Explanation of Benveniste

The following letters are triggered by an article by Davenas et al. (*Nature* **333**, 816–818; 1988).

SIR—The article stating that high dilutions of a protein (containing no protein molecules) are biologically active has all the traditional properties of homoeopathic claims: insufficient description of the methods used (what is the source of the 0.1 per cent human serum proteins in the diluent?), suggestive hearsay ("similar results were obtained in other laboratories (Toronto, preliminary results)") and wild statements with no data shown ("our results can be summarized as"; "we can confirm that").

This will turn out to be yet another case of artefacts (or worse) but the harm has already been done; worldwide recognition of this important paradigm of homoeopathy by a major scientific journal. The homoeopathic industry (supplying for example 15 per cent of all medicines in France) will not care about a short retraction in *Nature* (which will get much less attention in the popular press than the original claims).

Nature should have insisted on an independent confirmation of these results before and not after publication.

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SIR—Scientific belief belongs on a flat earth. There is no danger, no threat to science, in the restatement of the drug-diluent paradox — we need only apply the scientific method and then seek the verdict of experience.

In this way the inquiry by me and my colleagues reluctantly judged the placebo hypothesis redundant and homoeopathic dilutions active[1]. We agree with Benveniste's suggestion that his results relate to ours and we consider that both teams' research represents a development from homoeopathic science. Those who adopt the position that there is no such link are standing on ice so thin that even the weight of the author list will crack it — there are at least three homoeopathic doctors on it. It may be deep water but we must face the facts that homoeopathic physicians introduced and developed this area and that those wishing to examine this 'new' discovery will be well served by homoeopathic history. Fifty years before *Nature* had the courage to publish, Boyd began to demonstrate in a series of classical scientific experiments similar on/off effects up to 10^{-56} in biological assays such as mercuric chloride affecting starch diastase[2]. His methods were scientific but his results 'unbelievable' and so they joined a body of experience accumulated and ignored over the very same 200-year period that you invoke in your leading article (*Nature* **333,** 787; 1988). If we now rise to this challenge, we have nothing to lose. If we prove the observations wrong, we will have exposed homoeopathy as one of medical science's greatest misadventures — a folly so massive it will merit study in itself — why have 1 in 4 French doctors prescribed it[3]? If confirmed, we open up a vista of fundamental discovery and development. If this strikes at the heart of some current scientific models, that will be good for science. Right or wrong, such cross-fertilization has yielded benefit in the past. Some claim it laid the foundation of modern immunology[4], certainly tangible benefits to medicine accrued when homoeopaths proved pollen the cause of hay fever[5] and introduced low-dose allergen desensitization[6].

Moving from experiment to speculation, how are we to conceptualize memory in water? (If it *is* there, then the later stages of reaction with biological systems are easier to imagine with the models of pheromones, receptor sensitivity and biological amplification.) As a point of departure for criticism, I have visualized this first link in the chain as 'liquid snowflakes' modelled from the parent drug — one concentration but with unique biophysical information or pattern, 'seeded' in the new diluent in the reorganizing post-vibrational phase like liquid crystals growing in the order after chaos. But my snowflake analogy melts if we become fixed on the idea of 'shape' — best to say for now that the quality and nature of this ghost in the machine is unknown. And what of sinusoidal change in activity? Might the first generation antagonist grow in dominance through successive dilutions until at a critical threshold (concentration?) it itself becomes the template for a second generation agonist, the relative activity of these opposing patterns alternating in a sinusoidal curve as one continues the process of dilution/vibration — an agonist/antagonist template shift. In this respect, other work by Poitevin, Davenas and Benveniste[7] shows that certain dilutional points are not just ineffective as agonists but show an opposite inhibitory effect on the action of a second agonist. Similarly, we have shown clinically that although most patients reacting to a homoeopathic allergen dilution improve, unpredictably some aggravate and then improve while others only aggravate without subsequent improvement. In clinical practice, this raises questions of safety but in this context it suggests that Benveniste's agonist/antagonist curve may correlate with clinical responses. We are already exploring this possibility of *in vitro* and *in vivo* overlap.

