] Letter of J. Benveniste "to the participants in transmission experiments" of July 4th, 1996.

[6] J. Benveniste. Ma vérité sur la mémoire de l'eau, p. 175.

[7] E. Fottorino. La mémoire de l'eau. Une vérité hautement diluée. *Le Monde*, January 23rd, 1997.

Chapter 16. "We should open a chip shop"

The last session?

Encouraged with the last results obtained between Clamart and Chicago, J. Benveniste was determined to pursue the transmission experiments at the Cochin institute by benefiting from the lessons learned during the collaboration with the researcher of Chicago. Among these lessons there was the "cautious" manipulation of the computer files. J. Benveniste then wrote to the participants – whose number steadily decreased – in these experiments:

> "As you perhaps remember, before the holidays, we had left off on the following observation: when the activities are "played" from the hard disk the results are erratic while if one "replays" the original floppy disks they fit to what is expected. These results were consolidated by the third series of experiments with Chicago […]. I remind you the principle: the laboratory of Chicago records activities (ovalbumin or water) and sends us by phone, two by two, the blind or open-label recordings. These recordings are made on individual floppy disks and received on individual floppy disks". [1]

It is useless to insist again on the irrationality to consider that the "inversions" could find their source in the fact that the various recordings on the same IT medium could "interfere" at this level. But J. Benveniste hanged on to this hypothesis and he decided to do experiments again at the Cochin Institute according to the following principle inspired by the experiments with Chicago:

> "We will record 10 series of 2 pairs of ovalbumin/water, pair by pair. We will return the results as we go along for every pair, avoiding a work of several weeks if there was another technical problem. These recordings will be made on floppy disks because we did not solve the mystery of the jamming of the recordings on hard disk."

And, undoubtedly very optimistic, J. Benveniste concluded his letter with: "with the hope to see you in what could be the last session." But on September 23rd, which was the date scheduled for the experiment, the recordings could not be correctly performed due to "a poor electronic connection" and the experimental session was postponed.

"Where is the bug?"

The demonstration was finally performed on September 30th, but the initial protocol which planned to record the samples by pairs was finally not followed. The records were tested on the isolated heart device from September 30th to October 4th.

Tested recordings	Number of measurements	Maximal changes of coronary flow (%)	Biological activity in increasing order	Unblinding
Blind tests				
n°1	2	2.6 ± 0.0	1	**Digital Ova**
n°4	4	4.2 ± 1.3	2	Digital water
n°8	2	5.0 ± 0.1	3	**Digital Ova**
n°9	2	5.2 ± 0.1	4	Digital water
n°7	2	13.6 ± 16.2	5	**Digital Ova**
n°5	1	15.8	6	Digital water
n°3	3	23.1 ± 10.7	7	Digital water
n°10	1	23.7	8	Digital water
n°2	2	34.0 ± 7.2	9	Digital water
Open-label tests				
Digital water 1	1	16.3	-	-
Digital water 2	1	45.0	-	-
Digital Ova 1	2	4.0 ± 0.1	-	-
Digital Ova 2	1	9.8	-	-
Ova 0.1 µmol/L	4	30.7 ± 14.4	-	-

Table 16.1. Public experiment of September 30th, 1996 (unblinded on October 8th). An incorrect number of active samples was found (5 active while only 3 had been included). Note that the open-label recordings were also unsatisfactory (they had been given blind to the experimenter). In this picture and the following ones, the results are given as mean ± standard deviation. NB. There was no recording n°6.

The blinding was performed by a researcher of the CNRS. When the experiments were finished, the latter communicated the code to J. Benveniste by fax. The results and the code were incoherent. "It is a mess. But it is not a mess" commented then J. Benveniste in a letter to the "coder" of the experiments. [2]

J. Benveniste illustrated his words through examples that were derived from this last experiment which demonstrated that once again something surprising occurred. Thus, samples supposed to be only water modified very clearly the coronary flow in animals immunized with ovalbumin, but were without effect in non-immunized animals. Furthermore, the profile of variation of the coronary

flow obtained with such a sample which was supposed to be "inactive" was identical to that of ovalbumin at "classic" concentration. This "water" thus possessed all the characteristics of an ovalbumin activity. It seems that there was "transmission" of a biological activity but not at the right place! J. Benveniste concluded: "where is the bug?" Always clinging on to IT problems, he suggested redoing in-house experiments before launching again public demonstrations:

> "If the unused floppy disks give nothing better, it means that the bug remains unidentified and it will be necessary to do experiments by telephone, floppy disk by floppy disk, as with Chicago where it worked 29 times out of 29".

"The results were excellent"

On October 24th, J. Benveniste sent a letter to his usual correspondents to review the recent experiments previously described:

> "The last three experiments in Cochin did not work. According to the logic at present dominant in the "research", we should open a chip shop on N-306.[3] "

He nevertheless drew up the inventory of what was "absolutely sure":

> "1. Water that has been recorded and "replayed" by a computer to water cannot influence the parameters of an isolated organ infused by the same water. […]
> 2. What we record is indeed ovalbumin. All the criteria, which I will not detail again, are present. Except that it is found on a floppy disk "water" and vice versa. […]
> 3. It means that the system stumbles (do not ask me how) as if there was "persistence" and that, although we believe ovalbumin is recorded, we sometimes record water and vice versa."

An issue that is not addressed by J. Benveniste is the fact that the "inversions" are quite infrequent as we previously noticed with the open-label recordings performed at the same time as the blind recordings.[4] Besides, he did not evoke either the fact than the experiments performed "in house" – and not during public demonstrations, such as the "High Masses" at the Cochin Institute – are most often successful. This was involuntarily illustrated by J. Benveniste during his letter where he reported the results of experiments of limited size and completely performed in house:

> "We have just made two experiments at Cochin, perfect successes in the following conditions: laptop computer, naked sensor, no

> box of Faraday, no cylinder of mumetal. Recording of "water" files one after the other on floppy disk coming from a brand new box. One switches off the computer, one talks 5 min and then recording of "ova" files, saved without blinding. All is thus done open-label without a screen, etc. Then two operators using a software on the laptop erase the hours of recording and rename the files with random numbers".

I report these technical details to show again the obsession of J. Benveniste for the IT media which could be the source of a possible "persistence", what led him to use floppy disks "coming from a brand new box". We also note that all the processes which had previously been considered as progress, for example protection from ambient electromagnetic waves (Faraday cage, box of mumetal) are now forgotten and neglected. He pursued :

> "The results were excellent. For the first one, I only knew the code. The second one was recorded in Cochin by Pete Jurgens alone and then coded at Clamart by Francine Joly and Francis Beauvais. Neither me, nor Jamal knew the codes. Here are the results of the second one […]. A third experiment is on going. […]"

The results of these "second" and "third" experiments mentioned by J. Benveniste are presented in Table 16.2. The first experiment was performed on October 16th, 1996 and the two next ones on October 22nd and 25th. In these last two experiments, which took place in-house, but blind for the experimenter J. Aïssa, one notices that it was a success because the lowest effects fitted indeed "water activity" and the highest effects fitted "ovalbumin activity". It was then very difficult to understand why such successful results were not obtained during the public experiments.

In-house experiment of October 22nd, 1996 ("second experiment")

Tested recordings	Number of measurements	Maximal changes of coronary flow (%)	Biological activities in increasing order	Unblinding
Blind (in-house) tests				
A	2	2.4 ± 0.1	1	Digital water
F	2	3.1 ± 1.4	2	Digital water
B	2	5.7 ± 1.7	3	Digital water
E	2	21.0 ± 5.7	4	**Digital ova**
C	1	27.3	5	**Digital ova**
D	1	31.1	6	**Digital ova**
Open-label tests				
Ova 0.1 µmol/L	2	28.6 ± 1.1	-	-

In-house experiment of October 25th. 1996 ("third experiment")

Tested recordings	Number of measurements	Maximal changes of coronary flow (%)	Biological activities in increasing order	Unblinding
Blind (in-house) tests				
D	3	2.9 ± 1.2	1	Digital water
C	2	3.9 ± 1.8	2	Digital water
F	4	7.4 ± 5.5	3	Digital water
B	3	14.3 ± 10.9	4	**Digital ova**
A	2	22.7 ± 1.6	5	**Digital ova**
E	1	42.2	6	**Digital ova**
Open-label tests				
Ova 0.1 µmol/L	2	39.4 ± 9.8	-	-

Table 16.2. In-house experiments of October 22nd and 25th, 1996.
The "second" experiment mentioned by J. Benveniste in his letter of October 24th, 1996 (see text) included 6 recordings (3 ovalbumin and 3 water); the recordings were performed in Cochin institute on October 22nd and were tested blind for the experimenter on October 22nd and 23rd. The "third" experiment was recorded on October 25th in Cochin institute. The recordings were tested from October 25th to 30th; for technical reasons, only the results of October 28th and 30th were included in the analysis. Despite the variability of the results of these two experiments, after unblinding it turned out that the 3 most active recordings (on average) were indeed the 3 "active" recordings (Digital ova). These experiments were performed in blind conditions for the experimenter; there was a new interim blinding during the experiment of October 25th, but not for the experiment of October 22nd.

"An irritating problem, which has nothing to do with the content of the experiment"?

After these successful, but in-house experiments, a new "public" attempt took place on November 4th. Public is perhaps not a very appropriate term because only two people not belonging to the team were present in the Cochin institute to help J. Benveniste and one of his collaborators. [5]

Tested recordings	Number of measurements	Maximal changes of coronary flow (%)	Biological activities in increasing order	Unblinding
Blind (in-house) tests				
n°9	2	2.1 ± 0.0	1	Digital water
n°3	4	3.0 ± 1.2	2	Digital water
n°6	2	3.2 ± 0.1	3	Digital water
n°7	2	4.0 ± 0.0	4	**Digital ova**
n°5	2	5.1 ± 2.3	5	**Digital ova**
n°2	3	8.6 ± 4.2	6	**Digital ova**
n°4	1	14.3	7	**Digital ova**
n°8	1	16.7	8	Digital water
n°1	3	17.4 ± 4.1	9	**Digital ova**
n°10	2	22.6 ± 13.2	10	Digital water
Open-label tests				
Digital ova	2	14.7 ± 1.9	-	-
Ova 0.1 µmol/L	4	35.2 ± 14.3	-	-

Table 16.3. Public experiment of November 4th, 1996. The experiment was tested from November 5th to 8th, 1996 and the unblinding was done on November 8th. There was no in-house blinding.

As we can notice on Table 16.3, the experiment was once again a failure. These results were received with fatalism. Nevertheless, as Sisyphus and his boulder, J. Benveniste did a new "private" experiment. A "Cochin-type experiment" was thus performed on November 13th, 1996. And again, in spite of important variations of the measurements for some samples, if we consider the means of the 4 more active and the 4 less active, the samples were in the expected order (Table 16.4).

Tested recordings	Number of measurements	Maximal changes of coronary flow (%)	Biological activities in increasing order	Unblinding
Blind (in-house) tests				
n°1	2	3.1 ± 1.5	1	Digital water
n°7	6	4.2 ± 3.3	2	Digital water
n°4	5	4.6 ± 6.2	3	Digital water
n°2	3	5.7 ± 5.7	4	Digital water
n°6	8	9.7 ± 9.0	5	**Digital ova**
n°5	4	16.2 ± 6.7	6	**Digital ova**
n°8	1	18.0	7	**Digital ova**
n°3	1	20.0	8	**Digital ova**
Open-label tests			-	-
Ova 0.1 µmol/L	4	25.9 ± 6.2	-	-

Table 16.4. In-house blind experiment of November 13th, 1996.
The recordings were tested from November 13th to 18th. There was an additional blinding for the last measurements. The recordings that were on average the most active correspond well to the recordings which were supposed to be active (digital ova).

At the end of November, J. Benveniste summarized the situation in these terms:

> "Here is where we stand:
> We have just made 5 in-house blind experiments, among which 4 were in Cochin. In spite of some irregularities of response of the sensor which we detected (thus showing the difficulty making blind experiments with this biological system where we inject the samples one after the other on the same organ during 6-8 hours), we did not make errors. […] On the other hand, during the last public experiment, on 4/11/96, many activities were inverted. Recordings of ovalbumin had no activity, something which is still possible if the recording is missed. Indeed, the recordings of 4/11, made without external amplifier were weak. Much more surprising, some recordings of water had the typical activity of ovalbumin […] what is obviously impossible. This is indeed a substitution because the recordings are "true" or "false" but always work in the same way. How these substitutions occur? No hypothesis is likely. What can we do? We are going to redo a public experiment (4 Ova and 4 Water) by adding an additional precaution which we tested in the last two in-house experiments: every step will be recorded on an external hard disk. In this way we can compare the profiles of each

> recording […]. The cartridge of the hard disk will then be entrusted to the manager's assistant of the ICGM of Cochin where the recordings are done. We will get back it only after the unblinding. We should understand this irritating problem, which has nothing to do with the content of the experiment, but which blocks us for one year." [6]

One has the feeling that J. Benveniste did not know which solution to opt for. In spite of these improper substitutions, he clung up – with good reasons – to the fact that some recordings of "water" had an incomprehensible ovalbumin-type activity. It is his own "*E pur si muove*". As to whether "this irritating problem does not have nothing to do with the content of the experiment", nothing is less sure and one may be entitled to disagree with J. Benveniste.

J. Benveniste concluded by scheduling a public experiment for December 4th. This experiment was in fact the swan song of the "Cochin experiments". Indeed, because of a lack of sensitivity of the hearts of guinea pigs, the experiment was not pursued until term and only the first 7 recordings were tested (Table 16.5). After unblinding, the most active samples were supposed to be inactive!

Tested recordings	Number of measurements	Maximal changes of coronary flow (%)	Biological activities in increasing order	Unblinding
Blind tests				
n°6	2	4.0 ± 2.0	1	**Digital ova**
n°3	8	4.4 ± 0.9	2	**Digital ova**
n°2	10	4.5 ± 0.9	3	**Digital ova**
n°4	7	9.1 ± 3.5	4	Digital water
n°5	7	12.8 ± 8.8	5	Digital water
n°7	1	13.9	6	Digital water
n°1	5	19.3 ± 12.1	7	Digital water
Open-label tests				
Eau num	7	5.2 ± 5.7	-	-
Ova num	12	12.9 ± 4.2	-	-
Ova 0.1 µmol/L	9	19.0 ± 4.0	-	-

Table 16.5. Public experiment of December 4th, 1996.
The measurements were performed from December 4th to 24th. The experiment was unblinded only on April 28th, 1997. There was in-house blinding during the tests. Ironically, there were the recordings which had the highest mean biological effect which were supposed to be inactive.

The year 1996 finished in such an experimental mess that it was difficult to imagine how to escape this obsessing and incomprehensible circle. Nevertheless, quite unexpectedly the year 1997 offered to J. Benveniste the possibility of believing in brighter future.

Notes de fin de page

[1] Letter of J. Benveniste "to the participants in transmission experiments" of September 13th, 1996.

[2] Letter of J. Benveniste to P. Lacombe of October 8th, 1996.

[3] National Road not far from the laboratory…

[4] Except precisely for this experiment of September 30th, 1996 where samples from open-label transfers were nevertheless blind for the experimenter.

[5] The two participants who did not belong to the laboratory were Michel Troublé (Framatome) and Dominique Esclar (L'Oréal).

[6] Circulat letter of J. Benveniste of November 25th, 1996.

Chapter 17. The eve of a revolution in biology?

"We greatly developed the system"

About six months after the gloomy period of December 1996, J. Benveniste wrote to the "participants in the transmission experiments":

> "It has been a long time since you heard about our "world-famous" experiments. The last experiment at Cochin was made in the presence of the only two survivors of the group. We were able to measure only 7 recordings because guinea pigs then stopped answering to ovalbumin. The result was remarkable because, according to the code, 3 "water" recordings were declared "ovalbumin" and 4 "ovalbumin" recordings were declared "water", thus a perfect inversion. We can always imagine an error of recording or labeling of tubes at first, but it is clear that we did not master the reliability of these experiments at that time. We are certain that there is transmission, but almost every time the code answers us that our positive transmissions take place with water, what, as I explained it to you on numerous occasions, is only proving not that the phenomenon does not exist but that there is an error of procedure." [1]

And J. Benveniste announced important news:

> "For several months we greatly developed the system because we no longer need "water" as an intermediary for heart stimulation. We achieve, with an experimental protocol, a higher reliability since we had 12 exact results out of 12 blind experiments including some experiments performed with outside participants. The whole experiment with 3 signals lasts 3 hours. The participants blind the positive and negative activities on the computer and perform themselves the experiment by "playing" the signals one after the other. They can then verify the effect of the biological messages which they have just sent on the heart."

Finally he invited the addressees of the letter to participate in new experiments:

> "We plan to do 3 or 4 experiments each with two or three people and with the 12 blind experiments which are already done, it would be a sufficiently large series to envisage a publication.

> Indeed, these results plus those of Chicago would be completely demonstrative. We can welcome you till the end of July."

All that is therefore very exciting. Especially after the last failures with public demonstrations described in the previous chapter and for which we hardly saw a possible exit. Did J. Benveniste finally succeed and find the source of his difficulties? We are thus going to examine all this new information and at first let us describe how the experimental device was modified.

The new prototype

J. Benveniste and his collaborators used since early 1997 a new prototype. In fact, from a technical point of view, there was only a small change, but from a practical and scientific point of view it was a major change. Indeed, the output coil of the computer, which "imprinted" naive water in a tube, was replaced by a new coil *directly* connected to the Langendorff apparatus (Figure 17.1). Placed above the heart, the coil surrounded the glass column where the physiological liquid came down to irrigate the heart. It was not obvious that this way of proceeding would be efficient because there were many parameters that could be a concern such as the speed of flow in the column or the time of exposition of water to the electromagnetic frequencies. But, strangely, this new device was immediately operational without particular adjustments.

The advantages of this new system were important. Indeed, there was no intermediary – tube or vial – and consequently a large number of possible errors, contaminations or interferences were eliminated. From an experimental point of view, this new system was extremely "clean" and one could hope that "inversions" or other anomalies would disappear.

A new organization

Moreover, this technological breakthrough came along with a new organization of the laboratory and with its financing. One remembers that the laboratory had received credits from Inserm – in a progressive decrease – up to the middle of the year 1995. J. Benveniste had to find sources of funding for the functioning expense of the laboratory and the salaries of his collaborators. As he explained himself:

> "Since 1994, due to the lack of sufficient grants, I am forced to dedicate a large part of my time and of my energy in searching contracts intended to finance the functioning of my team, or more precisely what remains: two technician scientists and some volunteers. For 1995 and 1996, I obtained subsidies of a few

hundred thousand francs from Bouygues group, via its water distribution subsidiary, and from the manufacturer of homeopathic medicine Dolisos. In 1997, these contracts were not renewed." [2]

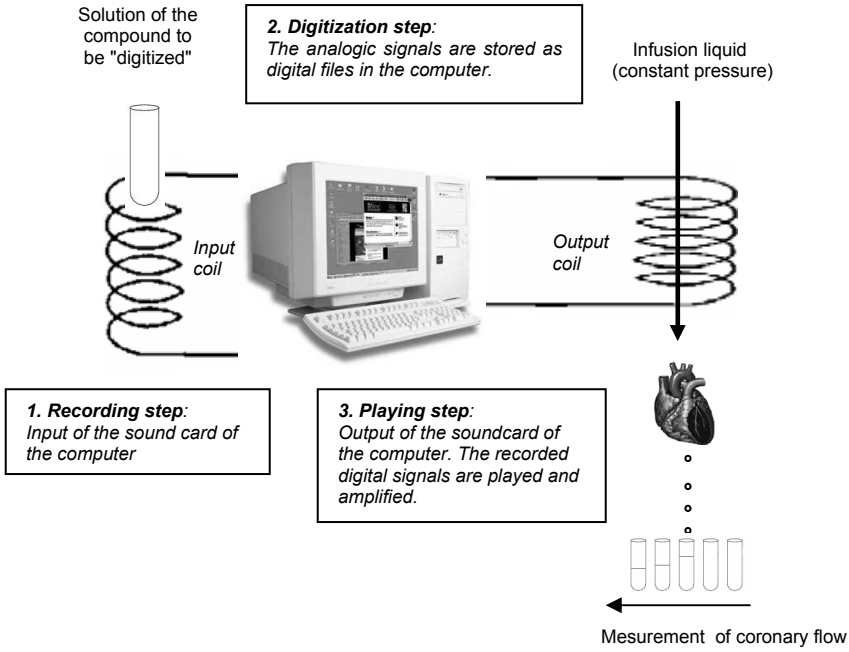


Figure 17.1. Third prototype for transmission of biological activity. The evolution is obvious after comparison with the two previous prototypes described in Figures 1.1 of Chapter 1 and 12.1 of Chapter 12 of the second part. Compared with the previous prototype, the "digital signal" was directly transmitted to the heart through the column of infusion liquid around which an electric coil (solenoid) was arranged. Therefore, intermediate water was no longer necessary.

Indeed, in February 1996, one of the sponsors who contributed most to the financing announced that he will not honor the commitment which he had taken for the coming year:

> "Martin Bouygues withdrew in his turn, depriving Benveniste of an annual 500 000-franc contribution. His last subsidies result

> from a Swiss banker and from a small penniless association, Innovative Science." [3]

Nevertheless, the laboratory survived and J. Benveniste wrote in 1997 [4]:

> "At present, new investors support my researches, in particular agri-food and water distribution firms and one French IT company, interested in the future possibilities opened by my studies in the field of the electronic transmission of the molecular signals. […]
>
> A friend Swiss banker, amateur of physics, continues too, for several years to grant me. Finally, the small association Innovative Science, created on my initiative, composed of a few hundred doctors and researchers, contributes to the survival of the team within its modest funds." [5]

The Swiss banker was Marcel Odier who, with his wife Monique Odier, led a small association which they created and was intended to support research in the controversial domain of parapsychology. This foundation was created in Geneva in 1982. Louis Pauwels was one of the founder members and Rémy Chauvin and Olivier Costa de Beauregard were among its scientific consultants.

