

## Letters to the Editor

Letters (~300 words) discuss material published in *Science* in the previous 6 months or issues of general interest. They can be submitted by e-mail (science\_letters@aaas.org), the Web (www.letter2science.org), or regular mail (1200 New York Ave., NW, Washington, DC 20005, USA). Letters are not acknowledged upon receipt, nor are authors generally consulted before publication. Whether published in full or in part, letters are subject to editing for clarity and space.

## A Serendipitous Purchase

I RECENTLY ORDERED A BOOK, *BASIC COLOR Terms: Their Universality and Evolution* (1), through an online book dealer. The book was simply advertised as a “used book, first edition, dust jacket, good condition.” When it arrived, I opened the front cover and found a bookplate from The Rockefeller University and a tag with the words “Laboratory book—Dr. Hartline.”

It has been 20 years since Haldane Keffer Hartline passed away. Hartline shared the Nobel Prize in Physiology or Medicine in 1967 with Ragnar Granit and George Wald. He was a mentor to many neuroscientists at the University of Pennsylvania, Johns Hopkins University, and Rockefeller University. I am a direct “academic descendant” of his. My graduate advisor lineage can be traced back through Maureen Powers, Stephen Easter Jr., and Edward MacNichol Jr. to “Keff” Hartline.

Words cannot express my feelings about owning a book that was owned by my graduate adviser’s adviser’s adviser. We in science need to give thanks to our mentors and those who have blazed the trails before us in our respective fields; we also need to continue to be cognizant of our students and how we may influence them directly or indirectly. In the words of Hartline from his banquet speech at the Nobel ceremony, “Tack sa mycket.” Thank you very much.

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1. B. Berlin, P. Kay, *Basic Color Terms: Their Universality and Evolution* (Univ. of California Press, Berkeley, CA, 1969).

## Iron Limitation in the Southern Ocean

LARGE-SCALE “IRON FERTILIZATION” EXPERIMENTS in the Southern Ocean provide

compelling evidence for the control of phytoplankton productivity by dissolved iron (K. O. Buesseler, P. W. Boyd, “Will ocean fertilization work?”, *Perspectives*, 4 Apr., p. 67) (1).

However, there is an intriguing conundrum when interpreting the annual development of primary production in this region. In autumn, about 14 million km<sup>2</sup> of the Southern Ocean freezes over, providing a seasonally variable habitat for marine organisms (2, 3). If iron is limiting to Southern Ocean phytoplankton growth, and sea ice is formed from the same iron-deficient waters, it seems reasonable to conclude that the ice-based primary production should also be iron limited. Some phytoplankton species become caught up in the ice. Maximum growth of these “ice algae” is often concentrated on the bottom few centimeters of ice floes (2, 4), where replenishment of inorganic nutrients from the underlying water sustains high standing crops, several orders of magnitude greater than those measured in the water column (3–5). If this replenishment is with



Sea ice in the Southern Ocean.

iron-deficient water, the growth of these algae presumably would be iron limited. In fact, sea ice algal growth is rapid within new sea ice (2–6), and in spring and summer, ice-based primary production remains high (4, 5). This suggests that the ice-based primary production is not iron limited. Blooms of sea ice algae occur throughout the pack and are not restricted to ice overlying iron-rich coastal waters.

Although logistically difficult, iron fertilization experiments extended to measure the fate of a “fertilized” patch when frozen into sea ice, or the “fertilization” of water just prior to freezing, would help a more complete interpretation of iron limitation of phytoplankton growth in seasonally ice-covered waters.

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## European Union R&D Spending

LIKE MANY WHO SHARE PIERRE PAPON’S vision of a more interlinked future for science among countries in the European Union (EU)—a “European Research Area”—I greatly appreciated his recent Editorial, “A challenge for the EU” (1 Aug., p. 565). The following points may add some relevant texture.

Papon begins by emphasizing the disparities in spending on R&D between the United States, Japan, and the EU: 2.8%, 3.0%, and 1.9% of GDP, respectively. Against this background, Papon outlines the European Commissioners’ plan to increase EU R&D spending to 3.0% of GDP and then devotes much of the rest of his Editorial to EU proposals about spending on basic research in general and for a European Research Council (ERC) in particular. To the contrary of the impression that Papon’s Editorial may unintentionally give, science base spending (1) is slightly higher in the EU than in the United States,

although lower than in Japan: 0.65%, 0.63%, and 0.85% of GDP, respectively. The differences in the R&D figures arise almost entirely from differences in spending by the private sector (business and industry), mainly on Development rather than Research. And within the EU countries, there is considerable variation, with several spending significantly more on their science base than the United States: Germany, 0.73%; France, 0.80%; Netherlands, 0.88%; and Sweden, 0.95%, compared with, for example, UK, 0.59%, and Spain, 0.42%.