This landscape is so unfamiliar that perhaps we cannot see around our favourite biochemical landmarks to the horizon beyond. Doctors already observe the altered nuclear spin of diseased tissue in their patients with magnetic resonance imaging. Now Franco Bruno of Citta Universitaria Rome has communicated (OMHI Conference, Rome, April 1988) apparent confirmation of earlier work[8] that the nuclear magnetic resonance spectra of homoeopathic dilutions are altered. Here may be glimpses of the territory we seek.

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1. Reilly, D.T., Taylor, M.A., McSharray, C. & Aitchison, T. *Lancet* **ii,** 881–886 (1986).
2. Boyd, W.E. *Br. Hom. J.* **32,** 106–111 (1942).
3. *L'Homeopathie en 1986 — une realité sociale, scientific, economique et industrielle* (Syndicat National de la Pharmacie Homeopathique, Paris, 1987).
4. Coulter, H.L. *Homoeopathic Science and Modern Medicine* 69–70 (North Atlantic Books, California, 1980).
5. Blackley, C.H. *Br. Hom. J.* **29,** 238–286, 477–501, 713–736 (1871). *Ibid* **30,** 246–274, 417–449, 656–678 (1872). *Ibid* **31,** 77–103 (1873).
6. Millspaugh, C.F. in *New Old and Forgotten Remedies* 16–17 (Boericke & Tafel, Philadelphia, 1900).
7. Poitevin, B., Davenas, E. & Benveniste, J. *Br. J. clin. Pharmac.* **25,** 439–444 (1988).
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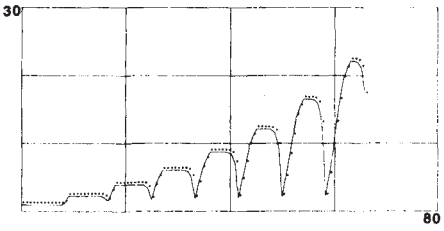
SIR—Davenas *et al.* (*Nature* **333,** 816–818; 1988) demonstrate that degranulation can be triggered at dilutions of anti-IgE antiserum in which not a single anti-IgE molecule is expected. In view of the revolutionary nature of this finding it is of the utmost importance to discuss all possible controls. As we feel an important control experiment has been overlooked, we would like to draw attention to a potential problem in the interpretation of the data of Davenas *et al.*

As described in the 'Methods' section of their article, Davenas *et al.* use microtitre plates to assay the basophil degranulation. Interestingly, these authors observe a periodicity in the basophil degranulation as a function of anti-IgE antiserum dilution. One might wonder to what extent this observation can be accounted for by contaminating, for example by aerosol, the contents of adjacent wells when filling the microtitre plate. As a contamination at the level of a single anti-IgE molecule might in principle corrupt the relevance of the findings, this criticism must be taken seriously.

In a microtitre plate, a contamination between adjacent wells will not result in a simple blurring of the measured titration profile. As the wells in a microtitre plate are placed in a matrix organization, any



Simulation of the filling of a conventional 8 × 12 well microtitre plate. The wells are filled sequentially from left to right. Upon the addition of a unit volume of anti-IgE antiserum (having a concentration which is halved at each step), 0.001 volume units are spread equally to neighbouring wells as described in the text. Abscissa: $-ln(2^{-n})$, where n is the dilution step number. Ordinate: ratio of actual versus expected (i.e. in absence of contamination) concentration of anti-IgE.

contamination provoked by filling a given well will affect both its neighbours in adjacent columns as well as in adjacent rows. When filling the wells in a sequential order, wells in adjacent rows represent a jump by several orders of magnitude in the dilution series. Consequently, possible contamination will not merely result in a local blurring of the titration profile. To demonstrate that one expects oscillations to occur in the measured profile, we simulated the filling of a conventional 8 × 12 well microtitre plate. Using a simple model, in which upon filling a well at position (i,j), a small fraction of its contents is spread out to its immediate neighbours having plate coordinates $(i\pm1,j\pm1)$, periodicities are observed in the concentration of effector molecules (anti IgE). This is illustrated in the figure which shows the ratio of actual to expected concentration of effector molecules at each dilution step using a 0.1 per cent contamination level.