As for the association Innovative Science that J. Benveniste had created, it allowed him to manage the diverse grants he received including the small gifts of a few hundreds of members. But the association was dissolved in November 1998. Indeed, J. Benveniste then created a limited company called Digibio in November 1997. At the same time, he met a 33-year old engineer, D. Guillonnet. Awarded a diploma from the *École Centrale* (French engineering school), the latter was an information technology specialist. His knowledge could allow analyzing the digitized information from biological molecules. D. Guillonnet brought not only his knowledge to the improvement of the system of digitization-transmission, but he also played an important role in the implementation of the limited company. A web site was then created to improve the "communication" of the company and an "industrial" strategy was set up including a search for financial partners and patenting.

These structural changes were thus a real transformation. Furthermore, in 1995, administrative reasons made J. Benveniste leave his premises which occupied a floor of the building of Inserm at Clamart. He thus withdrew in a prefabricated construction built in 1986 when the laboratory became too small. These additional premises had allowed accommodating a research team. It is now in this cramped place that the future of "digital biology" was going to

happen. J. Benveniste named his new laboratory "Laboratory of Digital Biology" when he could not longer use the name "Inserm U200".

The Digibio company was based on the model of a web-based start-up. At the end of 1990s, at the time of the speculative Internet "bubble", these young companies were on a roll and the economic newspapers were fond of some of these success-stories. The purposes of Digibio such as they were presented in the promotional documents or on the web site evoked the numerous possible applications of "digital biology", in particular in the field of agro-food industry and environment. It was thus planned to develop applications to detect contaminant microorganisms or genetically modified organism in food, to analyze the quality of water or to develop diverse biological tests to detect viruses and bacteria. Of course, biomedical applications were not forgotten and clinical tests to detect antibodies, antigens, bacteria, viruses and prions were evoked. The interest of these applications was also the possibility of realizing remote tests. The "recording" of the "digital signature" of a sample could be realized on the spot and its analysis could be centralized via the Internet network. It was also planned to improve the quality control of the manufacturing of the homeopathic medicines. Finally, "electromagnetic" pesticides, food additives, local treatments and obviously "digital" pharmacological treatments could be developed.

But the texts and the scientific results stemming from this new structure were then ambiguous. Was it always basic research or marketing? It is admittedly not specific to Digibio: the fundamental, industrial and commercial aspects are frequently entangled in young biotechnology companies. The peculiarity of the new structure of J. Benveniste was that the promises of development were based on fundamental principles that still needed to be proven.

One of the most visible consequences of this evolution was the disappearance of the public experiments. These "High Masses" which were formerly celebrated in the Cochin institute in front of numerous "believers" (at least at the beginning) did not take place any more. This retreat did not favor communication with other scientists who were now asked to sign "confidentiality agreements" as it is usual in industry, but rarely in academic circles.

New experiments rich in promises

The contribution of D. Guillonnet during this period was important, as was at their time the one of M. Schiff or A. Spira. D. Guillonnet was a regulating and structuring element who not only approached the problem with a new eye but

also brought rigor to the experiments of the team of J. Benveniste. The arrival of the engineer graduate of the *Ecole centrale* came along with a revision of the system of acquisition of the "biological signals". The team hoped that the "anomalies" were nothing more than a bad memory. The complete revision of the recording and playing system for the "biological activities" should protect from "wild transfers". The team once again trusted the future and it was in a more secure atmosphere that new experiments took place, sometimes with the cooperation of visitors.

Soon after his arrival, D. Guillonnet suggested an important modification of the recording system. Until now the "signals" supposed to be emitted by the sample were passively recorded. With the aim to escape from the "background noise" of the environment, the engineer built a system where the sample containing the substance to be recorded was placed between two coils: one coil transmitted an electromagnetic signal which was a "white noise" intended to "excite" the sample whereas the other one collected the resulting signal from the sample.[6] The first attempts with this new device were fruitful. As we have already indicated, the novelty was almost always followed with success in this story.

During spring and summer 1997, numerous experiments took place. Among the experiments intended to perfect the system of recording and replay of the "biological activities", experiments containing a limited number of blind recordings were performed. These latter experiments allowed convincing the team itself that everything worked as expected and that it did not run after a fancy. For this purpose, a new substance was successfully "digitized". It was a calcium ionophore, a compound that has the property to help penetrate calcium ions through cell membranes. This type of product is frequently used by biologists because it allows "activating" cells. Here again, it was an immediate success and "digitized ionophore" increased the coronary flow in numerous experiments.

For these experiments, the members of the team – or some visitor of passage – blinded the recordings. These blind experiments had a moderate ambition: detecting one "active" recording among 2–4 other ones. Performed in the informal frame of the laboratory, these experiments were not reported in the usual letters of J. Benveniste "to the participants in the transmission experiments".

The letter of June 30th, 1997 quoted at the beginning of this chapter reported 12 successful experiments out of 12. In fact, 22 blind experiments were performed from March 24th to July 17th, 1997. When J. Benveniste wrote this letter, 19 out of 22 experiments had already been performed. However,

J. Benveniste evoked only 12 experiments because some of the blind experiments performed between April 8th and 15th gave improper results. Once again, the team broke out in a cold sweat. The sword of Damocles of the "wild transfers" remained threatening in the sky of Clamart.

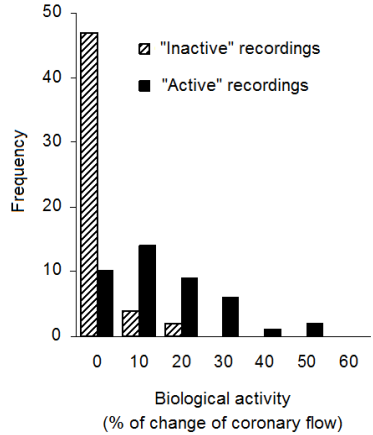


Figure 17.2. Statistical analysis of 22 in-house blind experiments performed from March 24th to July 17th, 1997 for a total of 53 measurements of water samples "imprinted" with "inactive" recordings and 42 measurements of water samples "imprinted" with "active" recordings. The mean change of the coronary flow with the "inactive" samples was 5.6 ± 5.2% whereas it was 20.3 ± 13.6% for the "active" samples.
Each percentage of *x*-axis is the lower limit of the corresponding interval (for example, "0" corresponds to changes from 0% to 10%).

However, if one were to globally analyze all the experiments – including those with problems from April 8th to 15th – everything indicates that the recordings of "digital ionophore" had a very different behavior from that of the controls which were supposed to be inactive. Indeed, the mean change of the coronary flow associated with "inactive" recordings was 5.6 ± 5.2% while the mean change with "active" recordings was 20.3 ± 13.6%. The distribution of the changes of coronary flow described in Figure 17.2 shows that the active and inactive recordings belong obviously to two very different "populations" as for their effects on the coronary flow, what the statistical tests easily confirm.

As already stated, some experiments were not a "success" according to the criteria of J. Benveniste who practiced an analysis on the model of "arrival of a horse race". In the present analysis, we simply tried to find out whether there

was a difference between two treatments, in other words if a "biological signal" emerged from the background noise.

Indeed many results in biology, medicine or epidemiology are presented using statistical tools. Nobody is surprised that in a clinical trial some patients are improved after having taken a placebo and on the contrary that an "active" medicine has no effect. What is requested in such a trial is that there are *statistically* more patients improved with the "true" medicine compared to placebo. One does not try to establish a link of causality at the individual level but *at the level of the population*.

The determination of J. Benveniste "to guess" the code without errors like the arrival of a horse rate was very demanding for these experiments of the summer 1997. If one places a limit at 10% to discriminate the biological "signal" (i.e. the change of the biological parameter) from background noise, one notices that approximately 3 times out of 4, a supposed active recording gave the "expected" effect and 1 time out of 9 a supposed "inactive" recording gave nevertheless an effect on the heart. A statistical approach was probably less spectacular and had certainly less "panache" than the announcement that "12 experiments out of 12 were a success" or "29 experiments out of 29 were a success" as it was the case with the experiments of Chicago. But if among all the experiments, some of them "failed", the result is less striking even though the overall result remains statistically significant and extremely interesting from a scientific point of view.

Indeed, by examining the results of Figure 17.2, it is difficult not to be intrigued because the possibilities to explain them are limited: 1) there was a real effect of the "digitized" biological activities, 2) there was an artefact, 3) the results were "made up". This last hypothesis is certainly an eventuality which as a matter of principle one should not neglect, but it supposes that the whole team was concerned including D. Guillonnet who had just joined the team. Among the coders of these experiments, there are a dozen of names (including mine…) corresponding to team's members, visitors as well as… the computer.

One thus understands why it was difficult for J. Benveniste and his team to just dismiss these results. Behind the closed door of the laboratory, the active digital signals induced clear-cut effects. Thus, in the experiments performed from 8th to 15th, April for which "oddities" (interpreted as "inversions") occurred, it is *a contrario* an argument in favor of the "sincerity" of the results. Indeed, the experiments were then performed "in house", without a skeptic public, without any particular stake or outside pressure. Paradoxically, the fact that "unexpected" results were obtained during this period is an argument in favor of the validity of the whole series.

Why is it then so difficult to set up a convincing experiment? A statistical presentation of the results – and not a presentation as a lottery – would raise maybe fewer issues. Such an approach would avoid focusing on the question of the "inversions" or "wild transfers" which in some cases could be only an *a posteriori* "explanation" of statistical fluctuations. Nevertheless, whatever the type of analysis, there was a real obstacle as soon as the stake was to "demonstrate" the reality of "digital biology" with an outside controller who blinded the experiments and assessed the rate of success. It is what we will be describing in the next chapter.

Notes of end of chapter

[1] Letter of J. Benveniste "to the participants in the tranmission experiments" of June 30th, 1997.

[2] J. Benveniste. Ma vérité sur la mémoire de l'eau, p. 172.

[3] E. Fottorino. La mémoire de l'eau. Une vérité hautement diluée. *Le Monde*, January 23rd,1997.

[4] The text of the book of J. Benveniste "Ma vérité sur la mémoire de l'eau" [*"My truth on memory of water"*] is overall not bery different of the version of 1997 which he drafted with the help of François Cotte.

[5] J. Benveniste. *Ibid.*, p. 173.

[6] Technical details can be obtained in patent n° 6,541,978 of US Office of Patents: J. Benveniste and D. Guillonnet. "Method, system and device for producing signals from a substance biological and/or chemical activity" (April 1st, 2003).

Chapter 18. From revolution to depression

Where does the message hide?

J. Benveniste was well aware that one of the main stumbling blocks of his research was the fact that the electromagnetic "biological activities" and the effect on the biological system defined themselves mutually in a circular reasoning. A way for breaking this circle was for example to show that the structure of water was actually specifically modified after exposure to the electromagnetic waves. Another possibility allowed by the recording/digitization method was to find proof on what differentiated an "active" recording from an "inactive" one using well-established methods of signal analysis.

Using various computing tools of signal analysis, D. Guillonnet tried to show a difference in the frequency spectra of the recordings. But classic methods such as the Fourier analysis did not succeed in discriminating the various recordings which appeared to be nothing else than "noise". However, one could not rule out the possibility that the "digitized biological activity" was present only in some frequencies. Moreover, spectrum analysis is a complex specialty and other methods requiring sharp mathematical knowledge exist. It was thus decided to call on specialists of signal analysis, Professors Jacques Neyrinck and Mura Kunt, from the *Ecole Polytechnique Fédérale* of Lausanne (EPFL).

But, before starting these complex analyses, the EPFL team wished, with good reason, to convince itself about the reality of the claimed biological effects. Marcel Odier, the Swiss banker whom we have already presented, was an intermediary in Geneva for the establishment of a rigorous protocol which was acceptable for both teams. A common agreement on the protocol was obtained at the end of August and the recordings were performed in Lausanne on September 25th, 1997.

The Swiss experiment

On the appointed day, in the premises of the EPFL, J. Benveniste performed at first two open-label recordings labeled "Water-initial" and "Ionophore-initial". Then, in the presence of the only members of the EPFL, three "water" recordings numbered from "Water 1" to "Water 3" and three "ionophore" recordings numbered from "Iono 1" to "Iono 3" were performed. These 6 recordings were then distributed in a random manner according to a software in

10 blind recordings numbered from "Test 1" to "Test 10" (Figure 18.1). Some of the 6 initial recordings could be thus present in several copies. Then, to make sure that the experimental conditions did not vary with time, J. Benveniste once again performed two open-label recordings labeled "Water-final" and "Ionophore-final".

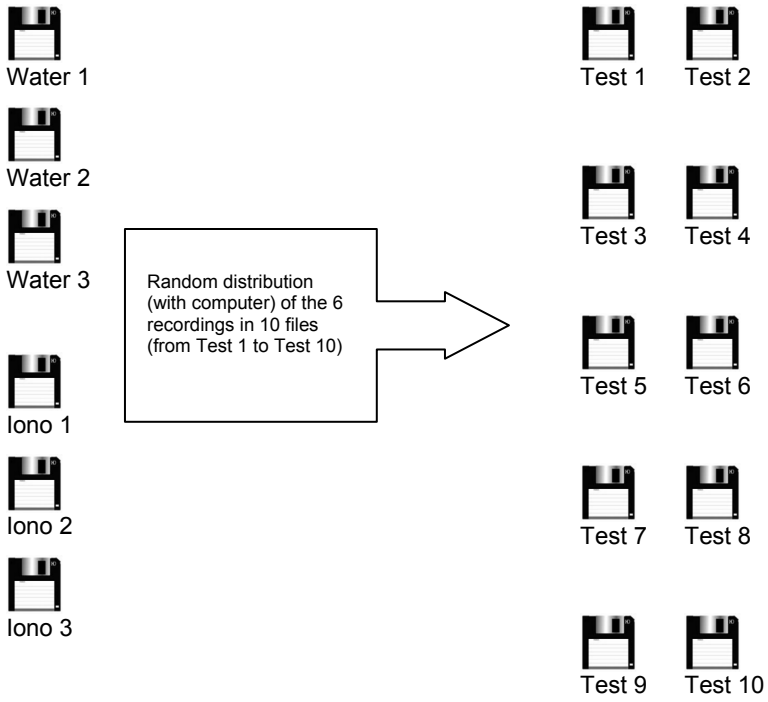


Figure 18.1. Design of the experiment at Lausanne of September 25th, 1997. The purpose of the experiment was "to guess" the order of the "active" and "inactive" recordings. Six recordings were performed (3 "active" named from Iono 1 to Iono 3 and 3 "inactive" named from Water 1 to Water 3). Then these recordings were distributed at random in 10 files. The only constraint was that each recording was present at least once among the 10 recordings to be tested (from Test 1 to Test 10). The number of possible "active" recordings varied thus from 3 to 7.
Two open-label recordings (one "inactive" and one "active") were also performed at the beginning and at the end of the experiment.

J. Benveniste came thus back from Lausanne with 10 blind floppy disks labeled from "Test 1" to "Test 10" and 4 open-label floppy disks (2 "water" recordings and 2 "ionophore" recordings). The recordings were tested during 12 sessions on 12 hearts from September 30th to October 15th. One of the two

systems of Langendorff having been unsettled since the recordings were now directly "transmitted" to the system, the recordings were not tested anymore on two devices of Langendorff in parallel. Nevertheless, numerous in-house blindings were performed and even the open-label recordings were tested blind for the experimenter. The results in increasing order of biological effects are presented in Table 18.1. We notice that 6 recordings induced a biological response (Tests 1, 3, 5, 6, 9, 10) whereas 4 others were inactive (Tests 2, 4, 7 and 8).

Tested recordings	Number of measurements	Maximal changes of coronary flow (%)	Increasing order of biological activities
Blind experiments			
Test 4	4	4.3 ± 0.2	1
Test 2	7	4.7 ± 1.6	2
Test 7	5	5.0 ± 2.4	3
Test 8	4	5.1 ± 4.0	4
Test 1	11	16.2 ± 9.1	5
Test 3	5	17.1 ± 10.8	6
Test 10	6	20.3 ± 15.8	7
Test 5	4	21.3 ± 11.3	8
Test 6	4	22.9 ± 10.3	9
Test 9	6	26.9 ± 16.2	10
Open-label experiments (in-house blinding)			
Digital Water "initial"	5	3.1 ± 0.3	-
Digital Water "end"	6	2.3 ± 1.2	-
Digital Iono "initial"	5	24.0 ± 4.5	-
Digital Iono "end"	7	25.2 ± 15.0	-
Iono 10^{-6} mol/L	8	36.7 ± 18.5	-

Table 18.1. Experiment of September 25th, 1997 (before unblinding) performed in Lausanne during the collaboration with the EPFL. We notice that 6 recordings increased the coronary flow with large changes (Tests 1, 3, 10, 5, 6, 9). Moreover, the open-label controls, which were performed to verify that the recordings were done in good conditions, were correct: some of them were done at the beginning of the session ("initial") before the blind recordings and others at the end of the session ("final"). This allowed making sure that the experimental conditions did not vary during the recording session. Note that these recordings were performed in open-label conditions but were tested after in-house blinding. [1]

An uncertain "genealogy"

At the end of the experiments – but before the unblinding – J. Benveniste, undoubtedly very careful for this experiment, wrote on October 15th a text

intended for the team of the EPFL in which he insisted on some possible issues:

> "Before interpreting the results, it is important to underline some points. We did not exactly reproduce the experiment of Chicago because in this last case files were separately transmitted to us every day, and especially we had made numerous preliminary trials (two months of on-the-spot development) to make sure that everything worked correctly in the setting of Chicago. On the spot, in Lausanne, we had to use our laptop computer in conditions which were different than in our laboratory, what obliged us, among other things, to keep a monitor switched on nearby. Furthermore, there is good reason to believe that the preamplifier of the input microphone of the laptop is clearly of less good quality than the Luxman preamplifier that we usually use."

J. Benveniste seemed to prepare the ground. He has already undergone so many setbacks during public experiments that he apparently has difficulty in believing that the trend could be abruptly reversed. But the technical arguments which he put forward to explain future possible "anomalies", even if they were acceptable, should also apply to the open-label recordings. Yet, one can notice that these open-label negative and positive controls were "as expected". J. Benveniste continued by evoking the various profiles of possible results:

> "Having clarified this issue, these experiments can give four types of results:
>
> 1. No influence on the heart indicating that we are not capable of recording a biological activity as we claim.
> 2. All the activities transmitted to the heart induce reactions on the coronary flow, which indicates that the effects are not specific and depend only on the presence of an electromagnetic field.
> 3. Some recordings induce cardiac reactions and others do not. However, after unblinding, we notice that the water recording (a control that should be negative in principle) induces reactions in a number *x* of cases, while ionophore recording induces no effect in a number *y* of cases. In this case, it is once again a purely technical problem of "crossing" that we show from time to time and that, for the moment, we do not understand and in fact have no control over it.

4. After decoding, it appears that we correctly identified the active and inactive recordings in a statistically significant proportion."

One understands that points 1 and 2 are envisaged only on a purely formal plan. The point 4 is a kind of Grail whose the quest remained fruitless until now. Thus, J. Benveniste was afraid to come again across the scenario of the point 3 with this problem of "crossing" which, as he soberly recognized, occurred "from time to time". We also note that for him this problem remained "purely technical". The foundations of "digital biology" are not being questioned. In any case, what alternative hypothesis could explain that some of the recordings had a biological effect in a repeated and coherent way? The results – unblinded – which he had in front of him allowed him to continue his analysis:

> "We already know that we are placed neither in the first case nor in the second one. We observed the usual series of activity between 20 and 40% and series of inactivity around 5%. However, in the preliminary experiments and in a once again inexplicable manner, open-label recordings corresponding to water gave typical activities while on the same day recordings corresponding to ionophore were inactive. On the next day, the activities were observed at their normal place. It is thus a problem of technical manipulation which makes some activities "inverted", but at present we do not understand why."

He finally specified how future efforts should improve the system:

> "In any case this experiment once again proves that our biological system reacts in a systematic way to some signals and never to others while the signals are quite similar and are replayed with identical power. We thus have to admit that the hearts of guinea pig reveal a message on the nature of the signal. It seems to us that the step replay/reproduction of a signal works correctly while the recording and the correspondence initial molecule/recorded signal must be again considerably improved."

And, he concluded, as if he anticipated the result of the experiment:

> "If after unblinding of the current experiment, we also found errors, we could exactly reproduce the experiment of Chicago by sending the activities one by one and probably by recording them on arrival on separate floppy disks (However Didier Guillonnet as an IT specialist cannot admit, on a strictly technical plan, that there could be the slightest difference between the recording on a hard

> disk and on a floppy disk). It seems more judicious to us to improve the recording because the anomaly – if there is an anomaly – is not apparent at the time of "replay".