Studies of research output, whether measured by numbers of papers, citations, or major international prizes, in relation to science base spending 3 to 5 years earlier, reveal very big differences—up to a factor of five—among Organisation for Economic Co-operation and

## Drug Discovery and Biotechnology Trends

DNA and Biochips 3: Smaller, Faster, Better

Life scientists have taken only slowly to microfluidic methods such as lab-on-a-chip. But recent advances make the technology more compelling for research in genomics, proteomics, and sequencing, as this coverage can show.

As research in the sciences has increased in volume and ambition, its participants have embraced a tradition of better technology. To speed up chemical and biological reactions and to reduce the size of other technologies, the scientific world has turned to microfluidic methods.

By moving very small volumes of fluid from one microchannel to another, such emerging technologies as lab-on-a-chip and lab-on-a-microchip enable a diverse range of capabilities in genomics and proteomics. Microfluidic devices use on the order of billionths of a liter to assemble, handle, cell-based assays, and fluid diagnostics. The use of microfluidics provides automation, integration, and reduction of sample processing.

Microfluidics has the potential to revolutionize the sciences laboratories. "There has been a lot of effort around microfluidics in the last few years," says Gidon Wolfberg, president, CEO, and cofounder of Fluidigm Corporation. "It is a very exciting area of the sciences that has been made up of a lot of small pieces."

"Lab-on-a-chip" technology, says Gidon Wolfberg, CEO of Fluidigm Corporation, is a very exciting area of the sciences that has been made up of a lot of small pieces. "There has been a lot of effort around microfluidics in the last few years," says Gidon Wolfberg, president, CEO, and cofounder of Fluidigm Corporation. "It is a very exciting area of the sciences that has been made up of a lot of small pieces."



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## LETTERS

Development (OECD) countries, with the top performers being Switzerland, Sweden, and Israel (2, 3). It is not simply how much you spend, but how you spend it.

The existing European Science Foundation (ESF) has modest funding, but I think it uses it wonderfully well for its designated task of creating collegial networks in response to theme proposals. Along with Framework VI's Marie Curie, Human Resources and Mobility, and other postdoctoral programs that enable the best young researchers in the EU to move freely among the best laboratories, this is a powerful force for breaking down hierarchical organizations and, indeed, creating a European research area. But any ERC, roughly aimed as a pan-EU analog of the U.S. National Science Foundation (NSF), should, in my view, meet several stringent criteria: It must fulfil clearly identified scientific needs that are not currently being met, be based on clear principles of scientific excellence, have minimum bureaucracy, complement existing organizations, and not be at the expense of national funding. Given the huge variety of scientific cultures currently within the EU countries, fulfilment of these criteria cannot be lightly assumed. I look forward to seeing how these issues are dealt with by the relevant EU Panel, chaired by Federico Mayor, former Director General of UNESCO.

These observations are offered in a constructive spirit and with real enthusiasm for the ideal of "one Europe" in science. The EU postdoctoral mobility schemes, despite the considerable bureaucracy too often associated with them, are truly building the scientific Europe of tomorrow. At this stage, however, I would put more emphasis on unleashing this creativity of the young in Europe, especially in countries where current hierarchical structures are correlated with relatively poor average return on research spending, and less on creating large EU-level research councils.

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### References and Notes

1. The term "science base" describes all research and postgraduate training undertaken in universities, government-funded laboratories, and private nonprofit organizations (charities or foundations) funded both from public and nonpublic sources. For more information on the science base and difficulties in its estimation [it is not a conventional OECD statistic, and the usual R&D spending by institutions of Higher Education (HERD) is not always a good measure of it], see reference (9) in (4).
2. R. M. May, *Science* 275, 793 (1997).
3. See reference (1) in (4).
4. R. M. May, *Science* 281, 48 (1998).

### Response

I THANK MAY FOR HIS COMMENTS ON MY Editorial. I wanted, indeed, to emphasize the growing gap in R&D funding between the

EU and the United States. Indicators reveal that Europe is investing globally less in research than the United States, and the recent trend is not favorable to Europe: U.S. industry has continuously increased its R&D funding (but not in basic science), while the NIH, for example, has doubled its budget during the last 5 years. As far as the figures regarding spending for basic science that May cites, I think they must be considered carefully. For example, May points out that France's science base funding corresponds to 0.80% of the GDP, with lower figures for Germany and the UK and higher figures for Sweden and the Netherlands. Actually, those figures for public expenses correspond to different types of spending in different countries: For France, the figure includes budgets for academic science (CNRS, universities, etc.) and also for space, nuclear energy, and defense activities (roughly half of the 0.80%) that are not, for the most part, science-related. I suspect that the situation is the same for Germany, which has an important space budget, and probably for the UK, which has kept an important military R&D effort, although the military/space spending is probably a lower proportion of the total than in France. The United States, which has by far the biggest military R&D in the world, spends a rather fair proportion of this effort on basic science; this is not the case in a country such as France. Furthermore, funds provided by foundations to academic science are certainly higher in the United States than in Europe (the UK being a positive exception in Europe).

