

logical inhibitors of PARP enzyme activity. These inhibitory compounds have other, additional effects on cells (2), and therefore it is not established beyond a doubt that NO toxicity occurs by means of PARP activation. The issue will be resolved by the use of cells with disrupted PARP gene.

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References

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3. M. Shimoyama *et al.*, *Physiol. Chem. Phys.* **7**, 125 (1975); M. Nowicki, C. Landon, S. Sugawara, G. Dennert, *Cell. Immunol.* **132**, 115 (1991); J. Hoshino, S. Schalge, B. Drevenstedt, H. Kröger, *Biochem. Int.* **20**, 135 (1990).

Response: Indeed, Kolb's paper (1) did deal with nitric oxide (NO) as mediating the toxicity elicited by macrophages in the pancreas. Our study, by contrast, dealt with NO mediating the neurotoxicity of glutamate by damaging DNA and activating poly(ADP-ribose) synthetase (PARS or PARP). Kolb points out that studies using drugs as probes are not necessarily definitive. Because of this, we did not use a single agent, but instead used four distinct PARP inhibitors and showed that their relative ability to prevent neuronal death after stimulation of the glutamate-NMDA receptor closely paralleled their potency in inhibiting PARP. Three of these agents are benzamides in which very small structural changes provide major differences in potency in inhibiting PARP and neurotoxicity.

In addition, we showed that novobiocin, which block mono-ADP-ribosylation, but not PARP, did not provide protection. Our study elucidates the mechanism whereby NO elicits this toxicity, as we directly demonstrated that NO damages DNA, which in turn activates PARP. Besides blocking NO neurotoxicity, PARP inhibitors blocked the toxicity elicited by stimulating glutamate-NMDA receptors, reflecting the neurotoxicity that occurs in vascular stroke. These findings provide a persuasive, if not definitive, case that excitotoxicity acts through NO activation of PARP with attendant depletion of energy stores.

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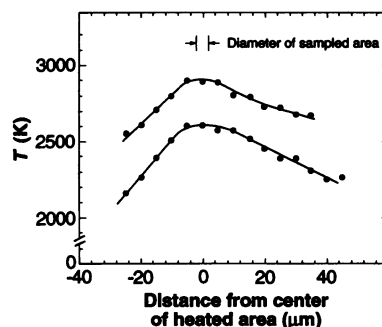
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Perovskite Temperature Profile

In our response of 8 April (p. 280) (1) to a comment by D. L. Heinz *et al.* (2) about our report of 22 October 1993 (3) on the melting of (Mg,Fe)SiO₃-perovskite to 625 kilobars, an incorrect curve for the temperature profile in figure 2 (1, p. 280) was provided. An already-drafted profile for Ar-laser-heated iron was mistakenly chosen and put on a scale that represented that for most of the CO₂-laser heating profiles that we have. Two actual subsolidus temperature profiles for CO₂-laser-heated perovskite at a pressure of 32 gigapascals are shown below. The profiles are slightly



asymmetric because of the incidence angle of the laser beam in the perovskite melting experiment. This change in figures does not affect the results on the melting temperatures of (Mg,Fe)SiO₃-perovskite (3) in any way. The original figure 2 in our response was shown to illustrate that temperatures from the heated samples were directly measured from small areas with a diameter of 3 to 5 μm and that the temperature gradients in the center of the heated spot were negligible.

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References

1. R. Boehler and A. Zerr, *Science* **264**, 280 (1994).
2. D. L. Heinz, E. Knittle, J. S. Sweeney, Q. Williams, R. Jeanloz, *ibid.*, p. 279.
3. A. Zerr and R. Boehler, *ibid.* **262**, 553 (1993).

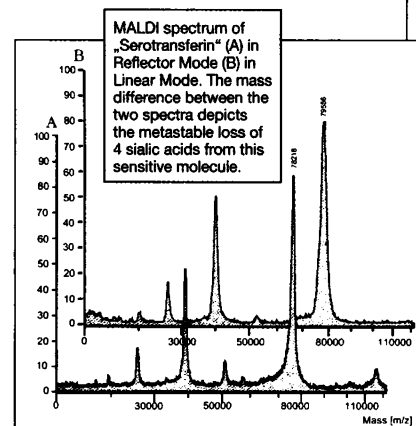
Corrections and Clarifications

In the News article "Finding 'sustainable' ways to prevent parasitic diseases" by Rebecca Kolberg (24 June, p. 1859), mention is made of nylon gauze that is being distributed worldwide free of charge to filter Guinea worm larvae from drinking water. The cloth is donated by E. I. DuPont de Nemours & Company, Inc., and Precision Fabrics Group for distribution by Global 2000, Inc.

Opinion

Progress in mass spectrometry hasn't been gradual at all but has happened in big steps, each opening a completely new field of applications. And each step was linked to the discovery of a new ionization technique. Remember "chemical ionization", "fast atom bombardment", "electrospray ionization" – and now "matrix assisted laser desorption/ionization" (MALDI).

So far MALDI has been considered as nothing more than a method to determine the molecular weight of a large biomolecule – but take Serotransferin, e.g. a glycoprotein of about 80 kDa. MALDI measurement on the VISION 2000 time-of-flight mass spectrometer in the **linear detection mode** shows the correct molecular mass, but in the **reflector mode** the apparent molecular mass is around 1200 Da lower, indicating the loss of four sialic acids from the carbohydrate moieties of Serotransferin.



Equally exciting is the "post source decay mode" (PSD) in which metastable ions – generated by the MALDI process – are measured. These metastable ions carry important structural information about the molecule – just like the daughter ions in classical MS/MS experiments.

PSD is now being used to determine the sequence of peptides, glycans and nucleotides. In fact, PSD appears as universally applicable as MS/MS. The sensitivity could be more than 100 fold higher and is principally limited by sample handling techniques only.

It may be too early to tell, but the odds are in favour of another big step in mass spectrometry.

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The OPINION column features technical tips & preliminary information relating to instruments designed & built at Finnigan MAT GmbH, Bremen, Germany.