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 phenomena of “inversion” was 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 wasone 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 autobreakable 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 endotoxins. 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

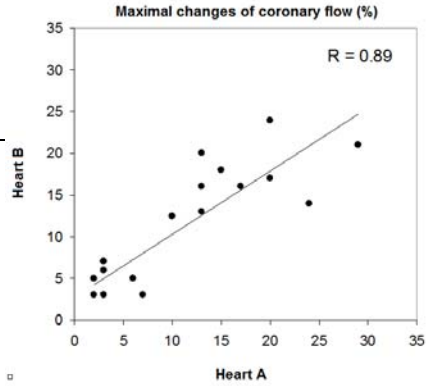

Figure 5.1. Blind experiment intended to show "contamination" of physiological salt solutions. Ten flasks of physiological salt solution (5 from a French and 5 from an American pharmaceutical company) were blinded and tested on rodent isolated heart model (from December 1st to 3rd). Out of 10 flasks, 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.

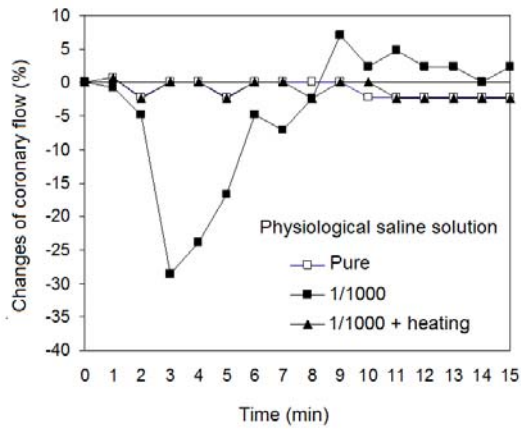

Figure 5.2. Experiment of February 17th, 1993 attached to the text submitted for publication to *The Lancet*. This experiment was performed on the same day the manuscript was sent to the journal in order to show both the current and dramatic aspect of the results. Moreover, this figure shows that dilution 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.