The code is sent to Clamart on October 16th by fax and what J. Benveniste anticipated occurs. Without being cruel, one must admit that the failure exceeded all expectations…

Tested recordings	Maximal changes of coronary flow (%)	Increasing order of biological activities	Unblinding
Test 4	4.3 ± 0.2	1	Digital water
Test 2	4.7 ± 1.6	2	Digital water
Test 7	5.0 ± 2.4	3	**Digital Iono.**
Test 8	5.1 ± 4.0	4	**Digital Iono.**
Test 1	16.2 ± 9.1	5	**Digital Iono.**
Test 3	17.1 ± 10.8	6	**Digital Iono.**
Test 10	20.3 ± 15.8	7	**Digital Iono.**
Test 5	21.3 ± 11.3	8	Digital water
Test 6	22.9 ± 10.3	9	Digital water
Test 9	26.9 ± 16.2	10	**Digital Iono.**

Table 18.2. Unblinding of the results of the experiment of September 25th, 1997 done in collaboration with the EPFL. In spite of the internal coherence of the results, the distribution of the "active" and "inactive" tubes is not better than random. Indeed, the recordings supposed to be more "active" (bold characters), that is digital ionophore, are not grouped at the bottom of the right column (in the frame) but are distributed in a random way.

It was indeed a complete chaos (Table 18.2). Moreover the simple idea to duplicate some of the recordings was devilish and gave completely destabilizing results. Indeed, except the fact that the number of active recordings – not known by the experimenters – was not found (5 and not 6), it was especially the results with the duplicated recordings that were particularly destructive for the credibility of the experiment in front of the Swiss specialists. Because, as for the experiments with G. Charpak, they can judge only the part of the experiment that they controlled, namely recording and blinding of the various samples. Let us see the "genealogy" of each of the recordings and the corresponding results that is displayed in Figure 18.2. The recordings "Water 1", "Water 3", "Iono 1" gave positive or negative tests after simple duplication! Nevertheless each of these recordings gave coherent results in numerous measurements (with blinding within the team of Clamart). It became difficult for J. Benveniste to assert that the problem would be situated rather at the time of the recording.

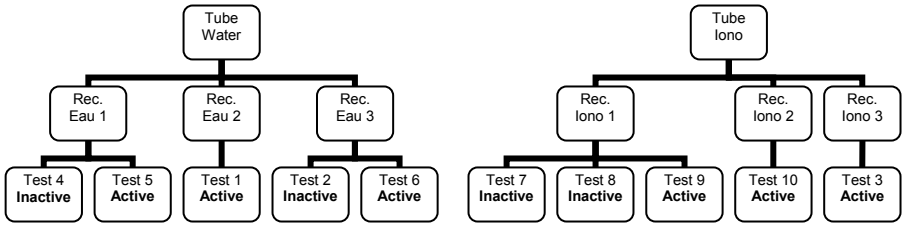


Figure 18.2. Three recordings (Rec.) of water supposed to be inactive numbered from "Water 1" to "Water 3" and three recordings "ionophore" supposed to be active numbered from "Iono 1" to "Iono 3" were performed. These 6 recordings were then distributed in a random way according to a software into 10 recordings numbered in a blind way from "Test 1" to "Test 10". There were thus several copies of some of the 6 initial recordings. The origin of the recordings seemed to have no influence on the associated biological effect ("active" or "inactive").
The open-label recordings "Water" and "Iono" performed at the beginning and at the end of the experiment (not shown here) were associated with "expected" results.

Consequently, despite the successive improvements which were supposed to discard the stumbling blocks, J. Benveniste and his team were back again in the same configuration. It seemed that there was no progress and that the successive technical improvements had no incidence on the results of the experiments. It was as if the team of Clamart found in experimental results only information which was already available. Yet, once again, in-house blinding was done. Needless to say that the collaboration with the specialists of signal analysis could not continue in these conditions. The EPFL team suggested to postpone the collaboration until the "technical problems" would be fixed.

Notes of end of chapter

[1] There are some minor differences in the reanalysis of the results for the calculation of the mean percentages of cornonary flow changes compared with the results calculated by the team of J. Benveniste and transmitted to the EPFL.

Chapter 19. When caffeine boosts memory

The "post Lausanne" period

After the results of the Swiss experiment of September 1997, one could think that the principle of the experiments with "digitization-transmission" would be profoundly questioned. Because of their merciless logic, the results of Lausanne indeed raised an extraordinary problem, which was scientifically fascinating, but particularly destabilizing for "memory of water" and "digital biology". However, J. Benveniste and D. Guillonnet interpreted again this failure as an unforeseen technical problem.

Nevertheless, we have *ad nauseam* already noticed in this text that it was not the first time that "coherent discordance" was reported throughout these years. Moreover, concerning the experiment of Lausanne, one could not speak any more about "wild transfers". As for D. Guillonnet, he did not seem aware or did not want to take into account the numerous experiments performed during the previous years. He seemed to think that J. Benveniste certainly had a brilliant intuition, but that the work which preceded his arrival was hardly reliable because of the rustic nature of the electronic devices which were then used. He did not seem to perceive that despite the notable improvements that he brought to the electronic system of recording and replay, one must admit that the question of the anomalies and other "wild transfers" remained totally unresolved. Was a long head rush into technique then the most suited answer to understand these phenomena?

If J. Benveniste had doubts on the future of his studies, he let nothing appear. Indeed, as a private company, Digibio must find financial partners that could help its development. Maybe he also thought that, over time, he would finally get out of this net where he locked himself. In the meantime, he must convince others of the legitimacy of this research and of its potential applications. As for D. Guillonnet, he was too much occupied by the writing of patents, the "improvement" of techniques, the visits of the laboratory or the supervision of the experiments. Indeed – and it is a major point – the experiments continued to convince the team that it worked not for nothing: hearts reacted to the "digital signals" that were administered to them.

Besides, a notable experimental modification was brought. Until now, only the absolute variations of the coronary flow were taken into account without worrying too much about the direction of this variation (increase or decrease of

the coronary flow). We indeed saw that the coronary flow could have several components – increase and/or decrease of the flow – with some stimuli and according to the experimental conditions. New experiments were then setting up where the experimental system allowed discriminating three different "signals". Thus, besides a signal "water" which had no effect and a signal "ionophore" which increased the coronary flow, the signal "caffeine" which decreased the coronary flow was administered to the heart. Therefore, it was not just a simple binary effect which was expected (it changes, it does not change) but a "language" with three words: it does not change, it decreases, it increases. It was extremely spectacular because the *specificity* of the transmission was thus directly highlighted.

The Sistine Chapel of "digital biology"

These experiments performed in 1997-1998 with "digitized caffeine" were one of the summits reached by J. Benveniste and his team to demonstrate the reality of the "electromagnetic biological activities" with the isolated heart model. The entire experiment could be indeed piloted from the computer: choice of the digital recordings on the hard disk of the computer, direct transmission to the heart (without injection and thus eliminating a possible source of artefact) and specificity of the "signal" directly visible on the changes of the coronary flow (Figure 19.1). Only the last step which consisted in measuring the volume of water infused every minute remained manual. But, even during this step, the experimenter did not "touch" the Langendorff apparatus. The reader could imagine that measurement errors of volumes were nevertheless possible. It is necessary to know that the variations of volumes were such that the effects were directly visible with the naked eye in the tubes which collected the liquid.

As an example, two experiments performed in 1997-1998 are shown in Figure 19.2. For any biologist, these experiments should give shivers. Only a cheating or a simulation, for example by injecting the "true" compounds at classical concentrations and not their "digital" counterparts would allow to obtain these profiles (let us repeat that this injection would then have been secret because these effects were obtained by "direct" transmission of the "signal" to the heart, without any injection).

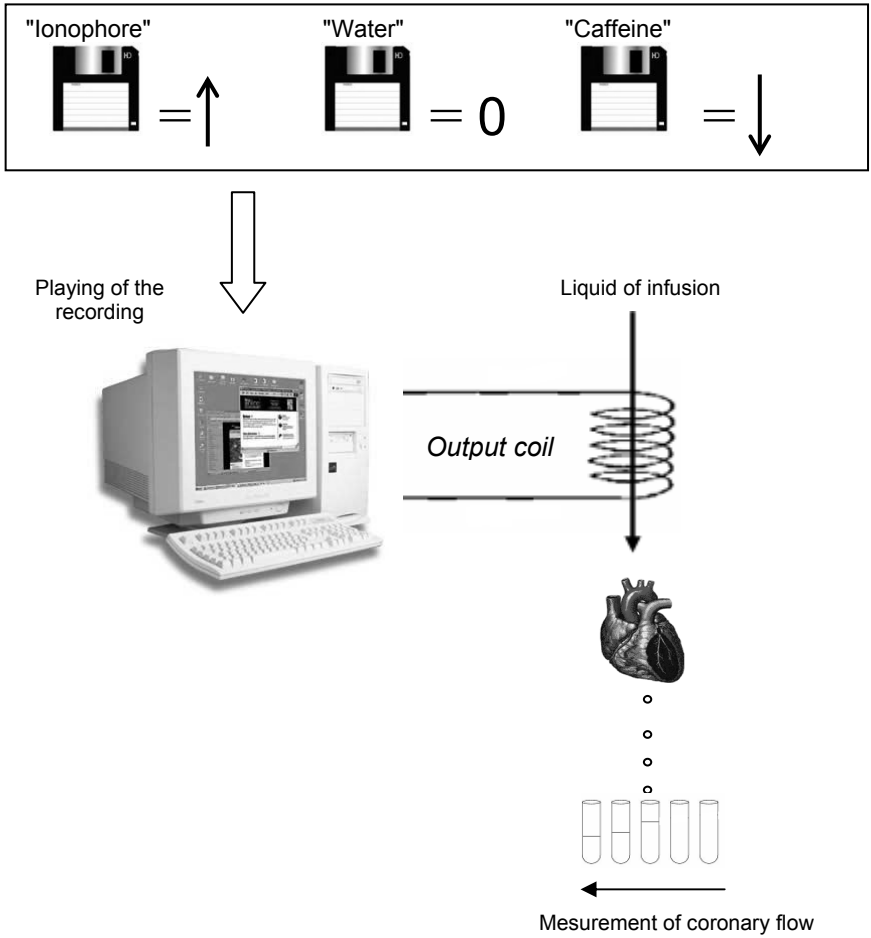


Figure 19.1. This experimental device was one of the summits of "digital biology". Indeed, three types of answers were obtained according to the nature of the recording: increase ("↑") of the coronary flow with the recording "ionophore", no variation ("0") with the recording "water" and decrease ("↓") of the coronary flow with the recording "caffeine". The important point is that the specificity of the recording was directly evidenced according to the direction of the change of coronary flow. Moreover, the fact that the electromagnetic flow was directly applied to the physiological liquid which infused the heart (without the need to inject a sample of "informed" water) avoided possible contamination. The only difference from an experiment to the other one rested on one of the three types of possible recordings that was "played" by the computer. Examples of the three types of results are shown in Figure 19.2 and Figure 19.3.

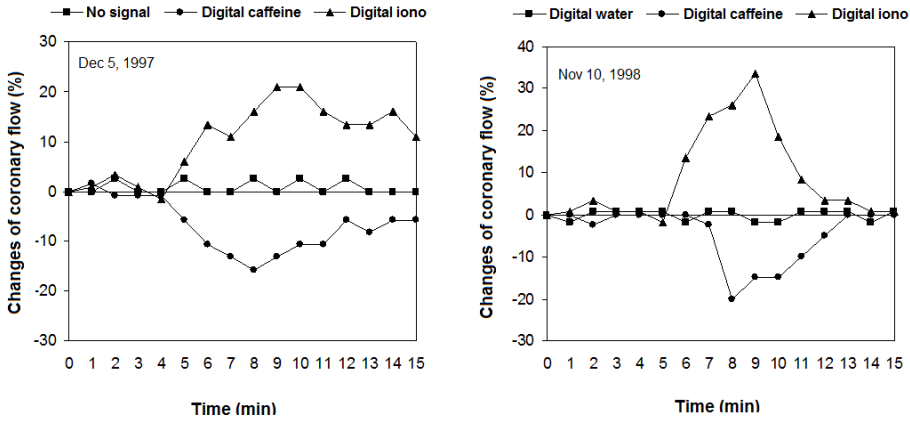


Figure 19.2. These figures represent two results obtained during routine experiments with "digital" caffeine or ionophore. The interest of these experiments was that the specificity was directly evidenced: decrease of the coronary flow for caffeine and increase for ionophore.

The experiment of November 10th, 1998, shown in Figure 19.2 was performed in the presence of visitors who were representatives of agro-food industry and gave rise to a funny scene. J. Benveniste brandished the tubes containing the fractions of liquid at arm's length so that the visitors and the staff of the laboratory could admire the results that were clearly visible with the naked eye. The scene irresistibly evoked the ceremony which the inhabitants of Naples periodically attend where a priest makes the believers notice that San Genaro's blood, as expected, miraculously liquefied.

In any laboratory and in a different domain of biology, these experiments would be included in an article intended for publication without any hesitation. These experiments were indeed particularly "clean" and without ambiguity on the outcome. Such "typical" experiments are always shown with pleasure to colleagues during scientific presentations. It is necessary to be aware that the only difference – if one admits that observed biological effects are different – is *a priori* only at the level of the digital recordings. The latter are in last analysis only a series of 1 and 0 in a computer hard disk; their reading is responsible of the variations of the electromagnetic flux which "imprints" water irrigating the heart. Well, the reader who has attentively read the previous chapters could say, but if the differences between the recordings are really so obvious, what happened if these recordings were "played" in blind experiments?

Where the Sistine Chapel is transformed into a labyrinth

During the summer 1998, attempts of public demonstrations were performed. The experiments were however not performed with all the ceremony of the "Cochin experiments". Discretion and low profile were more appropriate. J. Benveniste carefully avoided swaggering and he did not send his usual numerous mails to the "participants in the transmission experiments". The recordings and blinding were performed in "friendly" laboratories with tubes containing solutions of ionophore, caffeine or water. The recordings were then tested at Clamart on the Langendorff device.

It would be boring to present in detail all these experiments; therefore we show the results for the open-label recordings in Figure 19.3 and the corresponding blind samples are summarized in Table 19.1.

The difference of outcomes between open-label tests and blind tests was present once again with nevertheless an internal coherence. It was thus a splendid example of "coherent discordance". For each experiment, the expected biological responses were present, but their order seemed to result only from chance. In other words, one obtained the outcomes which were already known. One was thus able to find the various specific effects with the correct proportions (1:1:1 or 2:2:2). As usual, what was already known before the experiment was correct (the nature of the recordings and their number) but not what was precisely the object of the experiment (the order of the recordings). However, it could not be question to imagine that the experimenter had a secret pedal inducing at will the desired biological answer. Indeed some of the experiments received interim in-house blinding so that the experimenter tested them again without being influenced by the previous results).

Date	Place of recording and blinding	Sequence of recordings*	Observed sequence**	Concordance of sequences
June 26th, 1998	Lab. J. Testart (Inserm, Clamart)	↓ ↑ 0	↓ ↑ 0	Yes
June 30th	Lab. F. Russo-Marie (Inserm, Cochin institute)	↑ ↓ 0	↑ 0 ↓	No
July 8th	Inserm, Cochin institute	↑ 0 ↓	0 ↑ ↓	No
July 15th	Lab. of solid-state physics (CNRS Meudon-Bellevue)	↓ 0 ↑	↓ 0 ↑	Yes
July 20th	M. Odier (Geneva)	0 ↓ ↑ ↓ 0 ↑	↑ 0 ↓ ↓ 0 ↑	No
July 23rd	Lab. J. Testart (Inserm, Clamart)	0 ↓ 0 ↑ ↑ ↓	↓ ↑ ↓ 0 0 ↑	No
July 28th	Lab. J. Benveniste (blinding by a team member)	↓ 0 ↑ 0 ↓ ↑	↑ 0 0 ↓ ↑ ↓	No
July 29th	Lab. J. Testart (Inserm, Clamart)	0 ↑ ↓ ↓ 0 ↑	↑ 0 ↓ 0 ↑ ↓	No

Table 19.1. Results of the blind experiments. For each experiment, tubes containing water, caffeine or ionophore A23187 at classic concentration were blinded by people not belonging to Benveniste's team (except July 28th) and were then recorded by D. Guillonnet and/or J. Benveniste. The results obtained with the open-label recordings within each experiment to verify that the conditions of the recording were correct are represented in Figure 19.3.
* : ↓= caffeine ; ↑ = ionophore ; 0 = water.
** : ↓= decrease of coronary flow ; ↑ = increase of coronary flow ; 0 = no change.

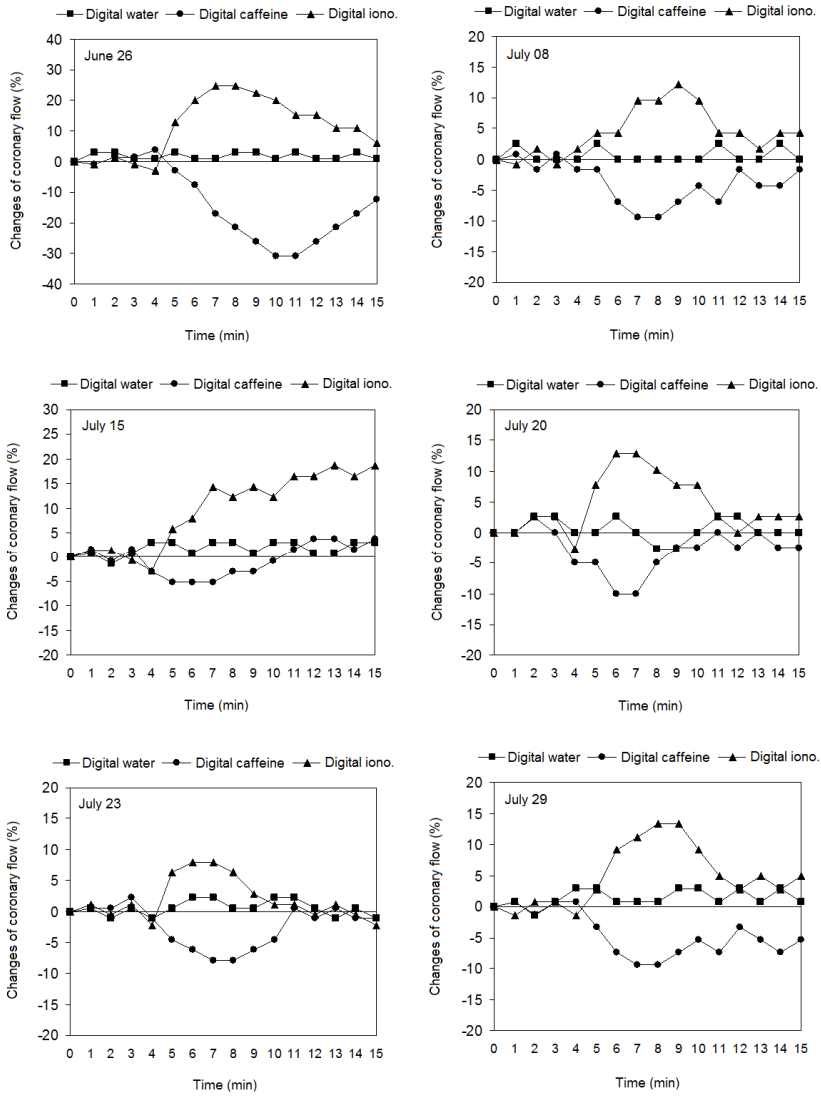


Figure 19.3. These 6 graphs correspond to open-label recordings performed during the experiments of June-July, 1998. The "signal" was directly broadcasted to the physiological liquid which irrigated the heart during 2 minutes (recordings of 1 second in loop). One notices that the results were homogeneous with a change of coronary flow which occurred generally from the 4th minute after the beginning of the broadcasting of the "signal". We also notice that it is easy to discriminate the 3 recordings, "water", "ionophore" and "caffeine", according to their effect on the coronary flow. The "specificity" of the different recordings is thus directly visible.

Headlong rush or salvation

As usual during this story, when the situation seemed blocked, an unanticipated new development occurred, generally as a new experiment or an experimental variant rich in promises. In this case, there was a new experimental system. Indeed, other biological systems were explored by J. Benveniste during these years. Some results had been announced a little bit quickly. Thus, the experiment of the mouse which was injected with water "imprinted" by "Valium signal" did not contribute to strengthen the credibility of "digital biology". Barely announced by J. Benveniste – with his well-known assurance – the experiment could not be reproduced however by the collaborators of J. Benveniste themselves. But it was too late, J. Benveniste had already informed many scientists, including G. Charpak:

> "Useless to speak to the laureate of the Nobel Prize in Physics about the new experiments of Doctor Benveniste with mice or Internet. After having "played" to a tube of "naive" water the frequency of Valium, the researcher catches a mouse and pricks it in the peritoneum. After a few minutes, the mouse stands still. Another, pricked with aqua simplex, continues to scamper on the lab bench. "We know how to record molecular activities on an IT medium, he wrote in October 1995 to Georges Charpak. I can go wherever I want along with a laptop computer and mice, and I can immediately demonstrate the presence of a powerful activity of water causing death of the animal."
>
> Today, Jacques Benveniste is however less categorical and admits that this experiment does not work any more with regularity. The Nobel prize laureate sees only a fraud here. "Ask to prick the mouse yourself, he advised us. He can very well touch the liver and administer a lethal dose with only water. Get the syringes analyzed. Nothing prevents him from introducing a product." [1]

An element seemed then inescapable to J. Benveniste. If he finally wanted "to break through", he had to find a biological system less "heavy" than the Langendorff device, which appeared difficult to be transposable in other laboratories, in spite of the spectacular effects it allowed. He also needed a model simpler to manipulate than a "whole" animal such as the "Valium model" in mouse. What J. Benveniste needed to convince was a simple experiment that most laboratories could reproduce. Moreover, a totally automatic system would be useful because it would allow in principle avoiding a possible influence of the experimenter and would be less questionable.