I agree that research output varies considerably within Europe and that the way money is spent is also important. The performance of Swedish and Swiss science is certainly very good, but those countries have focused their activities on a limited number of areas (biomedicine, for example) in which they can manage to have a better concentration of material and human means.

I fully agree also with May's remarks about the ERC, and the criteria that he proposes are those that were highlighted in the ESF high-level expert group's report to which I refer in my Editorial. An ERC should react more quickly to the science evolution than the present R&D Framework Programme, which has been able to launch positive initiatives as the Marie Curie fellowships. Lastly, I agree with May that the absolute priority for Europe and the European Research Area is to support the young generation of scientists. It should be also the task of an ERC.

PIERRE PAPON

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## The Structure of *D. radiodurans*

IN THEIR RECENT REPORT ("RINGLIKE STRUCTURE OF THE *Deinococcus radiodurans* genome: a key to radioresistance," 10 Jan., p. 254), S. Levin-Zaidman *et al.* propose that single genomes of *D. radiodurans* assume a tightly packed toroidal morphology, each within its own cellular compartment. They suggest that this structure passively protects *D. radiodurans* from DNA double-strand breaks by preventing the ends of adjacent DNA fragments from diffusing apart during a first stage of repair. In thinking about the organism and the model, we believe that several additional considerations should receive attention.

First, we do not consider transmission electron microscopy images alone sufficient evidence to justify categorizing the nucleoid as toroidal. Second, the *D. radiodurans* genome is divided into four circular genetic elements that are repaired with equal efficiency. It is difficult to envision how all four segments of the genome could conform to the proposed structure and repair model. Third, it is unclear why the authors refer to the tetracoccus as a single cell with four compartments. Every previous study has concluded that the tetracoccus represents four separate cells, each with four or more genome equivalents of DNA. The DNA content detected in earlier studies argues for much more than one genome per compartment. Fourth, the work of Hud and Downing (1), cited by Levin-Zaidman *et al.*, does not address diffusion of DNA fragments within a toroid. The authors argue that the restricted diffusion might allow for error-free end-joining as a repair process. However, DNA ends damaged by radiation have a variety of structures and may have missing nucleotides. They are thus unlikely to be spliced together in an error-free manner, regardless of restricted diffusion.

We share the authors' fascination with this unusually adaptable bacterium. New efforts at quantitative examination of the morphological features of this bacterium, complemented by work in other disciplines, may help to resolve these issues.

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1. N. V. Hud, K. H. Downing, *Proc. Natl. Acad. Sci. U.S.A.* **98**, 14925 (2001).

## Response

THE PROPOSED CORRELATION BETWEEN DNA repair in *Deinococcus radiodurans* and the toroidal chromosome organization exhibited by this radioresistant bacterial strain has instigated heated debates.

In the most general terms, we do not claim that efficient and probably unique enzymatic pathways do not contribute to the exceptional resistance of *D. radiodurans*. Rather, we contend that error-free repair of multiple double-stranded DNA breaks represents an informational problem that cannot be solved solely by such pathways.

The next issue concerns the actual presence, uniqueness, and physiological relevance of the chromatin toroidal morphology in *D. radiodurans* cells. This morphology should be assessed in light of our knowledge on DNA packaging modes in other bacterial strains and the techniques used to identify these modes. *D. radiodurans* cells were prepared for transmission electron microscopy by several fixation methods, including chemical and ultrafast cryo techniques, which are generally considered as highly reliable (1). When these techniques were applied on actively growing *E. coli*, *salmonella*, *B. subtilis*, *M. xanthus*, and other bacterial strains, they invariably indicated an amorphous and irregularly dispersed chromatin organization. The fact that an identical array of fixation methods regularly reveals distinct DNA toroids in *D. radiodurans* attests to both the credibility of the observation and the uniqueness of this packaging mode. But does this organization represent indeed a decisive factor in promoting DNA repair?

