Follow-Up

The contributions in this section continue the discussion of issues arising from the Benveniste controversy, as reported worldwide last year and in a Special Report in our Winter 1989 issue.—EDITOR

When *Not* to Believe the Unbelievable

Wallace I. Sampson

"WHEN TO Believe the Unbelievable" read the headline of an editorial commentary in *Nature* (337:787, June 30, 1988). It explained that *Nature* had published an article whose conclusions seemed to support the principle of homeopathy, in that very dilute "solutions" of an antibody, so dilute that no molecule was likely to be left in them, seemed to have the same power that was present in optimal concentration. *Nature*'s editor, John Maddox, hoped that "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."

Nature selected a three-man panel, John Maddox, James Randi, and Walter W. Stewart, to investigate the homeopathy team's methods. The panel found sloppy controls, and fudging of data, and demonstrated that the experimenter could not replicate her results when the controls were tightened. A storm of letters reporting negative results of repeated experiments followed as well.

However, the question remained: By a critical reading of the original paper, could one show the claims to be invalid? Careful analysis of the study shows that, even if the experiments and the results were authentic, (1) they are unreproducible, thus of no use to homeopathic practice, and (2) the results suggest that homeopathy is more likely to worsen a patient's condition than to heal.

The first clue to nonreproducibility is in the third paragraph of the Benveniste report: ". . . Similar results were obtained *at one or the other part* of the high dilution scale in the participating laboratories (Toronto, preliminary results)." If the experiment were reproducible, the specific dilutions would have been consistent at all parts of the scale from one lab to another. This was the first clue that the peak activities reported were actually random.

Later in the paragraph is the statement: "The repetitive waves of anti-IgE-induced degranulation *could shift by one or two dilutions with every fresh sequential dilution of anti-IgE and depended on the blood sample.*" Each dilution in homeopathy is usually tenfold. The mean number of dilutions between each peak and the adjacent troughs in the paper's Figure 1 was 3.94 dilutions. If the peaks and troughs of activity could vary by one or two dilutions either way, the peak value of activity in one could shift toward a trough value of the next. Since this variation pertains to the same solution in sequential runs, predictability from any single solution is impossible. In other words, a homeopath might "prove" a specific dilution to be effective in a patient once, but could not be certain of the same effect at the time

of the next dose. The researchers should have tried to explain this inconsistency, but the problem was not recognized or was ignored.

The second problem is the conclusion that these results support the theory and practice of homeopathy. The authors state: "These results may be related to the recent double-blind clinical study of Reilly et al., which showed a significant reduction of symptoms in hay-fever patients treated with a high dilution (1×10^{60}) of grass pollen vs. placebo. . . ."

However, the results show that very dilute "solutions" (in this case, water only) seem to produce the same effect as solutions of optimal concentration of material. If the water still shows effects quantitatively the same as those of concentrated solutions, it should reproduce quantitatively the symptom of the illness. In this case, the water causes just as much histamine release from basophil granules as an optimal amount of an allergy-causing substance. Therefore, the treatment solution would cause just as much asthma or hayfever as that produced by maximum stimulation by the allergenic material. One must conclude that the results paradoxically support the view that if homeopathic treatment "works," it must make one worse or prolong the illness.

On a practical level, since homeopathy has never been "proved," analysis of the Benveniste paper supports the skeptical view that homeopathic solutions are in reality ineffective, that the results of these experiments have other explanations, such as contamination or fudging of data, and that any improvement in symptoms from homeopathic solutions is probably from placebo effect or suggestion. •

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The Benveniste Case: A Reappraisal

Elie A. Shneour

Most people who have followed the unfolding of the Benveniste case are royally surfeited with it, and for good reason. But the case raises a very troubling issue for the skeptics movement, and for the scientific community worldwide. It is disturbing because of the way the following question has been raised and, in the view of this writer, too glibly answered: Was there scientific impropriety or fraud involved?