Among the various biological systems which were then assessed in the laboratory of Clamart, one of them emerged: it was easy to perform in any laboratory and it could be potentially implemented in an automatic device. As basophils had been replaced by the isolated heart, the latter was going in turn to be replaced by plasma coagulation.

Notes of end of chapter

[1] E. Fottorino. La mémoire de l'eau. Le temps des passions. *Le Monde*, January 22nd, 1997.

Chapter 20. Jacques Benveniste at Newton's house

A particularly simple biological model

This new promising system was simple and it appeared to satisfactorily respond to the electromagnetic transmissions. It consisted in making coagulate blood plasma in a tube. As we all know, plasma is the liquid in which blood cells are suspended. After a simple centrifugation of blood to which an anticoagulant has been added, blood cells are removed and plasma can be then frozen for storage and later use. For these experiments sheep plasma was generally used.

When one wanted to perform an experiment, plasma was defrosted; calcium chloride was added to overcome the effect of the anticoagulant and to activate the coagulation process. The "biological activity" of heparin, an anticoagulant, was recorded and digitized by J. Benveniste and his co-workers to demonstrate the reality of digital biology in this biologic model.

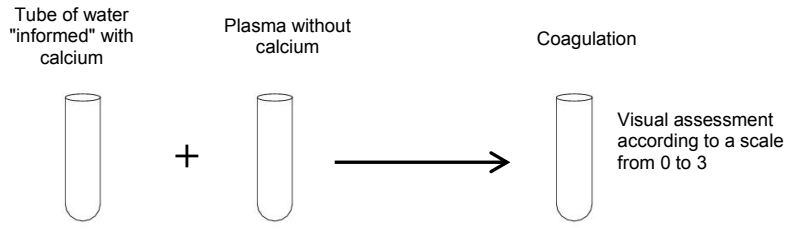


Figure 20.1. Principle of *in vitro* plasma coagulation. A solution of calcium ("informed" or not) was added to plasma. In the first experiments, coagulation was assessed with the naked eye (0: no coagulation; 1: starting coagulation, which is liquid plasma with a coagulation point; 2: moderate coagulation, which is viscous plasma; 3: complete coagulation).

The first experiments were performed in January 1999. As for the previous experiments of "digital biology", "naive" water was "imprinted" on the coil wired at the sound card of the computer. The recordings which were "played" to water were anticoagulants (heparin or hirudin) or water as control. In the first version of the experiment, coagulation was evaluated with the naked eye (Figure 20.1).

Besides this new model, J. Benveniste made a new observation which was not related to "digital biology", but that could be an argument on the role of water in the "amplification of the biological signal". This experiment which was firstly performed on the isolated heart, was also reproduced with the coagulation model. The experiment consisted in diluting a biological solution – a solution of hirudin in this particular case – until a very low concentration (10^{-12} mol/L). At this concentration, there were still molecules, but their concentration was too low to have any biological effect. However, J. Benveniste noticed that if the dilutions were made by shaking, then the solution at 10^{-12} mol/L had nevertheless a biological effect! "Controls" that were not shaken had no effect. For J. Benveniste, it was an argument in favor of the role of water in the transmission and amplification of the biological signals. It was maybe less spectacular than the electromagnetic transmissions, but this result could be easily reproduced in other laboratories and moreover without any electronic and IT equipment.

Other previous results were confirmed by the team of J. Benveniste on the system of coagulation, in particular with high dilutions. Thus homeopathic pills "heparinum 30 CH" bought in a pharmacy and dissolved in water exhibited anticoagulant properties in this biological model. The link with the previous experiments with high dilutions was thus maintained.

To Cambridge

One remembers the words of G. Charpak considering the results of J. Benveniste – if they were true – as the "biggest discovery since Newton". On March 10th, 1999, J. Benveniste went to Cambridge – "at Newton's home" – to make a conference on his experiments entitled "*Electromagnetically activated water and the puzzle of the biological signal*". J. Benveniste was invited by Brian Josephson, a Nobel Prize laureate in physics from the Cavendish Laboratory of the Cambridge University whom he had met during the conference in Bermuda of April 1988 about which we spoke in the first part. Since this conference, both men kept in touch. The Cavendish Laboratory is in fact the department of physics of the Cambridge University. It is there that the structure of the molecule of DNA was elaborated by J. Watson and F. Crick, a founding episode of the history of molecular biology.

Contrary to the ultra-rationalist G. Charpak, B. Josephson is interested in subjects in the margins of the science. It is true that Newton himself who taught at Cambridge set an example by studying alchemy during a large part of his life. As for B. Josephson, having received a Nobel prize at the age of 33 for the work he realized at the age of 22, he tempted to reconcile parapsychology and

quantum physics. He was a director of the Mind-Matter Unification Project of the Theory of Condensed Matter Group at the Cavendish Laboratory. This project was "concerned primarily with the attempt to understand, from the viewpoint of the theoretical physicist, what may loosely be characterized as intelligent processes in nature, associated with brain function or with some other natural process".

B. Josephson explained why J. Benveniste was invited to present his work to this weekly seminary of the Cavendish Laboratory:

> "While the results claimed may seem surprising, the Cavendish Laboratory has been host to many surprising discoveries during the 125 years of its existence, and the controversial nature of the claims was not seen as good cause to follow the herd and veto his making a presentation. In regard to the Nature condemnation of 1988, my conclusion at that time was that its authors had made an insufficient case for its headline claim "High-dilution experiments a delusion", and nothing since has led me to see the frequent denunciations of the work as anything other than the hysteria that frequently accompanies claims that challenge the orthodox point of view." [1]

The presentation made by J. Benveniste was for him the occasion to present his vision of the biological world and more exactly to explain "how molecules communicate". His "doctrine" had evolved. One is far from the few lines of the article of *Nature* of 1988 which briefly suggested that "water could act as a 'template' for the molecule, for example by an infinite hydrogen-bonded network, or electric and magnetic fields". Nevertheless, the presentation in front of the public including eminent physicists in the Pippard Lecture Theater of the Cavendish Laboratory was rather a personal conception of the world of the biological molecules than a real theory supported by experimental facts. Among the listeners, besides B. Josephson, other illustrious physicists attended the conference, such as Sir Andrew Huxley, Nobel prize laureate in Medicine and Physiology (with John Eccles in 1963) and former president of the Royal Society. J. Benveniste gave a first overview of the possible applications of his "discoveries":

> "Benveniste suggested that the specific effects of biologically active molecules such as adrenalin, nicotine and caffeine, and the immunological signatures of viruses and bacteria, can be recorded and digitized using a computer sound-card. A keystroke later, and these signals can be winging their way across the globe, courtesy of the Internet. Biological systems far away from their activating

> molecules can then – he suggested – be triggered simply by playing back the recordings." [2]

Then, J. Benveniste explained why his researches had exceeded the "simple" frame of high dilutions because now the aim of his studies was nothing less than "deciphering the language" of biological molecules:

> "Benveniste started by asking some apparently childish questions. If molecules could talk, what would they sound like? More specifically, can we eavesdrop on their conversations, record them, and play them back? The answer to these last three questions is, according to Benveniste, a resounding "Oui!" He further suggested that these "recordings" can make molecules respond in the same way as they do when they react. Contradicting the way biologists think biochemical reactions occur, he claims molecules do not have to be in close proximity to affect each other. "It's like listening to Pavarotti or Elton John," Benveniste explained. "We hear the sound and experience emotions, whether they're live or on CD."

He continued by explaining why the current vision of the molecular mechanisms was insufficient to understand the biological phenomena:

> "For example, anger produces adrenalin. When adrenalin molecules bind to their receptor sites, they set off a string of biological events that, among other things, make blood vessels contract. Biologists say that adrenalin is acting as a molecular signalling device but, Benveniste asks, what is the real nature of the signal? And how come the adrenalin molecules specifically target their receptors and no others, at incredible speed? According to Benveniste, if the cause of such biochemical events were simply due to random collisions between adrenalin molecules and their receptors (the currently accepted theory of molecular signalling), then it should take longer than it does to get angry."

In front of a public of physicists who were nothing but amazed about how molecules could emit electromagnetic waves of low frequency, J. Benveniste developed his argument of "beatings of frequency":

> "Benveniste's explanation starts innocuously enough with a musical analogy. Two vibrating strings close together in frequency will produce a "beat". The length of this beat increases as the two frequencies approach each other. Eventually, when they are the same, the beat disappears. This is the way musicians tune their

> instruments, and Benveniste uses the analogy to explain his water-memory theory. Thus, all molecules are made from atoms which are constantly vibrating and emitting infrared radiation in a highly complex manner. These infrared vibrations have been detected for years by scientists, and are a vital part of their armoury of methods for identifying molecules. However, precisely because of the complexity of their infrared vibrations, molecules also produce much lower "beat" frequencies. It turns out that these beats are within the human audible range (20 to 20,000 Hertz) and are specific for every different molecule. Thus, as well as radiating in the infrared region, molecules also broadcast frequencies in the same range as the human voice. This is the molecular signal that Benveniste detects and records."

If one were to summarize the reasoning, besides "high frequencies" there would also be "low frequencies" because of beatings and these low frequencies would be captured and recorded by the devices of J. Benveniste. But how to explain that one can then transmit the recording of a biologically active molecule to a biological system? Here again, J. Benveniste could exercise his innate sense of the metaphor:

> "If molecules can broadcast, then they should also be able to receive. The specific broadcast of one molecular species will be picked up by another, "tuned" by its molecular structure to receive it. Benveniste calls this matching of broadcast with reception "co-resonance", and says it works like a radio set. Thus, when you tune your radio to, say, Classic FM, both your set and the transmitting station are vibrating at the same frequency. Twitch the dial a little, and you're listening to Radio 1: different tuning, different sounds.
>
> This, Benveniste claims, is how millions of biological molecules manage to communicate at the speed of light with their own corresponding molecule and no other. It also explains why minute changes in the structure of a molecule can profoundly alter its biological effect. It is not that these tiny structural changes make it a bad fit with its biological receptor (the classical lock-and-key approach). The structural modifications "detune" the molecule to its receptor. What is more, and just like radio sets and receivers, the molecules do not have to be close together for communication to take place."

And at which moment water and its memory intervene?

> "Benveniste explains this by pointing out that all biological reactions occur in water. The water molecules completely surround every other molecule placed among them. A single protein molecule, for example, will have a fan club of at least 10,000 admiring water molecules. And they are not just hangers-on. Benveniste believes they are the agents that in fact relay and amplify the biological signal coming from the original molecule. It is like a CD which, by itself, cannot produce a sound but has the means to create it etched into its surface. In order for the sound to be heard, it needs to be played back through an electronic amplifier. And just as Pavarotti or Elton John is on the CD only as a "memory", so water can memorise and amplify the signals of molecules that have been dissolved and diluted out of existence. The molecules do not have to be there, only their "imprint" on the solution in which they are dissolved. Agitation makes the memory."

But some of the listeners asked: "So what do molecules sound like?":

> " "At the moment we don't quite know," says Didier Guillonnet, Benveniste's colleague at the Digital Research Laboratory. "When we record a molecule such as caffeine, for example, we should get a spectrum, but it seems more like noise. However, when we play the caffeine recording back to a biological system sensitive to it, the system reacts. We are only recording and replaying; at the moment we cannot recognise a pattern." "

J. Benveniste specified, abruptly caught up by his "transatlantic" dreams:

> "The biological systems do. We've sent the caffeine signal across the Atlantic by standard telecommunications and it's still produced an effect."

As for B. Josephson, although he was certainly not representative of the physicists who were present, the speech of J. Benveniste did not excessively shock him. He later made this remark about the hypotheses of J. Benveniste on "memory of water":

> "What science tells us about the possibility of the existence of "memory of water"? The scientists who are not erudite about water tend to have a naive vision of it: a liquid composed of H_20 molecules more or less isolated, in movement. In fact, water is more complex, with individual molecules temporarily agglutinating to form a network. It is not inconceivable that the interaction of

> these molecules could produce a mechanism that would allow memory of water. The scientists who are well informed about water take the proposal of memory much more seriously than those who are not informed." [3]

Demonstrations

J. Benveniste, D. Guillonnet and J. Aïssa came also to Cambridge to do demonstrations. A first experiment was performed on March 10th. It did not concern the electromagnetic transmissions strictly speaking, but rather the role of water as amplifier of the biological information. Indeed, as previously said, J. Benveniste noticed that biological solutions at low concentrations such as 10^{-12} mol/L which had no effect due to precisely this too low concentration could nevertheless have an effect if the solution was shaken. It was according to him the proof that water was capable of amplifying the "molecular signal".

Two blind experiments were performed at Cambridge: one was blinded by B. Josephson himself and the other one by D. Guillonnet. Each of the experiments included one shaken tube of hirudin 10^{-12} mol/L (= active tube), a tube of hirudin 10^{-12} mol/L that was not shaken (= inactive tube), a shaken tube of water (= inactive tube), a tube of water that was not shaken (= inactive tube). It was actually a success because the unique active tube was correctly designated in both experiments because it was the only one who delayed coagulation (Figure 20.2).

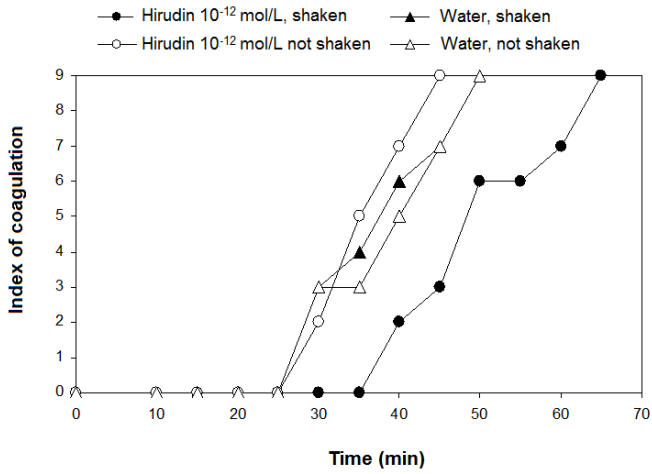


Figure 20.2. Experiment performed in Cambridge in the laboratory of B. Josephson on March 10th, 1999 and blinded by the latter. The purpose of this experiment performed with "low concentrations" of an anticoagulant (hirudin) was to illustrate the role of water as "amplifier" of weak biological signals: concentrations of hirudin at 10^{-12} M prepared with "shaking" had an effect and had no effect if not "shaken".
Each of the experimental points was performed in triplicate and coagulation was assessed from 0 (no coagulation) to 3 (maximal coagulation). The sum of 3 scores is shown at each time on the figure. Consequently the index of coagulation (sum of the scores of 3 tubes) cannot exceed 9 (maximal coagulation in 3 tubes). [4]

It was also planned to perform transmission experiments with "digitized hirudin", but the calibration of the experiment (determination of the optimal concentration of calcium) took time and a single open-label experiment was performed the next day. The experimental conditions were not ideal because coagulation was a little too fast; it was the tube with transmitted hirudin which had the shortest coagulation time, contrary to what was expected…

But, "fortunately", time was short and the team could hardly linger. Upon returning from this excursion, when J. Benveniste told the stay in the Cavendish laboratory to his collaborators stayed in Clamart, he confided with a half-smile and with the wrongly contrite look of a child who was caught with his fingers in the jam pot: "Maybe there was an "inversion" with the last experiment, but "he" did not realize it". As for B. Josephson, he told afterward the coming of J. Benveniste to Cavendish and he summarized the experiments he attended in these terms:

> "Benveniste had brought the experimental equipment and he reproduced his most recent experiments in front of us. These have proved as convincing as possible, considering the limited time which we had." [5]

And here is J. Randi again …

B. Josephson appeared to have been convinced by these experiments because a short time after, he was embroiled in a debate with the "skeptic" Robert Park. Advocating for J. Benveniste and his work, B. Josephson went perhaps a bit too far by proposing a public demonstration of the new results of J. Benveniste. *Time Magazine* echoed these exchanges:

> "Nobel laureate Brian Josephson was incensed. He had just read a column by physicist Robert Park poking fun at the work of a French biologist who maintains that the benefits of homeopathic medicine can be transmitted electronically. Josephson, who since winning the 1973 Nobel Prize for Physics has developed an interest in fringe sciences, fired off an e-mail challenge to Park, who promptly responded. Their exchange could lead to the first rigorous test of one of the world's most widely practiced alternative therapies." [6]

What would be this test?:

> "In his challenge, Josephson suggested a randomized double-blind test. Park, a longtime critic of homeopathy, was delighted to accept and is now close to agreeing with Josephson on a protocol. In one proposal, samples of water, some of which have been given the Benveniste treatment, would be examined by the biologist himself, who would then attempt to identify which, if any, had been rendered homeopathic (*sic*)."

J. Benveniste and D. Guillonnet confirmed these exchanges in one of Digibio's newsletters of 1999:

> "Further to an abundant correspondence between Brian Josephson, the physicist Robert Park and ourselves, the American Society of Physics (APS) expressed its interest to participate in the demonstration of a specific biological effect of a recorded signal."

But J. Benveniste was hardly favorable to this confrontation which was decided by others, even if one of them is a faithful support, furthermore a Nobel prize laureate:

> "Yet Benveniste seems hesitant. Some "variables," as he puts it, including financing, remain to be discussed. Until now, neither the effectiveness nor the putative mechanism of homeopathy has ever been subjected to what nonbelievers would call a scientifically valid test. Indeed, the U.S. National Center for Complementary and Alternative Medicine, which has $ 50 million to spend this year for just this kind of trial, has yet to sponsor even preliminary tests. Now it may be upstaged by a laureate and a skeptic." [7]

Another "skeptic" was J. Randi who suggested putting his million dollar prize at stake, which was still available to those who would demonstrate a "paranormal" effect… or related to homeopathy (what did not seem very different to him). The first reason which made J. Benveniste seemed reluctant was that he was well placed to know the danger to experiment on a stage. Indeed, as B. Josephson wrote to J. Randi:

> "I can only urge both you and Dr. Park to be patient. Dr. Benveniste considers he is in a kind of situation wished upon him by the scientific community where 'extraordinary claims demand extraordinary evidence', and he is taking steps to provide that 'extraordinary evidence'. This, however, takes time and, as I say, one must be patient.
>
> I must also make it clear that the idea of some official test such as one under the auspices of the APS was always my idea and not his, and he has always made his preference for going instead along the conventional scientific path involving submitting the evidence to a referred scientific journal clear. Given the way a past editor of Nature exploited his editorial privilege to publish a seriously flawed (on scientific grounds) denunciation of his experimental work, this rather negative attitude to 'investigations' can perhaps be understood." [8]

Another reason of these hesitations during this period when Randi continued to propose putting his pot of money at stake, was that J. Benveniste was in front of a new "miracle". After the "contaminated serum", "wild transfers" and "inversions", this was now a new challenge which was as unexpected and disturbing that J. Benveniste was once again confronted to: the "eraser effect".

Notes of end of chapter

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[1] B. Josephson. Molecular memory. *The Independent*, March 22nd, 1999.

[2] L. Milgrom. The memory of molecules. *The Independent*, March 19th, 1999.

[3] B. Josephson. Forword to "Ma vérité sur la mémoire de l'eau" of J. Benveniste, p. 8.

[4] Plasma coagulation is very sensitive to calcium concentration. Therefore, each experiment was preceded by a pre-experiment intended to determine the optimal calcium concentration. In the present case, the experiment had been performed with two concentrations of calcium chloride: 5.5 and 6 mmol/L. In order to simplify, we have shown only the experiments made with 6 mmol/L; the experiments with 5.5 mmol/L led to the same conclusions.

[5] B. Josephson. *Ibid.*

[6] L. Jaroff. Homeopathic E-Mail; Can the "memory" of molecules be transmitted via the Internet? *Time magazine*, US edition, May 17th, 1999 p. 77.

[7] L. Jaroff. *Ibid.*

[8] E-mail of B. Josephson to J. Randi of August 11th, 2000.

Chapter 21. When memory is erased

"One person in our lab was unable to see the effect"

Before talking about this new surprising episode, let us see first how the method of coagulation was improved a few months after the return from Cambridge. Indeed, coagulation was initially assessed with the naked eye and the effect was quantified using a semi-quantitative scale. This way of proceeding had the advantage of simplicity, but it was not very precise and one could blame its subjectivity.

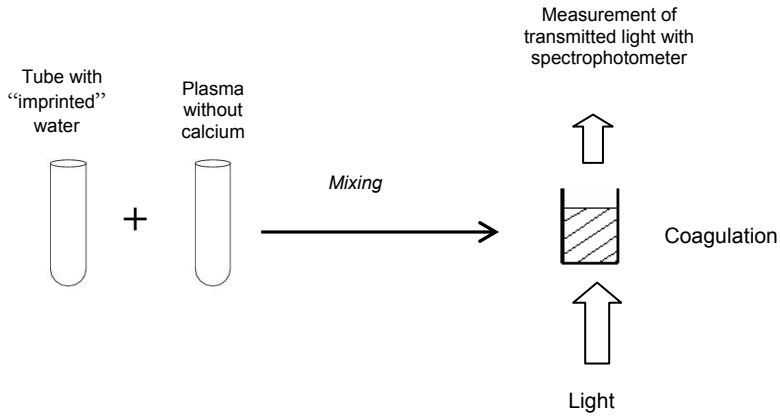


Figure 21.1. Principle of plasma coagulation measured by optical density. Water having received "anticoagulant" information (heparin) and containing calcium (which triggers coagulation) was added to plasma. Coagulation was assessed according to the quantity of light which crossed the sample: the more coagulation increased and the more light intensity decreased. A spectrophotometer (wavelength: 630 nm) measured optical density every 10 minutes.