We proposed that the tight toroidal organization prevents free DNA ends from diffusing away from each other, based not only on the high extent of compactness and order that characterize in vitro DNA toroids, but also on two additional observations. DNA repair in *D. radiodurans* is markedly promoted by freezing and desiccation (2) that slow down molecular diffusion. Repair is, in contrast, strongly attenuated at high temperatures (3) that accelerate diffusion. Moreover, conditions that induce

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toroidal DNA packaging have been shown to dramatically stimulate DNA ligation. These findings highlight the relevance of restricted diffusion within DNA toroids that act as a "molecular cage." Within the tightly packed DNA toroids, water content is reduced, resulting in a decreased formation of reactive radicals, as well as in altered photochemical properties of DNA (4). This, and the close proximity of free DNA ends within the toroids, is likely to substantially reduce the probability of nucleotide modifications at these ends. The observation that repair is enhanced by desiccation (2) further substantiates this claim.

The last point concerns the morphology of a *D. radiodurans* cell and its relevance to DNA repair. In their seminal structural studies, Murray *et al.* demonstrated that *D. radiodurans* strains separate into what the authors specified as individual tetrads, whereby the compartments are not fully separated but rather "remain in communication" (5). We probed a very large number of cells at different growth phases. All stationary *D. radiodurans* cells were scored as tetrads, as were ~85% of exponentially growing bacteria. The rest appeared as sextets or octets, corresponding to cells at various states of division. The tetrad morphology of *D. radiodurans* was highlighted in a light micrograph contributed by M. Daly, where the cells were defined as "tetrad growth units" (6). Our studies revealed that chromosomal copies in a *D. radiodurans* cell are segregated in the four compartments. Because chromosomal segregation has been proposed to promote different extents of DNA packaging per genome (7), we claim that the tetrad morphology is relevant to DNA repair, inasmuch as it allows for coexistence of dispersed and tightly packed toroidal chromosomes in a single *D. radiodurans* cell. Indeed, preliminary studies conducted in our laboratory on the highly resistant strains *D. radiopugnans* and *D. radiophilus* revealed DNA segregation

and toroidal chromatin packaging, implying that these factors contribute to radioresistance.

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## CORRECTIONS AND CLARIFICATIONS

**Research Articles:** "LMO2-associated clonal T cell proliferation in two patients after gene therapy for SCID-X1" by S. Hacein-Bey-Abina *et al.* (17 Oct., p. 415). The second and third authors, C. Von Kalle and M. Schmidt, should have had asterisks after their names, to indicate shared first authorship with S. Hacein-Bey-Abina. The asterisks were inadvertently omitted because of an editorial error.

**Reports:** "Wild-type nonneuronal cells extend survival of SOD1 mutant motor neurons in ALS mice" by A. M. Clement *et al.* (3 Oct., p. 113). The word "inherited" was deleted from the first sentence of the abstract. It should read as follows: "The most common inherited form of amyotrophic lateral sclerosis (ALS), a neurodegenerative disease affecting adult motor neurons, is caused by dominant mutations in the ubiquitously expressed Cu-Zn superoxide dismutase (SOD1)."

**Reports:** "A dearth of dark matter in ordinary elliptical galaxies" by A. J. Romanowsky *et al.* (19 Sept., p. 1696). In the third column on page 1697, in the 21st line, the number should be  $7.1 \pm 0.6$ , not  $6.4 \pm 0.6$ .

## TECHNICAL COMMENT ABSTRACTS

### COMMENT ON "<sup>14</sup>C Dates from Tel Rehov: Iron-Age Chronology, Pharaohs, and Hebrew Kings"

Israel Finkelstein and Eli Piasezky

We contest the interpretation by Bruins *et al.* (Reports, 11 April 2003, p. 315) of the Tel Rehov <sup>14</sup>C data from the points of view of method, provenance, interpretation of the calibration, and historical analysis. These data can be interpreted as supporting the Low Chronology for Iron Age IIA strata in the Levant.  
Full text at [www.sciencemag.org/cgi/content/full/302/5645/568b](http://www.sciencemag.org/cgi/content/full/302/5645/568b)

### RESPONSE TO COMMENT ON "<sup>14</sup>C Dates from Tel Rehov: Iron-Age Chronology, Pharaohs, and Hebrew Kings"

Hendrik J. Bruins, Johannes van der Plicht, Amihai Mazar

The entire 10th century B.C.E. is represented in the consistent Groningen radiocarbon series of Tel Rehov: Phases D3 and D2, and Strata VI, V, and even IV in its upper range. The results contradict Finkelstein's Low Chronology, but do support a Revised Traditional Chronology for the Iron Age in the Southern Levant.  
Full text at [www.sciencemag.org/cgi/content/full/302/5645/568c](http://www.sciencemag.org/cgi/content/full/302/5645/568c)