The Maddox committee, which investigated Benveniste's laboratory in France, published its report in the prestigious scientific publication *Nature* (Maddox, Randi, and Stewart, 333:816, 1988). It scrupulously avoided suggesting that either scientific impropriety or fraud might have been involved in the generation of the data published in *Nature* by Benveniste and his associates (Davenas et al., 333:816, 1988). The report acknowledges its gratitude for the gracious openness with which Benveniste received and treated the committee during its stay at Clamart. Benveniste allowed the committee access to and the extensive photocopying of all the relevant material it desired. In fact, Benveniste offered to extend the disclosures to other systems

purporting to show the same kind of results. This cooperation extended beyond Benveniste to his associates, in particular Elizabeth Davenas, on whom the committee relied most heavily for information about the experimental procedures in the laboratory.

The committee was justifiably puzzled by attitudes and biases exhibited by Benveniste and his associates, which in many instances would be considered unorthodox, to say the least, by most experimental scientists. The experimental system, the data-gathering procedures, as well as the results reported by Benveniste are claimed to have been tested and confirmed by several independent laboratories in Canada, Italy, and Israel, respectively. Benveniste provided this writer with the correspondence from the Hebrew University of Jerusalem confirming the results obtained at Clamart.

For example, a letter dated July 31, 1988, from Boaz Robinzon of the Faculty of Agriculture, begins this way: "I want you to know that no matter what the *Nature* investigating committee has written, I am still confident that the phenomenon observed is a real and reproducible one and it is only a matter of time until we shall be proven right [*sic*]." In this connection, it should be added that Elizabeth Davenas from Benveniste's laboratory did spend the period of February 23 to March 2, 1988, in the Israeli laboratory. This writer has no independent reliable information on the confirmatory work reportedly performed at the other laboratories.

This writer, a native of France and fluent in the language, went to France last September to visit INSERM, the medical-research institute sponsoring Benveniste's work. He met with high officials of INSERM, some of them personal friends and scientific colleagues of long standing. As a result, he was informally invited to visit Benveniste at his laboratory at Clamart to form his own opinion of the controversy. This he did at some length, receiving the same open and gracious welcome and cooperation reported by the Maddox committee. He also met with several of Benveniste's associates, including Elizabeth Davenas and a number of technicians.

The goal of this intervention was to attempt an independent determination of the following: Did the Benveniste *Nature* report represent: (*a*) a significant but unappreciated discovery of a new phenomenon; (*b*) an artifact due to some as-yet-unidentified systematic error or errors, perhaps overlaid by naive experimental biases; (*c*) the result of scientific misconduct or fraud, consciously perpetrated by one or more of the investigators involved?

A significant but unappreciated new phenomenon? It was fairly easy to dismiss this possibility on the basis of the available evidence, and for the reason eloquently stated as the prime conclusion of the Maddox committee report: "The care with which the experiments have been carried out does not match the extraordinary character of the claims made in their interpretation." The committee should have added this obvious further conclusion: The data and their interpretation did not deserve publication. *Nature* Editor John Maddox, a member of the group, should have had the courage to admit his appalling error of judgment.

The results are an artifact? This appears to be the most likely possibility. From Benveniste's perspective, it should be highly questionable whether it is worth INSERM's human, time, and technological resources to try to justify his prior results by protracted additional work that might be more profitably applied elsewhere. But it might be interesting to try to identify the systematic error or errors that might have been responsible for the published results. A number of scientists, including this writer, have suggested experiments to Benveniste that could perhaps provide an explanation for his results. Scientific research often advances by unwitting mistakes made in the design and execution of experiments, which may uncover unexpected results.

But it takes a great scientist to separate the wheat from the chaff and recognize the significant factor involved in the generation of puzzling results.

Was there impropriety or fraud involved? This question lies, from the standpoint of the Maddox committee report, at the unstated core of the controversy—unstated, to be sure, but strongly implied by the composition of the committee and by its reported behavior during the Clamart visit. Among the latter is the high-jink of a sealed envelope containing the experimental codes attached to the ceiling of the laboratory. Such codes, for example, would contain information as to which numbered experimental sample contained what anti-IgE concentration. The researcher determines with a microscope how many, if any, basophils can be degranulated with a given blind sample, so that experimenter bias is effectively eliminated. Only after all the samples have been counted blind are the codes broken and each sample identified and correlated with the microscope reading.