In order to precisely measure the evolution of the coagulation with time, the technique was adapted for "96-well plates" which are well known in biology laboratories. These plastic plates have 12 rows and 8 columns of small wells where reagents and cells are placed. The interest for the present experiment is that coagulation could be precisely quantified by an automatic

spectrophotometer. The coagulation was estimated by the measurement of the quantity of light that crossed the well: when the coagulation increased, the amount of light that crossed the content of the well decreased (Figure 21.1).

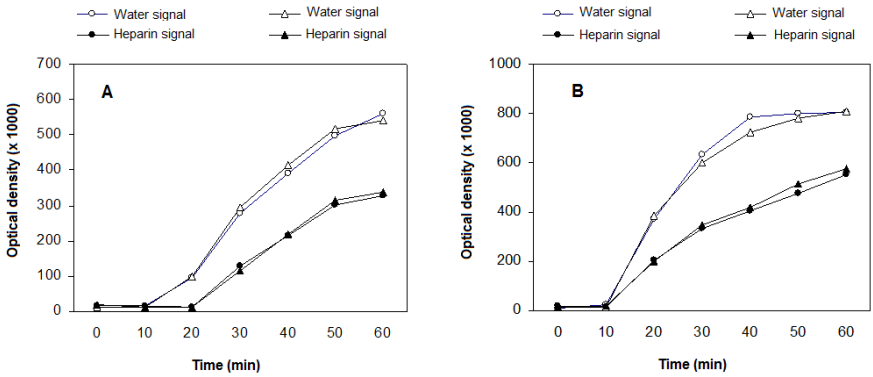


Figure 21.2. Examples of plasma coagulation experiments with digital signals. These two blind experiments were performed on October 19th (A) and October 20th, 1999 (B). The order of both "active" recordings ("digitized" heparin) and "inactive" recordings ("digitized" water) was randomly determined by the computer. The order of the blind recordings was WHHW for the experiment A and WWHH for the experiment B (W = water signal and H = heparin signal). The samples of "informed" water were added to sheep plasma in the presence of calcium. The coagulation was followed by a measurement every 10 minutes during one hour. The good repeatability of the experiment must be noted: very close values were obtained with "signals" of same nature. Moreover, each experimental point was performed in duplicate.

This simple system could consequently be easily reproduced in many laboratories and thus the principles of "digital biology" could be confirmed. Its repeatability in the hands of J. Aïssa was indeed very good (Figure 21.2).

Furthermore, a series of 15 blind in-house experiments were performed from June 24th to July 15th, 1999. Overall, 60 digitized biological activities were transmitted (35 "digitized water" as controls and 25 "digitized heparin"). Except for one "inversion", the success was total. Given these results, J. Benveniste tried to convince "friend" laboratories to reproduce these experiments with "digitized heparin" or with homeopathic pills of "*Heparinum* 30 CH". The method was thus standardized, meticulous protocols were drafted, frozen

plasma was sent to laboratories, visits of training were organized to explain and harmonize the methods.

But, alas, as usual when the experimental horizon of the laboratory of Clamart appeared to clear up, a "troublemaking" effect took place. J. Benveniste indeed noticed that when an experimenter other than J. Aïssa performed the experiment, the results were not as regular and sometimes were not as "expected". Thus, with Larbi Kahhak, another collaborator of J. Benveniste, the results were frequently "inverted". Nevertheless, there was generally a clear-cut difference between the various samples and repeated experimental points were consistent. Nothing particularly new with these "classic" inversions.

However, a new "oddity" was observed. Indeed, a new collaborator of J. Benveniste, Soo K. Lim, worked half-time in the laboratory. When she repeated the experiments of J. Aïssa, she observed no effect: there was no difference between the "active" transmissions and the "inactive" transmissions on the kinetics of coagulation. It was neither an "inversion" nor a failing technique; it was not a transient effect either because the phenomenon took its place with its brutal simplicity in the routine of the laboratory. According to the key for reading of the team of Clamart, S. Lim "erased the electromagnetic signals".

It was all the more surprising and spectacular given that the experiment was a model of simplicity. Without any exaggeration, the experiment could be easily performed by high school students during a practical class. No need for a long habit of laboratory techniques or manual skill as it was the case for example with the Langendorff device. It only needed to mix the contents of two tubes and to take samples with a pipette.

One could obviously interpret these results another way by considering that J. Aïssa was the exception or the "anomaly" whereas S. Lim was "normal", as is an experimental "negative control". But this point of view would naturally question the reality of "digital biology". A hypothetical inhibitory effect (erasing) was called in to explain the absence of a hypothetical effect (induced by digital signal) on which "digital biology" leaned on. Figure 21.3 presents an experiment performed during this period that shows how the effect (or rather the absence of effect…) was observed.

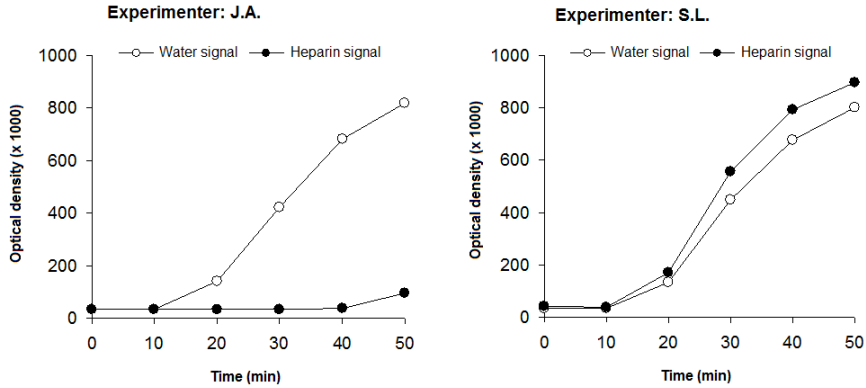


Figure 21.3. Typical example of an absence of effect with an experimenter (S.L.) while a particularly clear-cut effect was noticed with another one (J.A.); note that the same reagents were used in both cases (Experiment of March 8th, 2000). The experiment was very simple and consisted in mixing "informed" water with plasma, putting down the mixture in wells with a pipette and then following the evolution of coagulation with a spectrophotometer. This discordance of results between the two experimenters was noticed in an almost systematic way during this period. It was interpreted by J. Benveniste and his team as an "erasing of the signal" by S.L.
Each value of optical density on the figures is the mean of two experimental points.

Moreover, the interpretation of this phenomenon as an "erasing of the signal" was strengthened by a series of experiments performed from November 1999 to the spring of the year 2000 when the team tried to define the characteristics of the "erasing power" of the young woman. Thus, when S. Lim performed the same experiments in parallel with J. Aïssa by using the same reagents, it turned out that the crucial step was when the tube of "informed" water was handled by S. Lim (Figure 21.4). Besides, the "erasing" of the information contained in the sample could be done at a certain distance, without direct contact. Consequently new experiments were set up to assess which materials could "protect" against this influence and to determine the physical nature of this effect. J. Benveniste and his collaborators noticed that the protection of the tubes of water by a muff of mild steel or of mumetal blocked the influence of S. Lim. On the other hand, a protection of plastic was not sufficient and samples that were not sufficiently protected lose their properties acquired during the phase of "imprinting" (Figure 21.5).

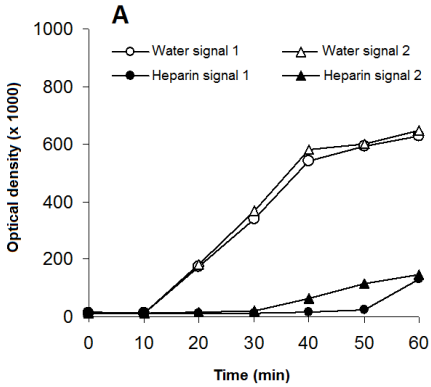
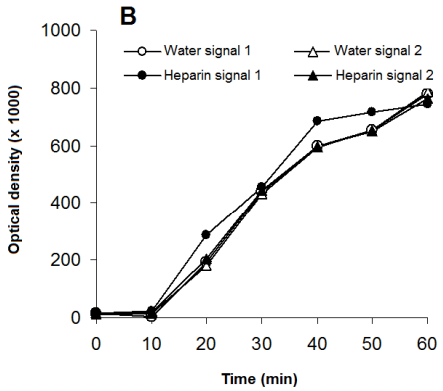


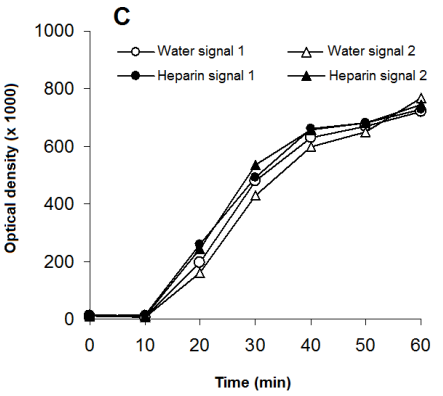
Figure 21.4. Evidence of the "eraser effect" (Experiment of November 4th, 1999).

These 3 experiments were successively performed to specify at which moment the erasing of the "digital signal" occurred. For these 3 experiments, J.A. prepared the materials as well as the "imprinting" of naive water by digital signals ("heparin signal" for 2 samples and "water signal" as control for 2 samples).



A. Firstly J.A. performed the experiment by mixing and distributing the samples in wells. During this time, S.L. remained at a distance (experiment A).

B. Secondly, S.L. was allowed to take the "informed" samples and performed the experiment by mixing and distributing the samples in wells (experiment B).



C. Thirdly, J.A. took the "informed" samples *which had been touched by S.L.* and performed the mixing and distribution of the samples in wells (experience C).

One observed that if the tube which was supposed to contain the "heparin signal" had been touched by S.L. (experience B and C), the results corresponding to "heparin signal" were comparable to those of "water signal". The conclusion of this experiment by Benveniste's team was that S.L. "erased information in informed samples".

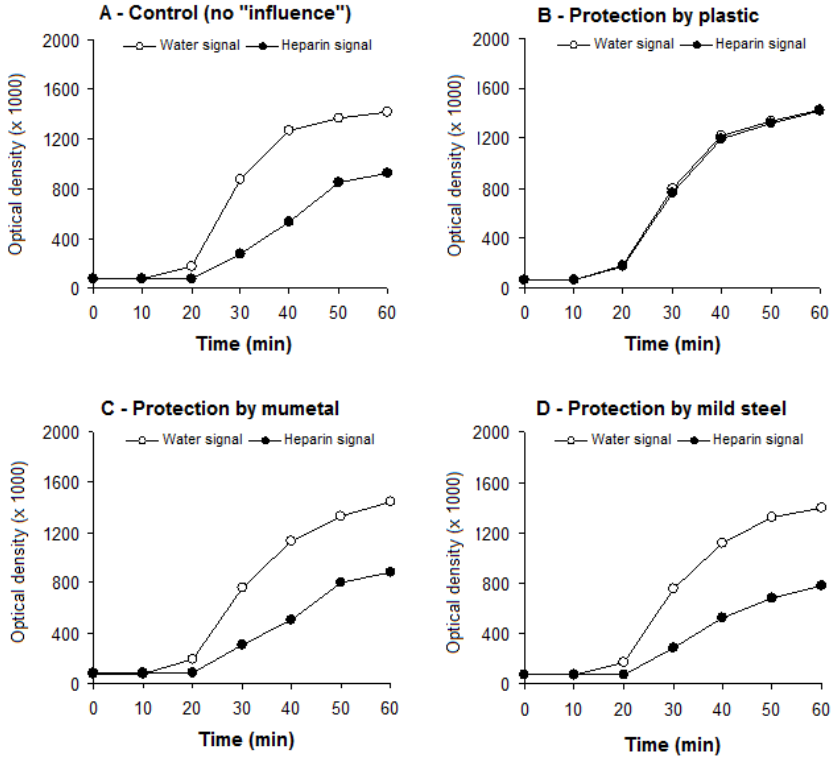


Figure 21.5. Assessment of materials protecting from the "eraser effect" (Experiment of December 20th, 1999). The purpose of this experiment was to assess which materials could block the "negative influence" of S. Lim on the experiments of digital biology. Tubes containing "informed water" were placed in muffs of different materials (plastic, mumetal, mild steel) handled by S.L. Results were as if mumetal and mild steel – and not plastic – were able to block the "negative influence" of S.L.

Previous experiments had shown that homeopathic pills of "*Heparinum* 30 CH" dissolved in water had also a specific inhibitory effect in this *in vitro* coagulation model. Thus, tubes of "*Heparinum* 30 CH" were bought in a pharmacy and the "eraser power" of S. Lim was also demonstrated! It was a discovery that would be of interest the homeopaths and the manufacturers of homeopathic pills if it turned out that some pharmacists – and probably some patients – were also "erasers" of granules…

But, for the moment, the interests of the homeopathy manufactures were not the concern of J. Benveniste. His main purpose was to confirm the effects

of digital biology and the last experiments intended to understand the problem of the "erasing" of the signals made him lose several months. For an experiment which seemed at first sight particularly simple to implement and consequently to reproduce by other laboratories, it was very irritating. In a letter which he planed to send to the researchers wishing to reproduce the experiment), J. Benveniste, having explained the method, recognized this problem:

> "At this point, you must be informed of an important event. In the last six months we have been confronted to a difficulty: one person in our lab was unable to see the effect of the heparin signal which was nevertheless routinely reproduced blind by another operator. An extensive study of this phenomenon has shown that this person was able to erase the electromagnetic signal carried by water up to one meter. This influence is electromagnetic in nature since it is blocked by mumetal, iron, but not plastic or aluminum. The coagulation process by itself remains unperturbed. We have detected the presence of such operator in an external lab, where 8 out of 10 experiments were positive, the 2 negative ones occurring when this person was present in the lab. No other "signal eraser" has been spotted among a dozen lab workers or visitors. [...] This means that in case such phenomenon would occur in one of the participating laboratories, we have set up a protocol able to detect it."

A robot in Clamart

Faced with this "negative influence", J. Benveniste decided to automate the method so that the operator had only minimal contact with the experimental system. It would be ideal if the experimenter had to only push a button to launch the experiment and finally got printed results. Once again, it was an unexpected obstacle that forced J. Benveniste to make a new technological jump intended to avoid a supposed artefact or a "strange effect".

At the end of March 2000, J. Benveniste and D. Guillonnet went to a "Laboratory exhibition" in Paris. The specifications required to find a robot analyzer capable of distributing the various reagents, "imprinting" the solutions with the electromagnetic signals and making the measures of optical density without human intervention. A robot analyzer was acquired a short time later and was installed early April 2000. Gradually, it was equipped to allow experiments of "digital biology" and to measure coagulation. An articulated arm took the sample to be "imprinted", placed it in the electric coil which "played"

the active or inactive signal according to a random order, added plasma and did the measurement of optical density at various time points. It was only at the end of the experiment that the operator knew the results recorded in the computer file (Figure 21.1).

Figure 21.1. Overview of the robot analyzer intended to automatically perform a complete experiment of transmission without human intervention. The "transmission" of the digital signal was made by the mobile arm of the robot which placed the tube of water to be "informed" in an electromagnetic coil. The "imprinted" water was then mixed with plasma. Coagulation was quantified by measurement of optical density at regular intervals by the spectrophotometer visible on the left of the device. The data transmitted to the adjacent computer and the operator knew all the results including the random choice of the different "signals" only when the experiment was finished. The only steps that required human intervention were starting the device and adding reagents and consumables. The different steps performed by the robot are precisely described in the legend of Figure 23.3 of Chapter 23 *(Photo Digibio)*.

The development was rather long because it was necessary to adapt the robot analyzer to the requirements of digital biology, but it was finally a success. The successive steps previously done by the experimenter were performed by the arm of the robot in a fascinating ballet. The role of the experimenter was simply to verify at the beginning of the experiment that consumables (tubes, single-use pipette tips) and the various reagents were in sufficient amounts and placed in the precise place where the robot expected to find them. It was thus a very important step because many of the previous arguments of the "skeptics" can be swept away. Indeed, the role of the experimenter was considerably reduced, all experiments were blind and no contamination was possible because

there was no manipulation of anticoagulant at "classic" dose inside the robot. The role of the experimenter was literally reduced to that of "push-button".

"We identified 104 blind heparin signals and 104 signals controls"

In the Digibio's newsletter of January 2001, J. Benveniste and D. Guillonnet could then summarize the various stages of the development of the robot:

> "For two years, we have a new method of detection of the biological signals recorded on computer. In brief, the coagulation of plasma is slowed down when it is mixed with water previously exposed to the signal of the anticoagulant heparin; the signal was recorded at usual concentration or at high dilution. Here is a summary of the experiment:
> 1) Water containing calcium (Ca^{2+}) is exposed to a digital recording of heparin (or control which is either heparin/protamine [1] or water).
> 2) Water-Ca^{2+}, mixed in decalcified plasma is distributed in 96-well microplates.
> 3) Coagulation is measured with a spectrophotometer and expressed in Optical Density."

They specified that this effect was also observed "with high dilution of the initial molecule […] or with homeopathic pills (*Heparinum* 30 CH) dissolved in water". As previously underscored, the link with high dilutions and homeopathy was thus not lost.

They continued:

> "During the first experiments in January 1999, the coagulation was estimated by a visual inspection of the tubes. Since then, we modified numerous technical points to improve reproducibility and reliability. The current method allows precise measurement through a spectrophotometer. These experiments were performed hundreds of times in our laboratory and successfully reproduced in 18 out of 20 in an external laboratory (6 successful blind experiments out of 7)."

But, as they prudently recognized, these attempts of reproduction were not completely satisfactory because of "unwanted effects of human factors" and they explained how they managed the development of a robot:

> "However, our attempts of reproduction in four other laboratories gave mixed results. We then understood the difficulty to "export"

> an unconventional biological method. Furthermore, the interpersonal variations of the operators as well as their inclination "to improve" the technique could explain these erratic results. We thus decided to automate this technique in order to eliminate the unwanted effects of the human factors. The robot has been functional in our laboratory since early October 2000. "Functional" means that the experimenter, having defrosted and centrifuged the decalcified sheep plasma kept at -20°C, places it in tube racks with water-Ca^{2+} intended to be "informed" and empty tubes. Once the program has started, the data are displayed on the screen 90 minutes later. The operator intervenes again only after three experiments (including four signals for each) to put back empty tubes in the rack. A few weeks were still necessary to finalize the machine, to build additional parts and to understand the conditions of reproducibility of the experiments. Since then, we obtained positive results in approximately 90% of experiments. As an example, between November 15th and 24th, 2000, we identified in a blind manner 104 heparin signals and 104 control signals. Twelve heparin signals were ineffective, because of mechanical problems of the machine and not reactive plasma."

To conclude, they announced that a robot would be installed in another laboratory to reproduce these surprising results:

> "Thanks to two generous donors, we were able to build the second robot, which is installed in an external laboratory the researchers of which are going to perform experiments within next weeks. A machine will be sent to a foreign laboratory, probably in Great Britain or in the United States (both if we find funds, approximately $40 000), to reproduce these experiments in a totally independent way."

Was a robot going to work outside the laboratory of J. Benveniste? What results have been achieved? Will J. Benveniste and his team finally free themselves from these diverse strange effects which perturbed the experiments?

Notes of end of chapter

[1] Protamine is an inhibitor of heparin (antidote). Consequently, a mixture of heparin and protamine has no effect on coagulation; it was also the case for its "digital signal".

Chapter 22. From Sputnik to "digital biology"

"Digital biology" to aid of America?

In order to follow the wanderings of this robot which must reproduce the experiments of J. Benveniste in a foreign laboratory, let us go to Washington, on November 14th, 2001 – that is two months after the events of September 11th, 2001. On this day, in the House of Representatives of the American Congress, hearings took place; they were intended to review the means of fight against bioterrorism and more particularly how non-conventional treatments – among others homeopathy – could be used for this purpose. In the extract below of the transcription which was made for these hearings, Dr. Wayne B. Jonas was questioned by representative Dan L. Burton who chaired the hearings and he gave particularly interesting information for our story (*NB.* The inaudible parts of the transcription are indicated by "--").

> "*Chairman Burton*: You talked about digital biology. Can you explain a little bit more about that and its potential applications?
> *Dr. Jonas*: Yeah. Digital biology is a concept that has been really developed by a French researcher by the name of Jacques Benveniste, who claims that he has been able to digitize biological signals, record them on a computer and then deliver them through an electromagnetic frequency off of a WAV file and produce -- reproduce those digital effects.
> If this is true, then -- and if it's something that could be developed, then it's a technology that could possibly allow us to both detect agents, as well as possibly deliver medical treatments in a electronic format. So, that's an exciting procedure. The Department of Defense actually is supporting some research in one of my labs to see if we can replicate some of those claims.
> *Chairman Burton*: How about our health agencies? Are they doing anything on this? Have you submitted -- ?
> *Dr. Jonas*: -- The only support of this that I know of is from DARPA, the Defense Advanced Research Products Agency, which -- a projects agency which funds what they consider "out of the box" types of things. This is one of those things that I wouldn't dare submit to an NIH review group. It wouldn't even get the time of day.
> *Chairman Burton*: It sounds like it is an exciting research project. I -- .

> *Dr. Jonas*: -- It's what's called a high impact/high risk. It may -- that's the terminology that's used. I mean, it's high risk in the sense that if you find nothing, you've wasted your money. But, high impact in that if you find something, it'll revolutionize medicine". [1]

There are two major and surprising news in this dialogue: the Department of Defense of the government of the USA was interested in the "digital biology" of J. Benveniste and furthermore it financed a project on this subject! Thus let us resume each of the elements. First of all, who is W. Jonas?

