

Citation Perspective on Jacques Benveniste—Dew Process at Last?

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Introduction

It is now more than six months since Jacques Benveniste, INSERM, Clamart, France, presented his controversial data.¹ He and others claim that the effect of a protein can be observed at dilutions that preclude the existence of a single molecule of the protein in solution. It is not surprising that we classified this controversy as a "Hot Topic" in the *ISI® Press Digest* section for September 26, 1988.² *THE SCIENTIST®*, too, recognized the significance of the paper and published articles and letters on the Benveniste affair.³⁻⁸

The *Press Digest* headline chosen was "Can publishing unbelievable results serve science?"² Three articles were digested: "A debate over discredited data," an article by science writer Walter Sullivan in the *New York Times*⁹ that noted arguments that the Benveniste paper presented "scientifically unreliable experiments" and that the report was "'more flimsy' than an editor would like"; "A public service?" an unsigned editorial in *Nature*¹⁰ defending its publication of the Benveniste paper; and "A conflict of interest?" an article by science writer Robert Pool in *Science*¹¹ that questioned the way *Nature's* editors handled the publication and follow-up (!) investigation.^{12,13}

Benveniste's Letter

Professor Benveniste wrote us expressing his displeasure with our treatment of the subject:

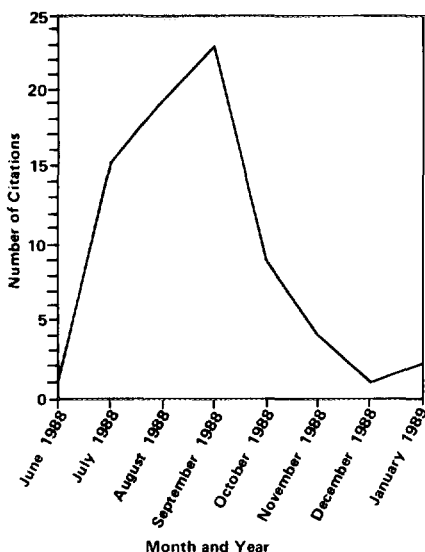
The [Press] digest [ED: September 26, 1988, issue #]39, pp. 9-10, is heavily tilted in favor of the *Nature* report. What is unbelievable and discredited is the latter. You are at risk, in taking this position, that our data are true. And, unfortunately, they are. It is enough to look *calmly* at our original paper, and the *Nature* report itself, to see that they are undisputable. Should the ligand be at normal concentration, nobody would have discussed them a minute. These "irreproducible" results have been reproduced in six laboratories all over the world. The "able" opinion of Metzger [ED: ref. 14] is deadly to science. Why not "digest" my answer presented in *Science* 241, 1028 [August 26, 1988] [ED: ref. 15]. It would add some fairness to the two *Current Contents* pages that will eventually prove devastating to all authoritative but unsubstantiated opinions that *Current Contents* reflected so eagerly.¹⁶

The Current Contents Response

Benveniste's egocentric remarks notwithstanding, we may inadvertently have done him a disservice to highlight this controversial subject so briefly. Since space is limited, the *Press Digest* section of *Current Contents® (CC®)* is not primarily intended to promote or to discredit any particular viewpoint. When we discuss papers in essays, then we may be concerned with their impact—how often cited and by whom.

It will be interesting to observe how often Benveniste's paper is cited in the future. Whether its fate is that of super water or other contentious developments, or to be a

Figure 1: Month-by-month SCT®/SSCT® citations to Davenas E et al. *Nature* 333:816-8, 30 June 1988.



Citation Classic® remains to be seen. Figure 1 shows the month-by-month citation count to the original *Nature* article by Benveniste and coworkers. However, citation in the scientific literature is only part of the influence (see Table 1). For example, a note in *Ms. magazine* suggests the use of tea as a treatment for fibroid tumors¹⁷ with an implicit reference to Benveniste's article and the follow-up articles in *Nature* as an analysis of homeopathy in a "prestigious British medical journal"!