In this context it is important to note that "reading" basophils in the microscope is far from a simple black-or-white determination. It is frequently difficult to tell an intact from a degranulated basophil, using a standard staining technique. Differences of opinions are possible in the making of such determinations. Nonetheless, there were fundamental and unexplainable discrepancies observed between blind and uncoded experimental readings that could be interpreted as involving scientific impropriety or fraud.

Although the Maddox committee report makes no statement suggesting fraud, two of its members have subsequently stated that scientific impropriety and fraud were, in fact, involved. This writer has heard both of them make this accusation without qualification. Although it is manifestly impossible at this point to unequivocally rule out scientific impropriety, trickery, or fraud, the circumstantial evidence alone, in the opinion of this writer, argues against such an accusation. This circumstantial evidence is briefly summarized as follows:

1. The openness, courtesy, and cooperation exhibited to all comers to Benveniste's laboratory and its staff. This writer is not aware of any attempt to withhold any document, any laboratory notebook, any interview, or even any humiliating requirement (i.e. the code taped to the ceiling). Any document, of whatever nature, could be freely photocopied and removed from the laboratory without any restriction. This is hardly the behavior to be expected from the perpetrators of fraud.

2. The obvious concern of Benveniste for recognition of his basic integrity that has compelled him and his staff to be repeatedly and mercilessly examined. This includes one item referred to in the Maddox report about a blinded experiment whose codes were sealed *in situ,* at the initiative of Benveniste, by a legal official in Clamart, Maitre Simart, but which were not available to the committee. This writer was able to obtain a copy of Simart's four-page sworn deposition of the detailed procedures he participated in on April 22, 1988, to maintain the integrity of the codes used in key experiments performed by Benveniste and his associates. This deposition seems to this writer to be an impeccable and one but too involved to be detailed here.

3. The unrecognized importance of the technician's role in a French laboratory. Most laboratory technicians in France, and especially in government-supported research laboratories, belong to a powerful trade union. This places them in a rather peculiar and, for all practical purposes, an invulnerable adversary position with respect to senior research investigators. Benveniste's laboratory has five such technicians, and this writer had the opportunity to interview two among them. Had there been any attempt at impropriety, trickery, or fraud, the technicians would have quickly

been able to detect it, and the news would have been in the press the very next day. These informal interviews, conducted in French, could elicit no suspicion of any possible malfeasance in Benveniste's laboratory.

4. Benveniste's public and private anguish and indignant responses. For example, he told this writer that on the first days of the committee's visit, while examining some experimental data, Walter Stewart is alleged to have bluntly and summarily concluded that "[thèse data] . . . are made up." In his several public statements, including those published in *Nature,* Benveniste challenges some of the committee's procedures, interpretations, and conclusions. The nature of some of the disagreements between Benveniste and the Maddox committee are fairly arcane and are not detailed here. They are not likely to be satisfactorily resolved without additional laboratory work, and in any event, they do not address the conclusions to be reached in this essay.

In a letter sent to *Nature* on September 20, 1988 (334:291), Benveniste asks: "A fraud implying five labs?" and complains of the circuslike atmosphere he claims was generated by the Maddox committee. He asks, for example, why [the] fraud-seeking pantomime of sticking the . . . code . . . to the ceiling . . . why not in their pocket since they know the code? Because they wanted to catch the villains tampering with the sacred paper. . . ." In another context Benveniste asks how it is possible to claim, as the Maddox committee did, that his published data is meaningless on the one hand and implies that it is fraudulent on the other. That it tries to have it both ways, continues Benveniste, demonstrates that the committee has not been able to come to any tangible conclusion regarding his *Nature* report.

Conclusions

What is one to make of this controversy? Actually a great deal. And it has nothing whatsoever to do with peer-judgment on the substance of Benveniste's *Nature* report. It has everything to do with the process by which this controversial work was evaluated and the conclusions reached. The fundamental fact is that the scientific community, which ought to be the final arbiter of published work, has not had the opportunity to respond to the *Nature* publication. Instead, "self-appointed keepers of the scientific conscience" (in Benveniste's words) with "no substantial scientific published record" took it upon themselves to pass judgment not only on the scientific worth of the work but also with what appears to have been a preconceived bias that Benveniste's data was fraudulently generated.