When he testified in front of this commission, W. Jonas had just retired the Army. Doctor and Lieutenant Colonel, he was Director of the Medical Research Fellowship at the Walter Reed Army Institute of Research in Washington. This institute which belongs to the Department of Defense is specialized in biomedical research. The Medical Research Fellowship is a university cycle intended for officers being interested in medicine and in research. Within the institute, W. Jonas did research on bioterrorism and on the possible effects of high dilutions. He studied in particular the neuroprotective effect of high dilutions of glutamate on brain damages. From 1995 to 1999, W. Jonas was director of the Office of Alternative Medicine in the National Institute of Health. This institute (now called the National Center for Complementary and Alternative Medicine) is one of the 27 institutes and centers which compose the National Institute of Health. The Office of Alternative Medicine explored in a scientific context and in a completely official way the therapeutic possibilities that practices such as homeopathy or acupuncture could offer. Finally, at the moment when he testified, W. Jonas managed the Samueli Institute for Information Biology. This institute is a private foundation which finances research programs having for purpose to study medical practices which are said alternative. So, besides homeopathy, he was interested in the placebo effect, "bioenergy", "bioelectromagnetism", etc. To finish, W. Jonas was a member of the White House Commission on Complementary and Alternative Medicine Policy.

These numerous details of the *curriculum vitae* of W. Jonas are useful to understand that the latter knew very well the domain of high dilutions and homeopathy. He published during his career numerous articles on this subject. It was thus not surprising that he was interested in the work of J. Benveniste who he met in 1989 at a conference in Baltimore.

What is the DARPA?

We can only speculate. But, it seems well that some members in the department of Defense in the government of the United States were intrigued by the results that J. Benveniste claimed to obtain with "digital biology". An agency of the department of Defense, the Defense Advanced Research Projects Agency (DARPA) then asked to W. Jonas – those days the director of the Institute Samueli and a former military – to study if something interesting could be obtained from the experiments of J. Benveniste.

The DARPA is an agency which was created in 1958 (under the name of ARPA) in answer to the launching of Sputnik, the first artificial satellite which allowed the Soviets to overtake the United States in the space race. The purpose was to create an organization capable of developing new technologies which could be exploited for Defense. The agency is a kind of spearhead which allows, by financing programs, to evaluate emergent technologies. The agency often had a driving role by helping projects which would not have been financed by civil agencies and institutes. As an example, the DARPA (formerly ARPA) was at the origin of the network Arpanet which gave birth to Internet.

During the more recent years, the agency was also interested in biology. One of the purposes was to be inspired by the functioning of living beings to imagine new materials or for example to understand the functioning of organisms that live in extreme conditions. Thus, a project aimed at developing genetically-modified plants as "sentinels" that could warn a terrorist attack with chemical or biologic agents, for example by quickly losing their color.[2] The DARPA is interested in disciplines on the borders of computer science and biology and some of its projects seem to be inspired by scenarios of science fiction, for example to connect human nervous system to computer chips. We understand that "digital biology" could indeed interest the DARPA. Of course, if the "digitization of biological activities" held its promises, it would then be possible to detect molecules in complex solutions. Thanks to the "digital recording" of a sample, the presence of potentially dangerous molecules could be evidenced with only a laptop. Within the frame of the fight against bioterrorism – and for many other applications – the DARPA quickly understood that it would be an extraordinary breakthrough.

A multidisciplinary team

The general idea which presided over the evaluation of the robot built by J. Benveniste was not to validate the theories of this latter, but to simply verify in a first time that the same results could be obtained by an independent team. The Samueli institute led this expertise with credits of the DARPA. A copy of

the robot was bought to J. Benveniste and the members of his team, including himself, were employed as consultants. Their task consisted in installing the robot in a U.S. laboratory depending on the Institute Samueli and to explain the functioning. [3] Then, after the departure of J. Benveniste and his co-workers, the team of W. Jonas could study the functioning of the system. It was thus a very pragmatic approach where one did not try to confirm or to falsify a theory, but to evaluate a device and by considering the team of J. Benveniste as a partner. Among all attempts of validation of the experiments of J. Benveniste, it was probably the one who was the most adapted and the most relevant. This team, asked to evaluate the experiments performed by the automatic robot, was multidisciplinary. The team constituted by W. Jonas indeed contained, in addition to W. Jonas himself, the following main members:

John Ives was a biologist, Doctor in Sciences, he was also military (colonel) at the Walter Reed Hospital and he was a member of the team of direction of the Samueli Institute. His role was to supervise the various phases of the evaluation.

Daniel "Chip" Denman had training in biostatistics and epidemiology, he was Director of the Laboratory of Statistics in University of Maryland. Before joining university, he was at the NIH as mathematician statistician during ten years. Contrary to W. Jonas and J. Ives who were clearly "believers" towards homoeopathy and alternative medicines, D. Denman was an official "skeptic". He was indeed a founder member of an association of "skeptics" in Washington. He was an activist for developing critical thinking and skepticism in education. He gave university courses entitled "Science and pseudosciences". In the lineage of J. Randi, he had also competence in conjuring. It is moreover a friend of this last one.

Dr Kenneth Hintz was a professor in engineering at George Mason University (Fairfax, Virginia). His role was to verify the functioning of the robot and in particular the recording and the replay of the "digital signal".

Dr Mc Donald Horne was a hematologist at NIH. His expertise was related to the biological system based on coagulation of blood plasma.

Finally, the team included Dr Mitchell Hammer professor at the American University in Washington, Director of Center for Crisis Response and Management. His expertise in the dynamics of group was wished in case of conflict, disagreement or incomprehension in this multidisciplinary team. His role was to make sure of the good communication between the members of the team!

The team was thus constituted by members of the Department of Defense, university professors and researchers of the NIH. The conditions of the expertise were opposite to those of the "investigation" of *Nature* in 1988 or of the experiments performed in Israel in 1987. Each of the members of the team had a very precise domain of competence and W. Jonas was in charge of coordinating the activities of these experts. Furthermore, the evaluation was performed in the respect of some "ethical" principles towards the scientists whose work was assessed. In other words, the members of the team of J. Benveniste were considered as partners and not as "guinea pigs" exploited to confirm some prejudices as *Nature*'s team did. As a consequence the conclusions of this evaluation would be of greater value.

Notes of end of chapter

[1] United States House of Representatives Government Reform Committee hearing on comprehensive medical care for bioterrorism exposure: are we making evidence-based decisions? Representative Dan Burton (r-in) Chairman; November 14, 2001; Washington, DC.

[2] S. Foucart. Contre le bioterrorisme, une université américaine veut créer des OGM sentinelles. *Le Monde*, February 15th, 2003.

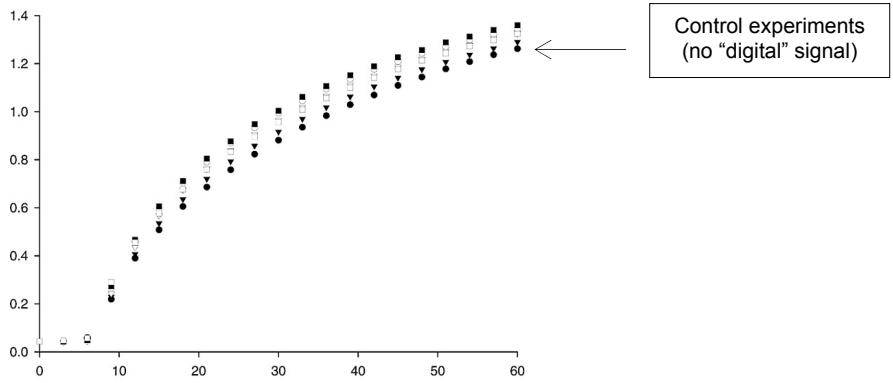
[3] Conference of J. Ives: "The Co-Creation Process in Energy Medicine: A Synergy of the Sciences and the Healing Arts" during the "Twelfth Annual ISSSEEM Conference"; June 14-19, 2002.

Chapter 23. "The digital signal appeared to work!"

"The results are highly significant"

The robot analyzer acquired by Digibio thanks to the credits of the DARPA was thus settled in a laboratory of the National Institute of Health in Bethesda (Maryland). J. Aïssa and D. Guillonnet came to run it from July 14th to 21st, 2001 during the phase of the expertise named pre-pilot study. The purpose of this pre-pilot study was to verify that everything worked correctly. J. Aïssa and D. Guillonnet also did some informal experiments which allowed to notice in a satisfactory manner that the inhibitory digital signal was also efficient on the other side of the Atlantic Ocean and they explained the functioning of the robot.

After the pre-pilot phase, the control experiments (without any digital signal) were performed by the American experts that indicated high degree of reproducibility. On the basis of these trials, it was calculated that four experiments would be sufficient from a statistical point of view to detect a 20% difference of the active digital signals compared with control conditions (Figure 23.1).



(Reproduced from W. Jonas et al, Faseb J 2006 ; 20 : 23)

Figure 23.1. Example of an experiment performed by the robot analyzer (in the absence of any "digital" signal) by the U.S. experts between the pre-pilot and pilot phases. These trials allowed evidencing the low variation from one sample to another. According to the U.S. experts, the variation was less than 1% for 10 experiments performed during 5 different days.
x-axis in min and *y*-axis in optical density units.

Before continuing, it is necessary to note that a modification was introduced by the team of J. Benveniste to make the experiments. In order to avoid being dependent on the supply of plasma, which could sometimes be difficult, it was now the effect of thrombin on fibrinogen that was measured. The purpose of the experiment did not change since fibrinogen is the soluble plasma molecule which is transformed into insoluble fibrin by thrombin and participates in clot. There was thus a purely biochemical system. This *in vitro* reaction could be also easily measured by a spectrophotometer because insoluble fibrin absorbs light.

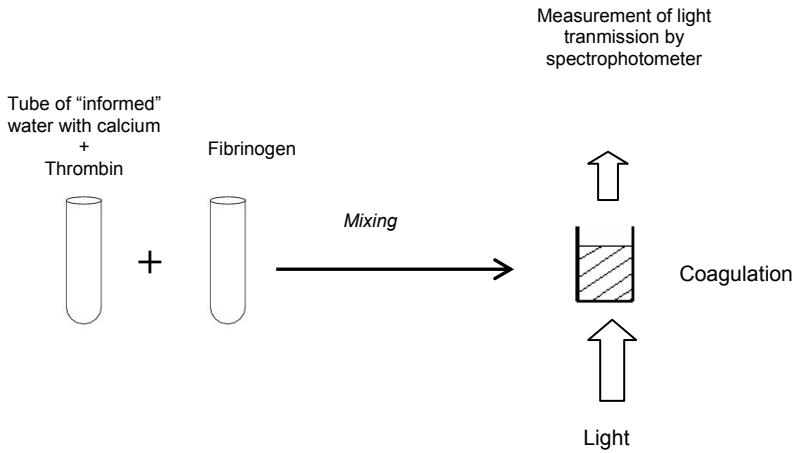


Figure 23.2. Principle of the transformation of fibrinogen (24 mg/mL) in fibrin by thrombin (0.3 µg/mL) *in vitro* with reading of the optical density by the spectrophotometer of the robot analyzer. Thrombin is an enzyme which transforms soluble fibrinogen into insoluble fibrin. The more fibrin is produced, the more light is absorbed. Water "imprinted" with "digital signal" which inhibits the effect of thrombin (active recording) could be assessed in comparison with water "imprinted" with "water signal" (inactive control).

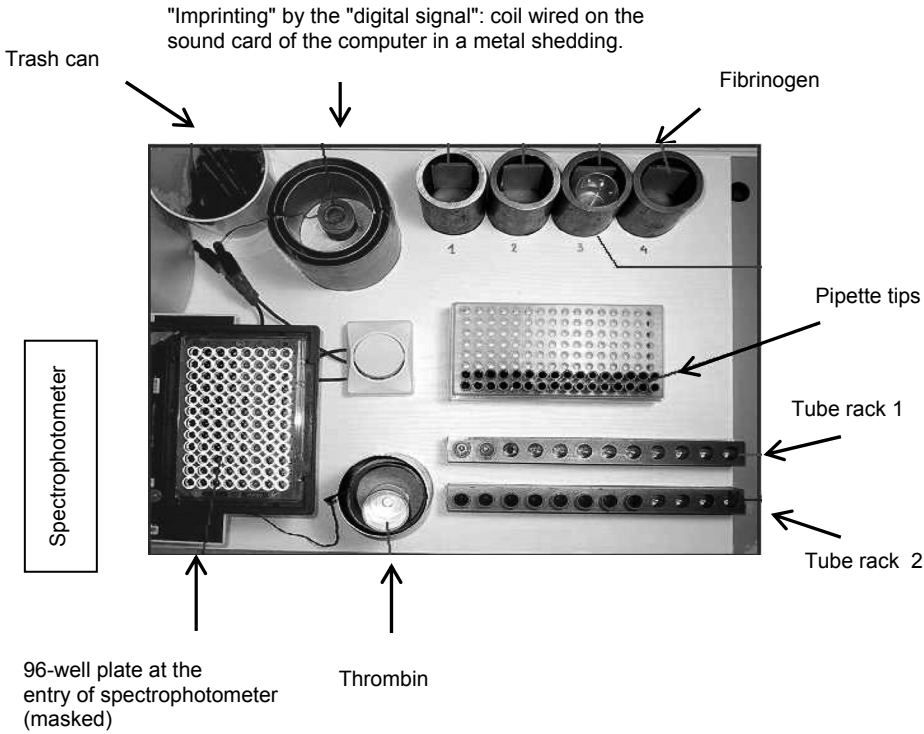
The solution of thrombin was exposed to the digitized thrombin inhibitor or to digitized water (control), mixed with fibrinogen and added to wells. Everything was automatic except the preparation of stock solutions of fibrinogen and thrombin. Indeed, the functioning of the robot was the

following one. Having placed the solution of fibrinogen and the solution of thrombin in their respective places, the software which piloted the machine was started. The arm of the robot which was equipped with a pipette distributed thrombin in tubes and placed them in the coil which broadcasted the digitized signal. The tube of water containing thrombin was "informed" during 10 minutes and replaced on the tube rack. The same tasks were performed for the other tubes. The order of the "digitized signals" was random. Fibrinogen was then added to each of the "informed" tubes the content of which was put into two wells of a "96-well plate". The optical density of the fibrinogen-thrombin mixture was automatically measured every 60 seconds during one hour (Figure 23.3).

Then, the next phase, namely the pilot study, was performed from October 30th to November 3rd, 2001 with J. Aïssa, D. Guillonnet and J. Benveniste. The aim of this phase was to verify in a formal way that the team of J. Benveniste obtained the claimed results. A protocol was defined and was accepted by all participants. The protocol consisted in "informing" samples containing thrombin according to the "information" of three different recordings: digital thrombin inhibitor (DTI), signal water and no signal, that is one active signal and two inactive signals. Every signal was transmitted to the output coil and "played" during ten minutes. The digital signals were recordings of 3 seconds played in loop during ten minutes. Every experimental point was performed in duplicate. The experimenter did not know in which order the various experimental points were performed. He knew the result of the experiment only at the end of the experiment.

J. Ives told how this pilot phase took place:

> "The next phase was the pilot phase. During this phase Benveniste's team were present and ran the experiments using the robot. They performed twenty-one (*sic*) experiments, each consisting of the three conditions in duplicate. A twenty-one to twenty-eight percent inhibition by digital thrombin [*inhibitor*] (DTI) was observed compared to the water signal (WAT) or the no-signal (NS) condition. Statistical analysis indicates that the results are highly significant ($P < 0.0001$). The digital signal appeared to work!" [1]



(Reproduce from W. Jonas et al, Faseb J 2006; 20: 23)

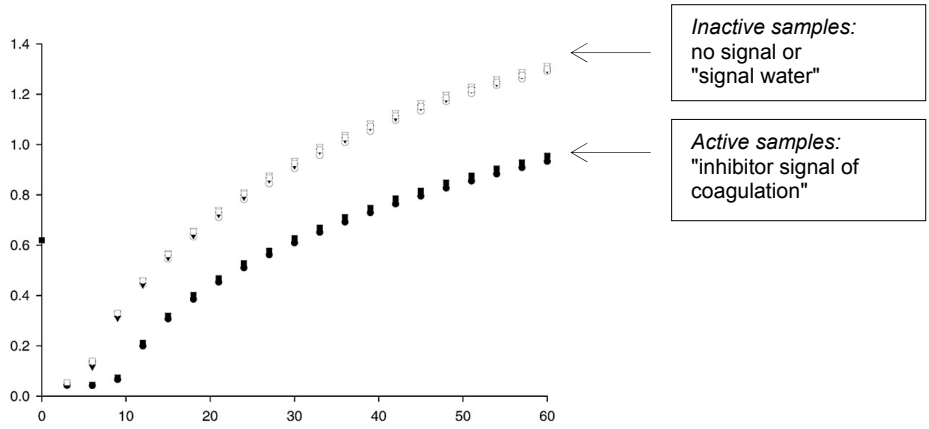
Figure 23.3. Sequence of the operations performed by the robot analyzer. In order to prepare the robot, 12 tubes were placed (manually) on the extreme left of the tube racks 1 and 2 (6 tubes per rack), containers for thrombin and fibrinogen are placed in their respective locations. Note that containers and tubes were placed in metallic shields (muffs or racks) to protect theirs contents from electromagnetic waves. Then the robot was started up.
(1) The articulated arm (not visible) of the robot which carried a pipette arms took a single-use tip and distributed equal volumes of thrombin in each of the tubes of the rack 2.
(2) The arm placed each of these tubes of the rack 1 in the coil to expose it to the electromagnetic field; the tube received one of the three possible signals: "signal water" as control, "anticoagulant signal" or "no signal". After 10 minutes of exposure, each tube was put back in place. The single-use tip was thrown in the trash can and a new tip was placed at the end of the pipette carried by the arm of the robot.
(3) After 60 minutes, fibrinogen was added to the first tube (on the left) of the rack 2.

(To be continued next page)

(continued from previous page)

(4) Thrombin of tube 1 in tube rack 1 was taken and added to tube 1 in rack 2 and then mixed by repeated aspiration-expulsions.
(5) The content was put down in two adjacent wells of the 96-well plate (duplicate).
(6) The same process from (3) to (5) was repeated for the 5 other tubes.
(7) The 96-well plate was introduced in the spectrophotometer and a measurement of optical density was performed for each well every 3 minutes for 1 hour.

More exactly, the article co-authored by W. Jonas indicated that 16 experiments were performed during the pilot phase. The differences of coagulation did not exceed 1% between the experimental points of "digitized water" (control) and "no signal" (that is the controls). In 7 experiments, a decrease from 21 to 28% of coagulation was observed with samples "informed" with digitized anticoagulant compared to controls (Figure 23.4).



(Reproduced from W. Jonas et al, Faseb J 2006 ; 20 : 23)

Figure 23.4. Pilot phase (October 30th–November 3rd, 2001): example of an inhibitory effect obtained during the expertise with a "digital signal". During each experiment, three experimental conditions were compared; each of the three experimental conditions was performed in duplicate. The three experimental conditions were: no signal (open circles, open square), signal "water" (closed triangle, open triangle), "inhibitory" signal (closed circle, closed square). On the figure, the effects observed with 4 controls (2 wells "no signal" and 2 wells "signal water") and 2 "active" signals (2 wells with "inhibitory signal") are represented. One notices that the "inhibitory digital signal" actually inhibited coagulation.
Out of 16 experiments performed during the pilot phase, inhibition was evidenced for 7 of them (mean inhibition from 21 to 28%). Consequently, the results obtained during the pilot phase were in favor of "digital biology".
x-axis in min and *y*-axis in units of optical density.

Everything was thus fine and the future of "digital biology" looked bright. Overall, during the pre-pilot phase and the pilot phase, 11 experiments out of 23 gave outcomes in favor of the reality of the effects of the "digital signals" which inhibited coagulation by 24% on average; statistically speaking, these results were extremely significant.

The successful experiments having been performed in blind conditions and with an automatic device, a complete failure would be surprising after the departure of the French team. Indeed, the manipulation of the robot did not require a great manual skill or specific expertise. As already mentioned, the work of the operator was limited to set up consumables (tips of pipettes, tubes) and reagents. Then, one pushed a button and the experiment was automatically performed from the random choice of digital recordings to the printing of the results.

However, the U.S. team made the following observation:

> "A subgroup analysis of pilot phase data showed that all DTI *[digital thrombin inhibitor]* effects occurred when experiments were conducted by one member of Benveniste's team (Jamal Aissa) and that this usually occurred when using a split sample technique in which he interrupted the operation of the ABA *[automated bio-analyzer]* machine to do manual plating followed by the automated plating. Two of the 16 experiments done only by the ABA machine (no interruption) showed effects when Jamal was present. In three instances Jamal set up experiments and then left for the day. None of these showed DTI effects." [2]

The French team was hardly surprised with this possible "influence" of J. Aïssa and it revealed to the U.S. researchers that indeed it had been noticed that some individuals were "facilitators" while others were "inhibitors"; J. Aïssa was obviously a member of the first category. But the fact that this observation could question the reality of "digital biology" did not appear to be a source of concern within the team of Clamart. Indeed, the U.S. researchers noticed that when the results were not in accordance with the expectations, the French team still put the blame on material failure.

What were the results obtained during the test phase after the departure of J. Benveniste and of his collaborators? Did the absence of J. Aïssa affect these promising results?

Notes of end of chapter

[1] J. Ives. Evaluating unusual claims and devices using a team approach: A case study. *Subtle Energies & Energy Medicine* 2002; 13: 39–59.