It is in the interest of the scientific community to note that Benveniste is indeed a

highly cited author. 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 (Table 2). 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. They are both *Citation Classics* and we hope he will comment on them in the near future.

An Updated Press Digest

We agree that more needs to be said about this controversial paper. In this issue of *CC*, the *Press Digest* includes not only the letter Benveniste wrote to *Science*¹⁵ (mentioned earlier), but also several other references to the controversy.

A Reflection on the Freedom to Publish

It is difficult to predict where the next major innovation in science will occur. Moreover, it is not unusual to find ideas or discoveries whose significance was unappreciated when they were first presented for examination and scholarly discussion. It is difficult to imagine a world in which we understand every innovation from the moment of its first announcement. And today we are inundated with new discoveries, both basic and applied. Certainly editors must preserve the role of the scientific press to publish con-

Table 1: Chronological bibliography of articles citing or discussing Davenas E et al. *Nature* 333:816-8, 30 June 1988.

When to believe the unbelievable. *Nature* 333:787, 30 June 1988.
 Browne M W. Impossible idea published on purpose. *New York Times* 30 June 1988. p. 9.
 Maugh T H. French scientist produces "unbelievable" solution. *Los Angeles Times* 30 June 1988. p. 3.
 Bell L. Dilutions or delusions? *Sci. News* 134(1):6, 2 July 1988.
 The incredible shrinking dose. *Economist* 308:78-9, 9 July 1988.
 Pool R. Unbelievable results spark a controversy. *Science* 241:407, 22 July 1988.
 Maugh T. Journal probe of lab test results spark furor. *Los Angeles Times* 27 July 1988. Sec. I, p. 3.
 Rensberger B. Research called "shoddy" by publisher of article; probe rebuts claim defying scientific laws. *Washington Post* 27 July 1988. p. A16.

Table 1 (continued)