Benveniste (1988) states: " . . . Salem witchhunts or McCarthy-like prosecutions will kill science. Science flourishes only in freedom. . . . Our colleagues are overwhelmingly utmost decent people, not criminals. . . . Indeed, there is today a tendency in the United States to assume the worst when a controversy about the validity of published scientific data emerges. It is true that there has been a plethora of deplorable examples of scientific fraud exposed in the past few years. But it is important to emphasize that these have been extirpated, and mostly by peer action. What is new is the emergence of watchdogs of scientific purity, whose well-meaning but ferocious zealotry has already had a significant chilling impact on scientific work. When honest mistakes, differences of opinion, and often the fierce infighting for priority among investigators are too readily labeled as fraud, the whole scientific enterprise is placed in jeopardy.

Another example of this type of witchhunt is the recent and distressing experience of David Baltimore, a Nobel laureate, head of the Whitehead Institute for Biomedical

Research in Cambridge, Massachusetts, and the coauthor of a disputed report in the scientific journal *Cell.* In an extensive letter of record dated May 17, 1988, which Baltimore sent to his colleagues worldwide in the defense of his integrity, he wrote: "I believe that it is of critical importance that I set the record straight, not just to clear my own name and the names of other authors who have been compromised by this attack, but for another, more compelling reason: A small group of outsiders, in the name of redressing an imagined wrong, would use this once small, scientific dispute to catalyze the introduction of new laws and regulations that I believe would cripple American science."

To accuse a reputable scientist of dishonesty, trickery, impropriety, or fraud is equivalent to pronouncing a death penalty on his reputation and credibility. Although Baltimore and his colleagues in the *Cell* report have been vindicated by a National Institutes of Health investigating committee, which found errors but no evidence of fraud, the damage has been done. At least one congressional committee, perhaps two has been looking into the possible legislation of honesty in the research laboratory. The powerful committtee headed by Congressman John Dingell (D-Michigan) continues to hold star chamber hearings that exhibit no understanding of how science is done. If legislation results to create an organism for the sanitization of science, longterm damage to the scientific enterprise in this country is likely to be the unfortunate result.

Although one can expect insensitivity and misunderstanding of the scientific enterprise in the U.S. Congress, this should not be the case among the skeptics community. Our credibility and the respect in which our challenges of pseudoscience are held too precious to squander by the quick or careless application of one of the most powerful weapons in our arsenal: the application of the label of "fraud."

Our primary task is to educate, not to debunk. We must provide the citizen with alternative options to optimize his ability to think on his own. A fundamental principle of Anglo-Saxon jurisprudence is that a person is considered innocent until proved guilty by his peers. And that it is better for society to let a few guilty persons escape the net of justice than to convict a single innocent one. This is even more critical in the scientific endeavor, if we are to make the fruits of science work for the collective benefit of our civilization.

On the basis of the available evidence, this writer does not believe that Benveniste's laboratory has knowingly engaged in dishonest behavior. In his opinion, there is no compelling evidence to sustain such a serious and damaging charge. Under the circumstances, the wisest and most constructive course for us to follow is to help the scientific community invoke the powerful and ultimately always effective self-correcting peer mechanism. It should be allowed to operate unhindered by the inappropriate mechanisms that have so badly clouded the Benveniste controversy. •

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'Remembering Water' and the Bell Curve

James Randi, in "The Case of Remembering Water" (*SI,* Winter 1989), asserts that "any data obtained by counting or measuring samples (people, cells, weights, stars, etc.) is subject to the rule that it must conform to a 'bell-shaped curve.' " Although the concept of a bell-shaped (Gaussian or normal) curve may be applicable to the remembering water controversy, it does not have the universality attributed to it by Randi.