[2] Jonas WB, Ives JA, Rollwagen F, Denman DW, Hintz K, Hammer M, Crawford C, Henry K. Can specific biological signals be digitized? *FASEB J* 2006; 20: 23–8.

Chapter 24. A strange small black box

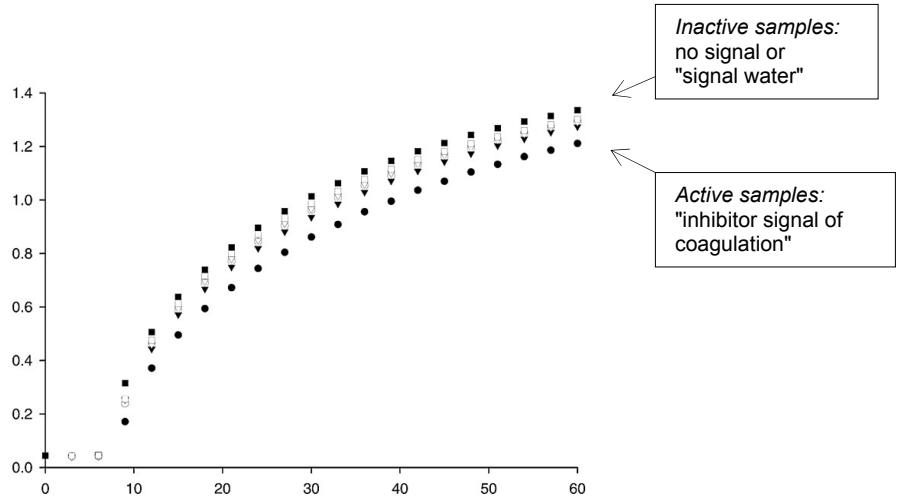
Is the experimenter a solution or a problem?

Early November 2001, the team of J. Benveniste left the U.S. laboratory as expected and returned to France. Their consulting role was finished. The pilot phase having been satisfactory, the test phase could thus begin. After November 3rd, 2001, 29 experiments were then performed by J. Ives and his collaborators during the decisive phase. Overall, these experiments involved six experimenters in two different laboratories.

But the U.S. experts could only notice the absence of effect related to "digital signals" with the automatic robot (Figure 24.1). During an ultimate control, the U.S. team checked that the inhibitor of thrombin at pharmacological dose gave expected results. In other words, the researchers verified that when there was an inhibition of coagulation in "classic" conditions, they were actually capable of detecting it with this device. For these last controls, more than 40 experiments with digital signals have been performed overall by 7 experimenters.

Due to the failure of the test phase, the U.S. team concluded that the automatic device was not capable of demonstrating – independently from the team of J. Benveniste – any effect related to "digital biology". As a consequence, the DARPA which financed this operation withdrew. The purpose of the expertise indeed was to verify that a biological activity could be recorded and then replayed by using the robot of J. Benveniste. The answer having been negative, the file was closed.

J. Ives nevertheless continued the experiments for a while with the robot to understand how it was possible that the experiments could be effective only in the presence of J. Aïssa. J. Ives suggested studying the influence of the operator by filming the experiment, by placing screens of various materials between the operator and the machine. These screens would allow determining if this possible influence was chemical, electromagnetic or anything else. He tried to resume the experiments with other operators and in another laboratory hoping to select an operator as "talented" as J. Aïssa. These researches were not pursued, at least officially.



(Reproduced from W. Jonas et al, Faseb J 2006; 20 : 23)

Figure 24.1. Test phase: example of the effect of the "digital anticoagulant signal" obtained after several dozens of experiments performed by the U.S. team and by several operators after the departure of the French team.
The means of optical density at 40 minutes obtained on 40 experiments were 1.08 ± 0.1, 1.08 ± 0.09 and 1.09 ± 0.08 for the inhibitory digital signal, water digital signal and in the absence of signal, respectively. No effect related to "digital biology" was thus highlighted during this test phase.
x-axis in min and *y*-axis in units of optical density.

However, on the side of the team of J. Benveniste, the possibility of such a narrow association between the operator and the device was difficult to accept. In this case, one would indeed implicitly recognize that digital biology had no scientific foundation. It would be turning towards a poorly delimited domain, flirting with parapsychology. Scientific credibility would be uncertain if J. Benveniste announced that, after all, "digital biology" was only a fancy and that he decided now to begin researches in the controversial domain of parapsychology and human-machine interaction. On one hand, his specificity as founder of "digital biology" would disappear and, on the other hand, the industrial supports would faint. But Digibio, as a private company, looked for partners to exploit its patents and the potential shareholders counted on the technological developments promised by "digital biology".

The members of the team explicitly acknowledged that the presence of the operator could influence the biological answer of the system. But at no time the hypothesis that the operator himself – and only him – could be responsible for the effects was suggested. Admitting it would indeed mean sawing the branch on which Digibio was sitting. One could understand the reluctance to take this step because the specificity of the effect was obvious and was not compatible with the only "influence" of the experimenter. One could – at a push – consider an unspecific experimenter effect that would interfere and disturb the functioning of the machine; but such an effect is unknown in the current state of the knowledge. Supposing a specific effect in some experimental wells but not in others – furthermore in blind experiments – require so many *ad hoc* and unproven hypotheses that one quickly gives up.

A family secret

J. Benveniste was certainly disappointed by the results obtained in the United States after the departure of the team. Nevertheless, deep within himself, was he really surprised? As we have seen, there were already many experiments where everything seemed perfect up to the last moment before unblinding. With the U.S. experiments however there was a step forward. The concern was not blind experiments that failed, but the presence of a given operator was questioned. The possibility of an influence of the experimenter could seem at first sight rather silly. As we just said, slowing down coagulation in an apparently specific way, moreover in blind experiments, and just because a given operator was present seems *a priori* more a miracle than a scientific fact.

Nevertheless, J. Benveniste did not seem as surprised as he should have been in front of these results. Moreover, he did not try to organize new public demonstrations with the robot, which nevertheless constituted a great way to convince. He kept indeed a memory which suggested that the same disappointment could occur in new attempts. This memory is the encounter with a strange "black box" that destabilized the laboratory in its *raison d'être*. Let us go back a few years.

In June 1996, J. Benveniste accepted to welcome a supporter of "radionics", Paul G., in the laboratory in order to participate in an experiment with the Langendorff device. Little known in France, this "discipline" is – to say things in a moderate way – an absolute nonsense.[1] Inspiring in part by the "vital force" of the psychoanalyst Wilhelm Reich, the partisans of radionics use devices which from the outside look like former radio sets: boxes with numerous buttons intended for obscure settings.

The black-coated device brought by the visitor did not exceed the size of a big box of matches – a travelling model probably… – and it was equipped with only a single potentiometer which showed a scale with figures if one turned the button. The visitor explained to the collaborators of J. Benveniste that this small black box allowed making homeopathic dilutions! For this purpose, it could not be easier; one had simply to place a tube of "naive" water in a hole in the box. A small paperboard square was put in a slit of the box. The visitor then presented an assortment of such paperboard squares among which some were specifically prepared to experiment with the isolated heart. He thus showed a cardboard that was marked "acetylcholine". On each cardboard, a graded circle was printed and some lines were drawn on the perimeter of the circle, which were different according to the nature of the "dilution" that was desired. In order to determine the dilution factor, the potentiometer must be turned until a number was selected thanks to a table which indicated the correspondence between the desired dilution factor and the number on the potentiometer…

The collaborators of J. Benveniste – taken aback – raised nevertheless some concerns. How are the inscriptions "read" on the cardboard square? There is no system of reading; the cardboard has just to be placed in the slit, their interlocutor answered. But where is the power supply? There is none. But to what is connected the potentiometer? To electric wires which are inside the device. By the way, the device was impossible to dismantle and it would be necessary to break it in order to examine the inside. But if there is no power supply, no system of reading of cardboard, how does this "device" work? It is all the mystery of radionics… But nevertheless "it works" in sick people the visitor insisted. The use of this device seemed to be essentially an act of faith.

As surprising as it might seem, the visitor was not ushered out. Some individuals advocating alternative therapeutic methods (healers, followers of diverse "bioenergy" medicines…) hardly more substantial than radionaics occasionally ventured into the laboratory of Clamart where J. Benveniste sometimes accepted them in an atmosphere of ambiguous tolerance. Until now, all these visitors had left without changing the movements of the heart in spite of their "mental concentration", fluid or conviction to be able to influence the biological model. But, after all, one could also consider these "experiments" as controls. It was simply the proof that just anything did not make the experimental system "move". But let us not deceive ourselves, "radionics" is pure magic. It is the belief that the word "dog" could bite or, in the present case, that the word "acetylcholine" could have any effect on a biological system.

The "experiment" was thus performed. "Naive" water which was "treated" by the device to acquire an "acetylcholine-type" activity (it was what was written on the cardboard inserted into the device) was injected by the end of the

morning of June 18th, 1996 in both devices of Langendorff which, on this day, was used to test the recordings blinded by the researcher of Chicago. What should have been a perfect control gave a positive answer without ambiguity, furthermore on both Langendorff devices which worked in parallel. J. Benveniste was more than amazed. Was this once again a contamination by endotoxin? He asked J. Aïssa to add atropine to prevent any effect other than an acetylcholine-type activity. The same sample "acetylcholine" was then injected again and it was ineffective. To perfect the experiment, atropine was washed out from the circuitry and the sample was injected once again. Hearts reacted once more without ambiguity! It was as if the tube of water indeed contained an acetylcholine-type activity… If samples had been "informed" by the devices of "digital biology", J. Benveniste would have considered these results as an additional proof of the soundness of his ideas. But, even if he was broad-minded, it was difficult for him to assume these results…

"One shuts one's mouth"

Soon after, I had the following conversation with J. Benveniste.[2] Extremely intrigued, I tried to raise the question of this destabilizing "experiment" which I did not attend, but I had heard some comments from colleagues. At first, I was only able to obtain pieces of answers because he obviously preferred no to speak about this subject. I asked him:

"— Rather surprising, the experiment on the other day, no?

— Yes, you said it.

A silence.

— But, you fully agree that "radionics", it's just hot air?

— (*Sign of agreement*)

— And consequently that or magic it is the same thing. It is thinking that the word or the sign is as effective as the object which it designates.

— (*Sign of agreement*)

— If what we consider as a perfect control gives nevertheless a positive result, it is rather boring, no?

— We agree."

Obviously, J. Benveniste who knew all that better than me, hardly wished to pursue the conversation on this subject. As he could not walk away because he was soaping hands, I could not resist asking him the following question:

"— But now that you know that, in practice what are you going to do at Digibio?

— What are we going to do? It is simple… At first, *one* shuts one's mouth.

— … Uh yes of course, needless to say … *One* is not going to talk about it everywhere. But does it change your way of envisaging the future experiments? Are you going to continue just like that?

After a silence during which he dried his hands, he answered me:

— You know, there are many strange things that we do not understand. But one thing's for sure, in the position where I am at present, it is the kind of idea that it is impossible for me to communicate. Later, maybe, when I will get back my influence, we will see if we can make it. But for the moment, the only thing to do it is to continue working in order to push digital biology."

Two days later, J. Benveniste slid the "informed" tube of June 18th among other tubes during an experiment that J. Aïssa was performing. Again, a change of coronary flow was observed. Several months went by and the "small black box" popped up from time to time in the conversation of the collaborators of J. Benveniste. The usual experiments – classical if we may call them! – continued during summer as before, in particular "transatlantic" experiments with the researcher of Chicago.

At the end of the summer however, Peter Jurgens (a collaborator of J. Benveniste) that this question disturbed, proposed to J. Aïssa to redo the "experiment". He also suggested to me about attending the experiment. It turned out that J. Benveniste was absent on this day. The small black box which had been left by the visitor returned to the light and the "protocol" was then scrupulously followed again: a "specific" card for acetylcholine was slided in the box, a tube of naive water was introduced into the adequate hole, the potentiometer was adjusted and, after the prescribed time, the content was tested on the Langendorff apparatus. Again, the coronary flow was modified when the solution was administered to the heart. One does not dare to write that same "causes" induced the same effects.

A few days later, J. Benveniste who had knowledge of the experiment being performed in his absence got back the black box and then asked about the cardboards which were tidied up in several places of the laboratory. He got back them one by one and put them away with the device in his office. The collaborators of J. Benveniste did not hear about the "small black box" anymore.

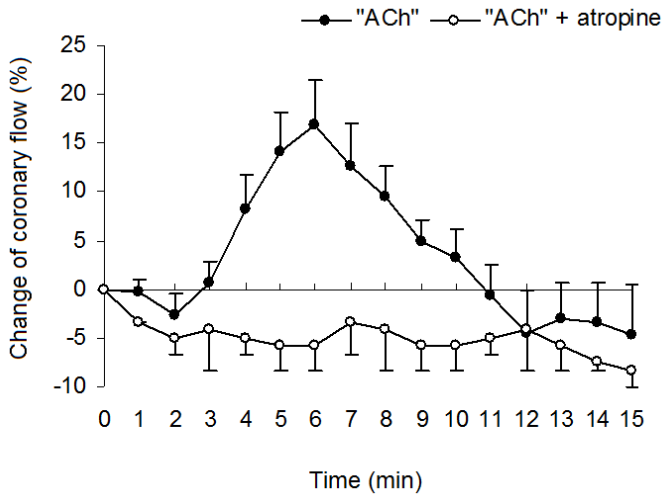


Figure 24.2. This figure is a summary of the experiments of "radionics" performed on June 18th ("Ach" alone and "Ach" + atropine) on two hearts in parallel and then again on June 20th and August 29th, 1996 on a single heart ("Ach" alone).
The results are given as means ± S.E. (n=6 for "Ach" and n=2 for "Ach" + atropine 1 µmol/L).
ACh: acetylcholine.

What is a control?

Several attitudes are possible in front of the "results" obtained with these last experiments. The first one – the most immediate – is to relate the results to a possible contamination (as it was the case for the "contaminated" physiological salt solution) or to a technical failure. But, in this particular case, the simplicity of the experiment is exemplary. Suggesting device problems during the "imprinting" of naive water was practically impossible because on this side the equipment is non-existent. One could – once again – suggest a contamination by endotoxin. The simplicity of the device as well as the results with the inhibitor of acetylcholine make it difficult – although not impossible – this explanation; on the condition naturally to give oneself the means to search for the possible artefact. The second attitude is to consider that both radionics and "digital biology" have effects which are independent one of each other. Nothing prevents obtaining the same effect by different ways.

But one can also consider that the experiment of radionics as just a mockery of experiment. Thus, it would be only a "control". Water which was naive before being placed in the "device" must remain in the same state. The problem with this "control" experiment is that it completely looked like a "real"

experiment since it also mimicked the "specificity" of the "digital signals". The validity of "digital biology" was thus questioned by an improbable "cause". The challenge on a scientific plan remains unresolved and it is both exciting and disturbing, if not more, as "digital biology". But, at the same time, it is the ruin of the latter. If a mockery of experiment gives the same results, what kind of role do the experimental devices and their theoretical grounds play? Are they only useful to establish a rite that gathers all participants for the same purpose?

The question here is the problem of the experimental control, a problem which is much less trivial than what could seem. According to the paradigmatic frame and the limits which we give ourselves of what is possible or impossible, the conclusions are different. The control is in fact a floor which indicates where we place the border of the possible. But, if the floor collapses, the experimental approach becomes impossible. It is necessary that "nature resists".

The fact that J. Benveniste did not multiply the experiments with the "black box" to demonstrate a dysfunction of the system and quickly dismissed them was indicative of his state of mind. It was the deep feeling that something – namely the "wild transfers" which he named a "devilment" one day – had maybe his source in this "fooled" experiment. A few years earlier, he would certainly have done new experiments to find an "explanation" (contamination, residual activity, state of immunization of animals, "jumps" of activities, etc.) But at this time he felt uneasy. He was in an uncomfortable position for two reasons: on one hand with regard to what he announced with strong conviction, namely the advent of "digital biology", and on the other hand with regard to his own paradigmatic frame which prohibited what appeared to be magical thinking.

At the end of the same year 1996, D. Guillonnet joined the team of J. Benveniste. As we said it, there were many hopes in the control of techniques, electronic equipments and computer systems. Not long after his arrival, D. Guillonnet learnt – but not by J. Benveniste – the story of this disturbing experiment. Apparently, it moved him hardly. He indeed tended to consider that what had been made before his arrival in the field of "electromagnetic transmissions" and "digitization" was not very reliable. If J. Benveniste obtained significant results before his arrival using "electromagnetic transmission" with his early equipment, it was because, according to D. Guillonnet, he was "tremendously jammy" (*sic*).

After the summer of 1996, the result of this experiment was thus repressed and the experiments of Lausanne in September 1997 (Chapter 18) and those of July 1998 (Chapter 19) gave the results that we described and that were more than disturbing for the future of digital biology. After each of these failures,

J. Benveniste was certainly disappointed, though he seemed to digest these setbacks with a certain fatalism. Maybe he thought about this experiment dated June 1996 and all the consequences that had not been drawn. The mists of the disappointment had hardly dissipated, the team continued "to improve reproducibility" in an experimental and technological headlong rush.

With the change of model – the coagulation model and then its automation replacing the isolated heart – maybe J. Benveniste hoped to definitively get rid of this disturbing "devilment" which destroyed his hopes every time he thought he was about to succeed. But, with the experiments intended for the U.S. expertise, the resurfacing of what had been repressed was all the more violent.

Notes of end of chapter

[1] One can rightly blame me for my bias when I talk about "radionics", a domain that I know only superficially. That reproach would be all the more right as my attitude is based on a prejudice of what is possible and what is not. It is completely right. But each of us has his/her own limits and, in the case of radionics, mine are clearly exceeded. To my credit, I must add that I looked into the approach of the upholders of radionics for some scientificity. In vain.

[2] I do not guarantee each of the terms of this conversation. I guarantee nevertheless the content of the questions and the answers.

Chapter 25. A phenomenon even more interesting than "digital biology"?

Another black box?

In fact, another "black box" had already crossed the pathway of J. Benveniste well before the one about which we spoke in the previous chapter. Indeed, when J. Benveniste told how he had the idea of "electromagnetic transmissions", the approach had some logic: first of all "memory of water" with high dilutions, then the theory of G. Preparata and E. Del Giudice with the long-range electromagnetic waves, then the erasing of "memory" by low-frequency electromagnetic fields and finally the low-frequency amplifier. In 1995, he summarized and explained his approach to G. Charpak from high dilutions to electromagnetic transmission in these terms:

> "[I] hypothesized that the effects observed on the first system (achromasia of basophils) after the disappearance of the active molecule with high dilution were caused by a EMF [*electromagnetic field*] induced by the active molecule, maintained by a rearrangement of the dipoles of water molecule. If it was the case, the EM trace must be erased by a magnetic field, what was verified in hundred blind experiments with Vladimir Cagan and Marcel Guyot (Laboratory of Magnetism of the CNRS-Meudon Bellevue). Thermal agitation by heating must also erase the signal; it was actually what was noticed. Also, if the signal corresponding to the properties of the active molecules was of EMF type, it should be possible to transfer these properties by an electronic device; that is exactly what was done. […] Overall, the hypothesis that the observed effect was related to EMF has been very successful." [1]

On another occasion, he told how he got the idea of electromagnetic transmission:

> "[…] the experiments performed in the Central Laboratory of Magnetism seem to establish that the fields present in high dilutions have low frequencies. Besides, I vaguely know the existence of devices supposed to transmit biological data through an amplifier. These installations are used by homeopaths. One of them, doctor Attias, presented me a few years ago the functioning of his machine of the German brand Mora. Originally, the use of this type of device is supposed to help homeopathic diagnosis by sending small electrical charges to the points of acupuncture.

> According to some homeopaths, among whom Attias, it would also allow transmitting the activity of homeopathic substances, from a vial containing a dose of such a product positioned in a place of the machine towards another vial at a second place.
>
> However, as often in the world of alternative medicine […] one does not find many scientific publications supporting these results." [2]

Then, J. Benveniste pursued by describing the experiments performed with the device designed by his friend electronics engineer.

Nevertheless, another version of the events circulated, resumed in particular by M. Schiff who at this moment began to frequent the laboratory of Clamart during the spring of 1992 when the first electromagnetic transmissions were performed. In this other version of events, the homeopath physician, doctor Elie Attias, played clearly a more decisive role that J. Benveniste evoked only half-heartedly.

In fact, as early as 1988, this physician suggested to J. Benveniste to use a curious device of the brand Mora. These devices are indeed used by some homeopaths for "diagnosis" or manufacturing "medicines" which are supposed to have healing virtues. This "bioenergy"-type approach is close to radionics. Needless to say that none of these instruments was the object of a serious evaluation. We are thus exactly in the same scenario as for radionics. A pseudo-scientific speech is stuck on a "device" and its supposed functioning rests on a complex technology that remains mysterious for the layman. But maybe the condition of its "efficiency" is there. M. Schiff reported in these terms how E. Attias intervened in the story of the "memory of water :

> "In June, 1988, a few weeks before the fateful visit,[3] a doctor homeopath, doctor Attias, convinced Benveniste to try his machine. This machine was supposed to transmit chemical information from the plate of entry to the plate of exit. At that time, Benveniste had just learned the theory of the coherent domains of Del Giudice and Preparata." [4]

And M. Schiff pursued:

> "It is difficult to reconstruct these events so long after the facts, but one can imagine that Benveniste, who looked for an explanation of his observations on high dilutions himself said: "after all, why not? We can try." Whatever the reason, Doctor Attias brought his machine to Clamart. According to the lab notes of Elisabeth Davenas, the result of this first experiment was

> positive. According to her notes, she seemed perplexed in front of this result."