Clearly, in view of this simulation, one cannot *a priori* rule out the possibility that the periodicity in degranulation observed by Davenas *et al.* is due to a contamination effect. In particular, our contamination argument questions whether the wells at highest dilution are really devoid of any anti-IgE molecule. We therefore suggest a control experiment in which microtitre plates are substituted with individual test tubes. Alternatively, one could interlace on a given microtitre plate the anti-IgE antiserum dilution and the control anti-IgE dilution series.

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SIR—Water has been the centre of many controversies during the past 20 years or so. In particular, scientists have repeatedly proposed unusual properties for this 'universal' biological solvent. The case of 'super water' involving 'high tech' probing systems such as (15 years ago), nuclear magnetic resonancing was used to demonstrate that water could mediate special long-distance interactions. This has been proved to be due to a tricky artefact.

In the present case, I am puzzled by the fact that there has been no control of impurities (for instance by atomic absorption or neutron activation). In particular, the need for strong agitation (which is contradictory to the 'memory' hypothesis) suggests that test tubes might be involved. It seems worth recalling the experiments by Sternweis and Gilman, who have shown that the well-known fluoride effect no longer occurs when experiments are performed with pure water, in the absence of traces of aluminium[1]. Indeed, they have shown that F^- is able to extract Al^{3+} from the glass surface, generating AlF_4^- which is responsible for the effects[1,2]. Since it is well known that antibodies strongly (and often specifically) interact with surfaces, it is possible that they extract some ion (or other contaminant molecule), which in turn acts as a trigger for further extraction (in the absence of antibody). This would account for the requirement of strong agitation.

Proper control protocols should be performed before the generally efficient physicochemical laws are broken.

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2. Bigay, J. *et al. EMBO J.* **6**, 2907–2913 (1987).

SIR—In the leading article accompanying the article on an inexplicable observation about basophil degranulation by very dilute antiserum against IgE, you invite the vigilant reader to pick holes in the reported work. One obvious flaw can be seen when looking at the standard errors (s.e.) given in Table 1 of the article. According to the legend to Table 1 and to Fig. 1, the data represent the mean ± s.e. of basophil number actually counted in triplicate in a haemocytometer. The mean counts range from 27.7 to 106.7 and the s.e. are with two exceptions below 3 (2.6 per cent of the mean in average). However, according to the Poisson distribution, the s.e. of counting randomly distributed events, like cells in a haemocytometer, is equal to the square root of (mean counts/number of countings), that is, it ranges from 3 to 6 (11 per cent to 6 per cent of the means) for the triplicate counts given in Table 1. It is very unlikely that the observed s.e. of the triplicates are so much below the expected s.e. of counting.

The reason for this discrepancy is not clear. It is, however, unlikely that the s.e. given in Table 1 are the result of an erroneous calculation, as the data of 4 triplicate experiments (Tyrode's–HSA) are actually displayed in Table 1, and again the s.e. of the experimental triplicates (lower than 1 per cent) are much below the s.e. expected already from counting 3×3 times 100 cells (3.3 per cent). The only way to explain the discrepancy would be to assume that actually more basophils have been counted and that the indicated numbers are somehow calculated values. However, in order to reach the average s.e. of 2.6 per cent as published in Table 1, at least 500 basophils would have to be counted in each sample.

In conclusion, the data in Table 1 are very unlikely to be derived from flawless experimental results and are certainly not the kind of data one would need to "throw away our intellectual heritage"[1].

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SIR—I find it rather curious that a scientific journal should be so wary of non-material real phenomena as to refuse to endorse the findings of the Benveniste group research on the effect of dilution on anti-IgE antiserum! Does *Nature* expect nature to accommodate academic disciplines in order to be vindicated?

Ignorance about such non-material energetic effects as those discovered and demonstrably utilized in human medicine since the early nineteenth century by Carl Hahnemann and his successors or, more recently, thore studied by Tesla, Morell and Popp in the field of physics, is hardly to the credit of a would-be authority on science; nor does it lend credence to *Nature*'s claim of reliable and impartial reporting of significant new research. Casting doubt on findings merely because they are inconvenient to established assumptions and patterns of speculation strikes me as a poor way of advancing scientific knowledge.

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SIR—The paper demonstrating that dilutions of anti-IgE must be vortexed rather than stirred in order to retain an imprint of the antibody on the solvent elucidates another long-standing question: how James Bond could distinguish Martinis that had been shaken or stirred.

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