Novel expansion of living chemistry or just a serious mistake?

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The recent online report in *Science* (Wolfe-Simon *et al.*, 2010; http://www.sciencexpress.org) that a newly isolated bacterial strain can apparently replace phosphate with arsenate in cellular constituents such as DNA and RNA either (1) wonderfully expands our imaginations as to how living cells might function (as the authors and the sponsoring government agency, the USA NASA, claim) or (2) is just the newest example of how scientist-authors can walk off the plank in their imaginations when interpreting their results, how peer reviewers (if there were any) simply missed their responsibilities and how a press release from the publisher of *Science* can result in irresponsible publicity in the *New York Times* and on television. We suggest the latter alternative is the case, and that this report should have been stopped at each of several stages.

This is the newest example following when *Nature* was absurd in publishing favorable reports on the magical spoon-bending telepathist Uri Geller (*Nature*, 251, 1974, pp. 602–607) and later immunologist J. Benveniste 'water with memory' (*Nature* 333, 1988, pp. 816–818, DOI: 10.1038/333816a0), and *Science* in 1989 published 'cold fusion' reports when competent readers thought the ideas just could not be correct.

The authors report three results with their new bacterial isolate, all of which seem reasonable to anyone with experience with arsenic microbiology. They interpret and basically claim as the inevitable conclusion that the results demonstrate a biochemistry that should not be imagined, except by science fiction authors such as Isaac Asimov (who was a university Professor of Biochemistry in his spare time) and Michael Crichton (whose 1969 block-buster science fiction novel, *The Andromeda Strain*, concerns a microorganism with silicon rather than carbon in its biomolecules). A microorgansim with arsenic replacing phosphate in such critical molecules as DNA and RNA appears to be equally science fiction.

The findings start with the gradual adaptation of a new gammaproteobacterial strain to resistance to up to 40 mM added arsenate (not a surprise) and high intracellular arsenic bioaccumulation (unusual, but also reported previously). There is no difficulty in believing these results. Growth curves show relatively good growth when 40 mM arsenate was added to medium that contained 3 μM phosphate (present as medium contamination). The cells look larger when grown in high arsenate than when grown in 1.5 mM phosphate, and the arsenate-rich cells have numerous vesicles (in cross-section transmission electron microscopy) that look much like polyhydroxybutyrate (likely) or polyphosphate (less likely) inclusions. There is no indication that the authors considered element-specific microprobing of those electron micrograph sections or whether such would be feasible, although Wolfe-Simon and colleagues have a figure with nanoSIMS (secondary ion mass spectroscopy) element-specific scanning of intact cells for ^{75}As, ^{31}P, and ^{12}C content, and not cross sections with visible vesicles. A table shows data that low P/high As-grown cells contain $20 \times$ less P as a percent dry weight than high P/low As cells, and that the high As-grown intact cells contain a total of 7.3 As atoms for every P atom. The data are sufficient to calculate whether there was adequate P in the low P/high As cells for the needs of DNA, RNA, and phospholipids (as our casual calculations indicate is the case). However, Wolfe-Simon and colleagues did not make such a calculation from their data, although they calculated that a bacterial chromosome might need 7.5×10^6 P atoms. There is evidence that the cells bioaccumulate arsenic, but no need to suggest that any arsenate is to be found in DNA or RNA diester linkages between sugar moieties. There is a figure showing gel electrophoresis pattern of total cellular DNA from high- and low-arsenic cells, with measurements indicating that the ratio of As/C in the DNA from high-arsenic cells was 1 As per 10^5 C atoms, while DNA has a ratio closer to 1 P per 10 C atoms.

The questionable conclusion of the paper appears as an established fact in the abstract (first paragraph of the report): 'arsenate in macromolecules that normally contain phosphate, most notably nucleic acids and proteins.' There are no data to support this claim, which is repeated. The data presented do not disprove the existence of arseno-ester bonds in cellular nucleic acids and proteins any more than they support such an interpretation. However, common sense and a little understanding of microbiology and biochemistry should have protected the authors from themselves. The Editor in Chief of *Science* is a biochemistry professor and author of the highly regarded basic text 'The Molecular Biology of the Cell.' What happened? How did this get through? It seem likely that Wolfe-Simon and colleagues have isolated a strain that bioaccumulates high intracellular arsenic when grown on 40 mM arsenate and 3 μM phosphate. That this high arsenic may be sequestered in intracellular vesicles of unknown composition (possible) or in the cytoplasm (less likely) has not been tested. Have the authors considered that As was incorporated into phospholipids (arsenolipids) thus freeing phosphate to be used in DNA? That would lead to fragility (observed) and swelling (observed as an increase in OD). Also note the low abundance of 16S rRNA (nothing visible) and 23S rRNA genes (Fig. 2a) indicating immediate RNA turnover, possibly to facilitate reuse of limited phosphate. There is no reason to conclude (as the authors have in their penultimate sentence) that they have found life 'substituting As for P'.

In this new millennium age of Internet, Blogs (e.g. http://rrresearch.blogspot.com/2010/12/arsenic-associated-bacteria-nasas.html), and e-mail, the basic claims of the report circulated globally within hours. The first author appears to have described her efforts in a Wikipedia posting (http://en.wikipedia.org/wiki/Felisa_Wolfe-Simon). An analysis appeared in *Nature* (http://www.nature.com/news/2010/101207/full/468741a.html, published online December 7, 2010), the *New York Times* (http://www.nytimes.com/2010/12/03/science/03arsenic.html?pagewanted=1&_r=1&partner=rss&emc=rss), the *Philadelphia Inquirer*, the *Chicago Tribune*, the (Manchester, UK) *Guardian* [Jha (December 2, 2010) http://www.guardian.co.uk/science/2010/dec/02/nasa-life-form-bacteria-arsenic], on CNN, and widely elsewhere (e.g. http://chronical.com/blogs/brainstorm/hic-haec-hype-little-green-men-or-arsenic-in-dna). Working at the time at Osaka University in Japan, that first morning S.S. was surprised by several overnight e-mails, one with a detailed analysis in an attached URL. Communications and the role of journals in communications have changed in the electronic age. However, the responsibility of scientific journals to hold off a little against the magic and nonsense that floods cyberspace did not work here.

One caveat: we consider two of the senior-scientist authors, R.S. Oremland and J.F. Stolz, to be microbiologists who have contributed in major ways to the understanding of the environmental microbiology of arsenic in recent years (including three reports published in *Science* in the last 10 years and several in FEMS journals). These caused no antihype flak. We hope our long-term relationships can survive this entirely negative and uncompromising analysis of their new report, which would have been much better handled before publication (Obama style over a bottle of beer), rather than with the excessive Internet hype that the authors initiated and the controversy that developed on newspaper and journal pages. However, this is only a current example of a report, where basically no one who can form a detailed technical opinion believes the conclusions (except the authors), based on the data shown. It is a sad story, reminiscent of the quip: déjà vu – all over again!

Reference

Wolfe-Simon F, Switzer Blum J, Kulp TR *et al.* (2010) A bacterium that can grow by using arsenic instead of phosphorus. *Science* DOI: 10.1126/science.1197258 http://www.sciencemag.org/content/early/2010/12/01/science.1197258.full.pdf and http://scim.ag/arsenicresponse.