- Sullivan W. Report in scientific journal is seen by panel as flawed. *New York Times* 27 July 1988. p. A14.
- Hudson R L. *Nature* debunks piece it just published that supported homeopath's claims. *Wall Street Journal* 27 July 1988. p. 30.
- Benveniste J. Dr. Jacques Benveniste replies. *Nature* 334:291, 28 July 1988.
- Plasterk R H A; Reilly D T; Lasters I & Bardiaux M; Danchin A; Fierz W; Optiz K; Nisonoff A. Letters to editor. (Explanation of Benveniste.) *Nature* 334:285-6, 28 July 1988.
- Maddox J, Randi J & Stewart W W. "High-dilution" experiments a delusion. *Nature* 334:287-90, 28 July 1988.
- Beil L. *Nature* douses dilution experiment. *Sci. News* 134(5):69, 30 July 1988.
- Maziere J C, Maziere C, Auclair M, Mora L & Polonovski J. PAF-acether decreases low density lipoprotein degradation and alters lipid metabolism in cultured human fibroblasts. *FEBS Lett.* 236:115-8, August 1988.
- Dagani R. *Nature* refutes research it had published earlier. *Chem. Eng. News* 66(31):6, 1 August 1988.
- Coles P. Benveniste controversy rages on in the French press. *Nature* 334:372, 4 August 1988.
- Metzger H & Dreskin S C; Gaylarde P M; Suslick K S; Glick J L; Escribano M J. Letters to editor. (Only the smile is left.) *Nature* 334:375-6, 4 August 1988.
- When to publish pseudo-science. *Nature* 334:367, 4 August 1988.
- Pool R. More squabbling over unbelievable result. *Science* 241:658, 5 August 1988.
- Delusion in Clamart. *Lancet* 2:347, 6 August 1988.
- Smith T. Drop of the weak stuff. *Brit. Med. J.* 297:377-8, 6 August 1988.
- The nature of science. *Los Angeles Times* 7 August 1988. p. 4.
- Langone J. The water that lost its memory. *Time* 132(6):73, 8 August 1988.
- Nature's* nostrums. *US News World Rep.* 105(6):11, 8 August 1988.
- When the canons of science take French leave. *Vet. Rec.* 123:165, 13 August 1988.
- Seagrave J C; Bonini S, Adriani E & Balsano F; Snell K. Letters to editor. (Evidence of non-reproducibility.) *Nature* 334:559, 18 August 1988.
- Wade N. Looking hard at science's self-scrutiny; a case of research based on "delusion." *New York Times* 21 August 1988. Sec. 4, p. E9.
- Benveniste J. Letter to editor. (Benveniste on *Nature* investigation.) *Science* 241:1028, 26 August 1988.
- Dixon B. A brief history of dubious science. *THE SCIENTIST* 2(16):5, 5 September 1988.
- Dixon B. Criticism builds over *Nature* investigation. *THE SCIENTIST* 2(16):1; 4-5, 5 September 1988.
- Dorozynski A. French scientists say little; the French press, too much. *THE SCIENTIST* 2(16):4, 5 September 1988.
- Garfield E. Contrary to *Nature*? *THE SCIENTIST* 2(16):12, 5 September 1988.
- Benveniste at bay. *New Sci.* 119(1629):33, 8 September 1988.
- Lipowicz P J; Petsko G A; Lane L C; Bland B H. Letters to editor. (Unreproducible results.) *Nature* 335:109, 8 September 1988.
- Gibson R G & Gibson S L M; Doublet-Stewart M & Doublet-Stewart C; Nevile G J; Taylor P. Letters to editor. (Controversy continues.) *Nature* 335:200, 15 September 1988.
- Grimwade A M; Findlay S; Jonas W B. Letters to editor. (From other letters.) *Nature* 335:292, 22 September 1988.
- Scott J A; Gillman M A; Fisher P; Clemens M J. Letters to editor. (Orthodoxy and homoeopathy.) *Nature* 335:292, 22 September 1988.
- Maddox J. Maddox on the "Benveniste affair." *Science* 241:1585-6, 23 September 1988.
- Can publishing unbelievable results serve science? *Current Contents* (39):9-10, 26 September 1988. (ISI Press Digest.)
- Maddox J. A too-polite silence about shoddy science. *New York Times* 26 September 1988. p. 27.
- Stanworth D R; Johnson M. Letters to editor. (Outlandish claims.) *Nature* 335:392, 29 September 1988.
- Claire J F; Schilling R M. Letters to editor. (More on Benveniste's dilution results.) *Nature* 335:584, 13 October 1988.
- Shakib F; von Hahn H P; Shoup J P; Dunthorn D; Van Valen L M. Letters to editor. (The debate continues.) *Nature* 335:664, 20 October 1988.
- Benveniste J. Benveniste on the Benveniste affair. *Nature* 335:759, 27 October 1988.
- Maddox J. Waves caused by extreme dilution. *Nature* 335:760-3, 27 October 1988.
- Cherfas J. Tale of the ghostly molecules draws to a close. *New Sci.* 120(1637):25, 5 November 1988.
- Benveniste J. Letter to editor. (Benveniste replies.) *THE SCIENTIST* 2(21):10, 14 November 1988.
- Burzynski S R. Letter to editor. ("Memory" molecules.) *THE SCIENTIST* 2(21):10, 14 November 1988.
- Arsone S & Reuben C. Take tea and see. *Ms.* 17(6):22; 24; 27, December 1988.
- Revkin A C. Dilutions of grandeur. *Discover* 10(1):74-5, January 1989.
- Coles P. Return to the good old days of plenty for French researchers. *Nature* 337(6202):7, 5 January 1989.

Table 2: Jacques Benveniste's papers cited over 100 times.