Both versions were not contradictory up to here. But M. Schiff specified:

> "After almost four years, Attias managed to convince Benveniste to resume transmission experiments. These experiments were done again in a more systematic manner during the spring of 1992. I remember the phone conversation in which Benveniste spoke to me about the transmission of a chemical activity by an electric machine. I was as sceptical as those who first heard about the possibility of transporting the human voice by an electric wire. I nevertheless attended some of the first trials which were made with Attias. After a few experiments with this machine, Benveniste had another one built, which consisted of essentially two coils connected by an amplifier of low frequency." [5]

Also, in an article of 1999 from the journal *Le Quotidien du Médecin* intended for physicians, it was this last version of the story that was reported:

> "The laboratory of Clamart begins then to use a device (proposed initially by a homeopath, Dr Attias) comprising of an input coil in which a tube of active solution is placed, a low-frequency amplifier and an output coil, in which a tube of naive water is placed that will be active after having received the amplified signal placed in the input. With this device which was cobbled together at first and then quickly improved, Benveniste confirms the first indications in favor of an electromagnetic nature of the signal." [6]

Even if one the sources of the article is perhaps the book of M. Schiff, it is interesting to learn that J. Benveniste then wrote to the editorial board of the journal. First of all, he congratulated it on this "remarkable" article which – it is true – presented his work in a detailed way and very favorably. Especially he wished to fix some "errors". Among them, he was anxious to specify:

> "Doctor Attias came to the lab with his Mora-type machine, *after* I "cobbled together" my amplifier. The principle is very different from it. No experimental series was made on this model." [7]

This was consequently a version that was at the opposite of the one of M. Schiff where E. Attias intervened much more prematurely in the story. Moreover, during the summer of 1992, E. Attias was a little bitter because he had the feeling that his contribution was long forgotten. Although J. Benveniste invited him, he did not participate in the sessions of blind demonstrations

organized in Clamart during the same summer. He also spoke about his "disappointment" with a collaborator of J. Benveniste. To retie the links with E. Attias, J. Benveniste sent him a letter where he explicitly confirmed the version of M. Schiff:

> "It is true that since I have the machine I do not need as much to go boulevard M. [*place of residence of E. Attias*] and you to come to Clamart, which imposed us with incompatible constraints with our timetable. […]
>
> Be assured that you are completely associated with the program. Although my patent attorney regrets that you were not able to give him the technical information about the machine, you are associated with full rights with this process. Also you will be a co-author of any publication on the subject. This is a commitment from my side." [8]

E. Attias was actually a signatory in 1993 of two communications in the form of "posters" at congresses which concerned electromagnetic transmission.[9] But his collaboration with the team of Clamart did not have any development later.

These details are intended to show that the use of the "machine" of E. Attias preceded during the spring of 1992 the construction of the first "official" prototype for electromagnetic transmission by the friend of J. Benveniste who was electronics engineer. It was logical that J. Benveniste "forgot" the exact moment of the appearance of E. Attias in the story or that he said he "vaguely knew" the existence of this type of machine. Reporting the events without omitting any episode and according to the exact chronology meant recognizing that an apparently rational step was in fact founded on a "black box". As for radionics, admitting that the machine of E. Attias produced positive results while it should have produced only mockery of experiments would be devastating for "electromagnetic transmissions" and besides also for high dilution experiments.

An endless pursuit?

Contrary to both "black boxes" which questioned the relevance of "digital biology" and "memory of water", the "eraser effect" was less destabilizing. According to the interpretation of J. Benveniste, one could indeed consider that digital biology is a reality and that its effects can be "modulated" by some experimenters, either "facilitators" (J. Aïssa) or "erasers" (S. Lim). Moreover, even if the "eraser effect" impeded him, J. Benveniste did not deny it and there was no "family secret" about it.

Despite these considerations on the "eraser" effect, Benveniste did not wish however to do any publicity on it. Therefore he preferred not to encourage the proselytism of B. Josephson on this subject. Even if this last one with his aura of Nobel prize laureate was a valuable ally for J. Benveniste, his flirt with parapsychology and his insistence on an "experimenter effect" were not in keeping with the line that the team of Digibio had set. Indeed, if this logic was pushed until its term, the foundations of "digital biology" would be undermined.

This difference on the purposes between the team of Digibio and B. Josephson clearly appeared when this last one answered to a "skeptic" who appeared to "worry" about the silence of J. Benveniste on his experiments. This interlocutor noticed that the Internet site of J. Benveniste became unchanged for two years that is since the announcement of the setting of the automatic device. B. Josephson answered to him early November 2003 via J. Randi who published the exchange of mails on his Internet site:

> "Further research by Benveniste has shown the samples to be affected not only by the "biological signals" applied intentionally in the experiment but, in some way not yet understood, by the experimenters, some of whom facilitate the effect while others inhibit it. [...] I have encouraged him to speak more openly about his findings, which make the phenomenon even more interesting from my point of view."

We indeed understand why these observations strongly drew attention of B. Josephson who wondered about the relations mind-matter. Consequently, for the Nobel prize laureate, these experimental "abnormalities" could be even more interesting than "digital biology" itself. But such a statement obviously offered a perfect target to the various "skeptics" and Randi did not hesitate to laugh:

> "Is there not another possibility that occurs to either Josephson or to Benveniste? Are the windows in their Ivory Tower so heavily frosted up?"

The conclusions of the American team which had examined the functioning of the robot – if we read them attentively – led also to a position which was not so far from the opinion of B. Josephson. The results of this expertise were indeed reported to the DARPA in 2003 [10] and were then published in 2006 in a scientific journal.[11] In their conclusions, the members of the American team – while underlining the failure of an *independent* reproduction of the results –

recognized however that the presence of J. Aïssa was an important condition of the functioning of the robot:

> "We observed apparent inhibition of thrombin/fibrinogen coagulation by a digital signal when one member of the Benveniste team conducted experiments in our laboratory. We did not observe systematic influences such as pipetting differences, contamination, or violations in blinding or randomization that would explain these effects from the Benveniste investigator. However, our observations do not exclude these possibilities."

Cautiously, they added however that their "observations do not exclude these possibilities" and they reminded that J. Benveniste himself had reported similar observations in his laboratory:

> "[*J. Benveniste*] posited unknown interactions with digital signals that produce these effects and states that he observed similar experimenter variability in his laboratory (personal communication). He stated that certain individuals consistently get digital effects and other individuals get no effects or block those effects."

Finally, the authors pointed out that unknown factors could be responsible for the claimed effects, but that it was not the aim of the expertise to assess them:

> "While it is possible that other, unknown "experimenter" factors, such as the influence of chemical residues, energetic emanations or intentionality from individual experimenters could be an explanation for these findings, we did not test these hypotheses nor developed a framework that would control for such factors. Without such a framework, continued research on this approach to digital biology would be at worst an endless pursuit without likely conclusion, or at best premature."

Let us remind to reinforce this conclusion that this expertise practiced an approach that was totally different compared to the other investigations or attempts of reproduction of the results of J. Benveniste. The expertise had been led by taking care to obtain the permission of all the partners at each stage, regardless if they were skeptics or partisans. The purpose, according to the terms of the authors of the article, was to obtain a "fair and collegial" scientific method. This conclusion of the expertise which did not totally exclude "unknown experimenter factors" – but whose the study, once again, was not

the purpose – left open the possibility for a development of future studies having their source in the results of "digital biology".

We thus find in this conclusion two constants which one has repeatedly noticed in this story when investigators studied with honesty, curiosity, "loyalty" and professionalism the experiments of J. Benveniste – not without skepticism for some of them as we have also seen. First of all, there was the recognition that "something", which was not trivial, was obviously at work; at the same time, one had the feeling that the idea of "memory of water" or "electromagnetic biologic signal" was insufficient or unsuitable to explain the claimed results.

Notes of end of chapter

[1] Letter of J. Benveniste to G. Charpak of January 9th, 1995.

[2] J. Benveniste. Ma vérité sur la mémoire de l'eau, p. 129.

[3] It is of course the visit of *Nature* at Clamart.

[4] M. Schiff. Un cas de censure dans la science, p. 57.

[5] *Ibid.* p. 59.

[6] V. Bargoin. « Mémoire de l'eau »: où en sont les travaux de Benveniste sur la signalisation moléculaire ? *Le Quotidien du Médecin*, March 18th, 1999.

[7] Letter of J. Benveniste to Richard Liscia of March 19th, 1999 (emphasis by J. Benveniste).

[8] Letter of J. Benveniste to E. Attias of July 27th, 1992.

[9] Aïssa J, Litime MH, Attias E, Benveniste J. Molecular signaling at high dilution or by means of electronic circuitry. *J Immunol* 1993 ; 150 : 146A ; Aïssa J, Litime MH, Attias E, Allal A, Benveniste J. Transfer of molecular signals via electronic circuitry. *FASEB J* 1993; 7: A602.

[10] Jonas W, Ives J, Rollwagen F, et al. Can specific biological signals be digitized? Unpublished report to the Defense Advance Research Projects Agency. Arlington, Va: Department of Defense, 2003. (This reference is for information; I do not know the content of this report).

[11] Jonas WB, Ives JA, Rollwagen F, Denman DW, Hintz K, Hammer M, Crawford C, Henry K. Can specific biological signals be digitized? *FASEB J* 2006; 20: 23–8.

Epilogue of the second part

"Here lies one whose name was writ in water"

Epigraph on the gravestone
of the poet John Kates

What must be concluded?

Having ended the reading of this second part – and more particularly the last chapters – the reader can feel his/her intelligence a little bit "scattered". What view should be taken of these "active" controls? of "black boxes"? of "wild transfers" and other "inversions"? of "facilitators" or "erasers" that appeared to interfere with the functioning of these machines supposed to work automatically? What is solid in this story? Should we not give up such a shaggy-dog story for a more substantial and more rational occupation?

In order for the reader to recover his/her senses, we are going to recapitulate at first the successive biological models and their variants which were set up by J. Benveniste's team. This recapitulation summarized in the above table enables to become aware how this technical evolution allowed obtaining successive experimental systems that were less and less exposed to criticism.

We notice that every step forward allowed freeing from the inconveniences and criticisms of the various experimental systems. To take only the most important stages, the electromagnetic transmission allowed eliminating the possibility of a residual contamination in high dilutions; the digitization allowed eliminating the possibility of an interference of the electromagnetic background with "informed" tubes during the transport and the storage of samples; the direct transmission to the biological system allowed avoiding the use of an intermediary, a possible source of "wild transfers". Finally this technological headlong rush peaked with automation of the system of coagulation thanks to the robot analyzer which was supposed be the ultimate in digital biology by avoiding the effects apparently related to the experimenter.

In spite of these improvements, it was almost always a failure when the order of samples or recordings must be determined in blind conditions during large-scale public demonstrations. By contrast, the results with open-label samples or recordings performed in the same conditions were almost systematically successful. It was as if it was forbidden to demonstrate the validity of what was nevertheless daily observed in the closed space of the laboratory. The reader who now knows the whole story can hesitate between several attitudes that will be successively considered.

Evolution of the successive experimental model set up by J. Benveniste and his team

Biological model	Advantages	Inconvenience
High dilutions and basophils *(First part)*	- Sensitivity of the method?	- Difficulty to discard arguments about subjectivity and possible contaminations - Needs trained experimenters
High dilutions and isolated heart *(Chapter 3)*	- Spectacular effect and "in live" - No subjectivity	- Argument of contamination still present - Cumbersome method
Electromagnetic transmission and isolated heart *(Chapter 1)*	- Spectacular effect and "in live" - No subjectivity - Independence from homeopathy but nevertheless related with high dilutions	- Cumbersome method - Interferences of the electromagnetic environment with "informed" water? - "Wild transfers"?
Digitization-transmission and isolated heart *(Chapter 12)*	- Permanency of the "recordings" - Possibility of "signal" analysis	- Cumbersome method - "Wild transfers" and "inversions" in blind conditions
Digitization and direct transmission to isolated heart *(Chapter 17)*	- No contamination (no water samples)	- Cumbersome method - "Wild "transfers" and "inversions" in blind conditions
Digitization and direct transmission to isolated heart with 3 signals (up, down, null) *(Chapter 19)*	- No contamination (no water samples) - Specificity directly evidenced	- Cumbersome method - "Wild transfers" and "inversions" in blind conditions
Digitization and coagulation (1) visual assessment of coagulation (2) measurement of optical density) *(Chapter 20 and 21)*	- Simplicity of the method - Easily "exportable"	- Experimenter effect? - "Inversions" in blind conditions
Digitization and coagulation (automatic method) *(Chapter 21)*	- Completely automatic experiment - Experiments always blind - No possible contamination	- Experimenter effect??

A collective mystification?

The reader may think that, after all, the easiest attitude would be to conclude this as a collective cheating. It is actually the most peaceful solution for the mind. Nevertheless, the number of experimenters and the successive experimental models lead to the same conclusion: there is something which is not banal and which has a scientific interest. I have certainly an advantage on the reader because if all results were obtained with cheaters, I must be one of them. I shall also add a psychological element. Indeed, it is necessary to have seen the successive collaborators of J. Benveniste working for years, having discussed their results with them in an informal way, having even joked with them about these disturbing results, having observed the hopes, the disappointments to understand that this idea of a collective and massive forgery does not stand up. And all of that during almost twenty years (from 1984 till 2004). Moreover, because of this long period, some of the successive collaborators of J. Benveniste never met.

To take just one example, let us reassess the experiments of July, 1997 which were caricatural (see Chapter 19). Performed in "friendly" laboratories, without publicity, with a limited number of participants, an incredible masochism would have been necessary to perform experiments whose results were almost systematically "in disorder", while there were various tricks to guess the "good code" unbeknownst to the coder. Cheating, certainly, but with convincing results! Is it necessary to add the charge of stupidity to that of fraud?

Of course, there were different versions of this charge which tried to separate the responsibilities, without being afraid of contradictions. It was – according to the rumor - J. Benveniste "who put pressure on his researchers" or on the contrary it was "somebody who cheated behind Benveniste's back" or "crooks who surrounded Benveniste" (in its most unpleasant version, the rumor sometimes compared the team to a "sect").

A collective incompetence?

The idea of a collective incompetence is the counterpart of the idea developed in the previous paragraph: "they are honest but they "crashed"" or in a more "psychiatric" version specifically targeting J. Benveniste: "he is honest but crazy" or more frequently: "he was competent, but he lost his mind".

Nevertheless we saw in the second part that the experimental systems were questioned at no time. Thus, the isolated heart device has not been criticized by the diverse specialists of cardiac physiology and a standard procedure had even been elaborated in common with the National laboratory of health. Likewise,

the robot for the study of coagulation had not been criticized in its functioning and in its principle by the U.S. multidisciplinary team. Let us specify also that during these years, identical or similar biological models were used in the same premises – sometimes at the same moment – to perform "classic" research (basophil degranulation, isolated heart device, platelet aggregation). The methods were not criticized, but the results or their possible consequences. Thanks to these diverse models, "classic" publications in high-level journals have been published during the same years by J. Benveniste and his collaborators. Some of his collaborators had even (successively or in parallel), a "classic" activity – published in high-level journals – while participating in these clearly more mind-blowing experiments. Except a collective case of mental dissociation, how can one explain that an experimenter could obtain wise results in the morning – accepted after inspection by the "peers" – and that the same individual with the same biological model would be committed in the afternoon in practices close to magic and hazardous for his/her professional future?

Perhaps the explanation is rather that results are differently treated by the "scientific community" according to their presumed (and often fantasized) consequences. One could see here a perfect illustration of the remark already quoted from the philosopher of the sciences, Feyerabend: "Facts, logic, and methodology alone decide – this is what the fairy-tale tells us".

An effect truly related to "memory of water"?

It is the heart of the subject. Indeed, it is under this form that the results of J. Benveniste were popularized. If one gives up the "memory of water" as a key for reading of these results, the price to be paid is important, as we have already said. Indeed, if we abandon this hypothesis, what are the other interpretations that can be suggested to explain the results? Another explanation has all the chances to need more hypotheses. Indeed, "memory of water", that is the idea that water is structured, is in fact the most immediate and the most "mechanistic" explanation.

However, one must recognize that in front of massive and repeated failures, it is increasingly difficult for the initial hypothesis to resist. We saw that the experimental "improvements" intended to rule out possible artifacts or interferences always faced in front of the same barrier: the supervision of these effects by independent observers. More exactly it seemed that the demonstrations became flimsy when the different components of the entity "experimenter-experimental device" were separated. It was the case when the samples of an experiment were coded by an external supervisor or when a "talented" experimenter was not present.

Concerning possible "eraser" effects which would be a cause of failure during demonstrations or attempts of reproduction of the experiments, it is very difficult to conclude. Indeed, this "inhibitory effect" would act on another hypothetical "effect" that appears to depend on the "presence" of a given operator! It then becomes very difficult to know who does what!

If the cause of the observed effects is indeed due to "informed" water, in other words if the answer is well present in the tube, then doing the experiment in blind conditions should not be a problem.

An effect related to the experimenter?

So, is this an effect related with the experimenter as suggested in the article of the U.S. team of DARPA? But are we talking about a "classic" influence, involving chemical mechanisms, for example diffusion of molecules on the model of pheromones that transmit specific information? Or about physical mechanisms such as broadcasting of electromagnetic waves? And in this case, how can one achieve such a degree of specificity?

Thus, some people speak about a "Jamal effect" to underscore that the experiments worked correctly only in the presence of J. Aïssa. It was the case for J. Ives about whom we spoke as for the DARPA expertise. Without going so far, J. Benveniste explained that J. Aïssa was a "facilitator" of the experiments – as E. Davenas was with basophils – whereas others on the contrary negatively interfered with the experimental system. Some commentators, including the inevitable J. Randi and other skeptics, mocked this idea because it was clearly distance oneself from science. Indeed, the experimental method is based on a strict separation between the observer and the object of study. Any "collusion" between the "observer" and the "observed" prevents an "objective" description of the world. Indeed, the answers obtained from "nature" are at risk of reflecting only the preconceptions and expectations of the experimenter.

What is a scientific research without adventure?

Maybe others will tell the period which extends from 2001 after the "U.S. expertise" until the death of J. Benveniste in 2004 and perhaps beyond if this work is pursued. As for me, I will be stopping the narration of "memory of water" here. The experiments with the robot intended to perform the whole experiment automatically and the expertise by the U.S. team appointed by the DARPA are indeed a "summit" – in my opinion the highest – which has been achieved during the story of the "memory of water". As suggested by W. Jonas

in conclusion of the investigation which he managed, to continue with the same conceptual framework has the risk of being an endless pursuit.

I shall nevertheless add this extract of a text of J. Benveniste published by the economics newspaper *Les Echos* a few weeks before his death. It was an answer to the newspaper which had made a "summer series" reporting several scientific controversies. The case of the "memory of water" was obviously mentioned. Faithful with his habits, J. Benveniste was anxious to correct a number of errors and approximations. Especially, he brought the following precision:

> "The non exclusive rights for seven patents held by the company DigiBio, including one validated by the US Office of Patents [1], concerning Hertzian digital biology […] have actually been bought by a North American company for a million euros.
>
> This cession was possible, not because this company was "intrigued" or charmed by my "music", but after a series of blind experiments. An anticoagulant drug was digitized at San Diego by our processes. The file/signal received at Clamart by e-mail was broadcasted to water, which has inhibited the coagulation as the molecule of origin would do. […] North Americans are not known to be poets who invest in anything when hearing the first music tune.
>
> The purchase of these rights is the sign of the emergence of the necessary change of paradigm in biology. The failure of structural biology is visible by all; let us make room now for information biology, for the molecular signal as rapid as light and digitized. We hope for a myriad of applications, for example detectors of toxic or microbial pollutions, either accidental or criminal, or electromagnetic antiviruses… It will certainly be an adventure. But what is a scientific research without adventure?" [2]

Beyond the debate and the scientific aspect (not to mention the commercial and industrial dimension evoked here) concerning the "reality" of the phenomena observed by the team of Clamart, I wish to end on this last sentence. It indeed enlightens the motivation of the action of J. Benveniste: research as last ground of adventure. It is on this ultimate apostrophe sent to all the researchers and especially to the future researchers, to all the "believers" and "unbelievers" of this iconoclastic work, that we shall close this narrative.

And now?

The story of the memory of water is still a fascinating puzzle and the perplexity associated with this affair can only continue to excite curiosity and stimulate explanations which are different from those that have been repeated over and over again. The remark of the newspaper *Le Monde* of August 1988 considering the affair of the "memory of water" as "one of the most fascinating scientific affairs of these last years" is thus still valid.[3] Today, looking back, in spite of the considerable experimental effort, we cannot help but continue to support this statement. Our wish is that the set of experiments and events that we reported during this narrative could be considered from a fresh perspective and be the Rosetta stone of the "phenomena of Clamart".

In a third part – which will be the subject of a new work – we will try to make a synthesis of this outstanding story. We will try to discern gray areas and anchor points. In particular, we will insist on a "hard core" of results which, presented under a previously unseen angle, will give a singular perspective on this adventure. And if homeopathic high dilutions, "memory of water", "digital biology" had been trees which camouflaged the forest? And if the focus on water and fascination had managed to divert the attention from another phenomenon which was even more fascinating and unexpected?

Notes of end of chapter

[1] This is an allusion to the patent #6,541,978 of the US Office of Patents "Method, system and device for producing signals from a substance biological and/or chemical activity" (April 1st, 2003).

[2] J. Benveniste. Mémoire de l'eau : le débat reste ouvert. *Les Echos*, August 28th, 2004.

[3] Jean-Yves Nau. *Le Monde*, August 9th, 1988.

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