To take an example of a sample he mentioned (counting people): If a large enough sample of the current population of the U.S. were obtained in order to determine the relative size of each ethnic group, including Caucasians, the concept of a Gaussian curve would be irrelevant. Many curves other than the Gaussian (normal) are possible. As Hayes puts it in his *Statistics for Psychologists* (1963): "The normal distribution is but one of a vast number of mathematical functions one might invent for a distribution; it is purely theoretical. . . . The normal distribution is not a fact of nature that one actually observes to be exactly true. . . . It happens to be only one of a number of theoretical distributions that have been studied and found useful as an idealized mathematical concept" (p. 218).

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James Randi's comment that "self-deception and data flummery are not as rare in orthodox science" as one might suspect struck a responsive chord. One needs only to spend a semester or so teaching experimental methodology or consulting on problems in data analysis to reach a similar conclusion. If *SI* were to examine "regular" research as eagerly as it does the fringes, each issue might well be a massive tome.

Nonetheless, I have some problems with Randi's report as it appeared in print. It is not clear to me exactly how he determined, from the data, that Benveniste and his team had used "unorthodox methods" to obtain their data. It is apparent that Benveniste's data do not fit the "appropriate" Gaussian distribution shown in Randi's Figure 1, but nothing explains why the distribution is "appropriate." Perhaps more space could have been devoted to a careful explanation of the Central Limit Theorem, its implications, and its limitations; appropriate statistical values could also have been reported to bolster Randi's case.

However, as it stands, Randi's report relies upon the same appeal to authority that has so often been, and should be, grist for *SI*'s mill.

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While it is true that the Gaussian bell occurs often enough that it is also called the "normal distribution," its *universality* is no more than a common misconception. To take an obvious example, I would not expect the number of X-chromosomes in our cells to show a bell curve no matter how many cells you count; the same goes for a variety of quantized genetic traits, such as eye color or the amount of B-antigen in blood.

Another common distribution is the exponential, which has a peak at zero and falls off by a constant fact or for each unit of measure. (A graph of such a distribution resembles that of the changing radioactivity of a sample over time.) We might expect "the number of hard facts in an issue of the *National Enquirer*" to show such a distribution.

Strictly speaking, most natural measurements cannot match the Gaussian bell as a whole, because it has a "tail" extending to infinity in each direction: For any value, no matter how extreme, a truly Gaussian population shows a finite probability. Human adult height, for example, may be roughly Gaussian over the range of, say, 4 to 7 feet; but no human is 18 feet tall, much less negative 2 feet! (Similarly, because the *National Enquirer* is limited in size, the distribution mentioned above should show a sharp cutoff.)

The more glaring error is the assumption that there is only one true Gaussian bell curve. Wrong. The curve is determined by two things: its mean and its "standard deviation," a measure of variability. Stewart apparently graphed a generic curve with a standard deviation of 1.

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The End of the Affair?

An Update: In July two committees reporting to the French national institute of health and medical research (INSERM) strongly criticized Jacques Benveniste's work on the "remembering water." In a statement to the press, the INSERM directorate said the two committees offered "a very favorable opinion" of the overall activities of Benveniste's laboratory, INSERM Unit 200, but were "extremely reserved regarding the studies of high dilutions." The statement criticized Benveniste for "an insufficiently critical analysis of the results he reported, the cavalier character of the interpretations he made of them, and the abusive use of his scientific authority *vis-à-vis* his informing of the public." The scientific committee's report said Benveniste's interpretations were "out of proportion with the facts" and appear as "a laboratory curiosity to which satisfactory explanations have not yet been given and whose import will remain limited." It recommended INSERM not continue funding high-dilution research.

However, Philippe Lazar, INSERM director-general, did not endorse that latter recommendation, suggesting to do so would interfere with the freedom accorded a laboratory director. In a four-page letter, Lazar asked Benveniste to look for sources of experimental error to explain his "unusual results" but also strongly criticized *Nature* for its handling of the matter, starting with its decision to publish an "insufficiently founded" paper, for the "oddness" of its visiting panel, and for the "offensive content" of its conclusions. He appealed to the media to "let Dr. Benveniste get on with his work." Benveniste, for his part, in a letter to *Le Monde,* said he *had* tried to find other explanations for his results and said the affair will "finish badly, in the utmost banality." He praised Lazar's letter: "Wisdom and courage have prevailed."

—*K.F.*