- Benveniste J, Henson P M & Cochrane C G.** Leukocyte-dependent histamine release from rabbit platelets. *J. Exp. Med.* 136:1356-77, 1972. (over 640 citations)
- Benveniste J, Tence M, Varenne P, Bidault J, Boulet C & Polonsky J.** Semi-synthese et structure proposee du facteur activant les plaquettes (P.A.F.): PAF-acether, un alkyl ether analogue de la lysophosphatidylcholine (Semi-synthesis and proposed structure of platelet activating factor (P.A.F.): PAF-acether, an alkyl ether analog of lysophosphatidylcholine). *C.R. Acad. Sci. Ser. D* 289:1037-40, 1979. (over 310 citations)
- Chignard M, Le Couedic J P, Tence M, Vargaftig B B & Benveniste J.** The role of platelet-activating factor in platelet aggregation. *Nature* 279:799-800, 1979. (over 260 citations)
- Vargaftig B B, Chignard M, Benveniste J, Lefort J & Wal F.** Background and present status of research on platelet-activating factor (PAF-acether). *Ann. NY Acad. Sci.* 370:119-37, 1981. (over 240 citations)
- Vargaftig B B, Lefort J, Chignard M & Benveniste J.** Platelet activating factor induces a platelet dependent bronchoconstriction unrelated to the formation of prostaglandin derivatives. *Eur. J. Pharmacol.* 65:185-92, 1980. (over 235 citations)
- Benveniste J.** Platelet-activating factor, a new mediator of anaphylaxis and immune complex deposition from rabbit and human basophils. *Nature* 249:581-2, 1974. (over 210 citations)
- Mencia-Huerta J M & Benveniste J.** Platelet-activating factor and macrophages. I. Evidence for the release from rat and mouse peritoneal macrophages and not from mastocytes. *Eur. J. Immunol.* 9:409-15, 1979. (over 200 citations)
- Vargaftig B B, Chignard M & Benveniste J.** Present concepts on the mechanisms of platelet aggregation. *Biochem. Pharmacol.* 30:263-71, 1981. (over 175 citations)
- Cazenave J P, Benveniste J & Mustard J F.** Aggregation of rabbit platelets by platelet-activating factor is independent of the release reaction and the arachidonate pathway and inhibition by membrane-active drugs. *Lab. Invest.* 41:275-85, 1979. (over 170 citations)
- Benveniste J, Le Couedic J P, Polonsky J & Tence M.** Structural analysis of purified platelet-activating factor by lipases. *Nature* 269:170-1, 1977. (over 165 citations)
- Chignard M, Le Couedic J P, Vargaftig B B & Benveniste J.** Platelet-activating factor (PAF-acether) secretion from platelets: effect of aggregating agents. *Brit. J. Haematol.* 46:455-64, 1980. (over 130 citations)
- Camussi G, Mencia-Huerta J M & Benveniste J.** Release of platelet-activating factor and histamine. I. Effect of immune complexes, complement and neutrophils on human and rabbit mastocytes and basophils. *Immunology* 33:523-34, 1977. (over 115 citations)
- Godfroid J J, Heymans F, Michel E, Redeuilh C, Steiner E & Benveniste J.** Platelet-activating factor (PAF acether): total synthesis of 1-O-octadecyl 2-O-acetyl sn-glycero-3-phosphoryl choline. *FEBS Lett.* 116:161-4, 1980. (over 100 citations)

troversial scientific data and ideas that may not at first be interpretable. However, it would be scientific anarchy to publish every unsubstantiated idea that comes along. Initially, presumably uninterpretable data must be verifiable to merit scientific publication.

Benveniste's controversial claims will eventually be tested in the way that all such controversies are. In the meantime, this whole affair has been handled more like a circus sideshow of personalities to help support magazine circulation drives. As Bernard Dixon, European editor of *THE SCIENTIST*, has described, this is not the first time *Nature* has taken this route to publish controversial claims:⁵ earlier were the Uri Geller^{18,19} and the Georges Ungar²⁰ affairs.

Clearly, Professor Benveniste has a substantial scientific reputation as judged by his publication and citation record. John Maddox is certainly one of our most distinguished senior science editors. Yet, there is no free ride! Celebrated scientists and editors, even Nobelists, have gone off the deep end in pursuit of private passions. Only time will tell.

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20. Ungar G, Desiderio D M & Parr W. Isolation, identification and synthesis of a specific behavior inducing brain peptide. *Nature* 238:198-202, 1972.