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 transmited 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 favour 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" cheeting! 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 climat 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 clearcut and spectacular (Figure 5.1).

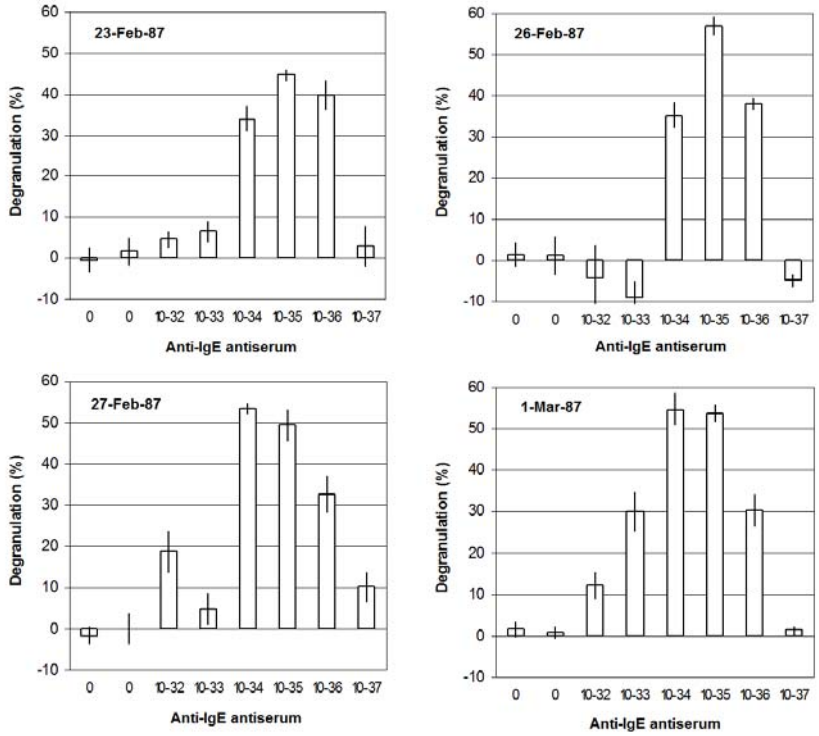

Figure 5.1. These graphs summarize the first four experiments perfomed in Israel by E. Davenas. Every bar represents the mean with its standard deviation of 3 repetitions within the same experiment. The tubes of dilutions were coded; the code of the experiment of February 23rd was a unique code and the 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 Rehovoth 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. Dekman, 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 randomely 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). Thre 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 advise 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 Israël 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 myself, 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 secretely 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 albumine 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 ben 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 commited 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, calcicum 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's 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.