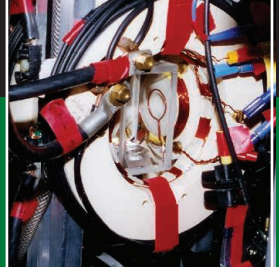

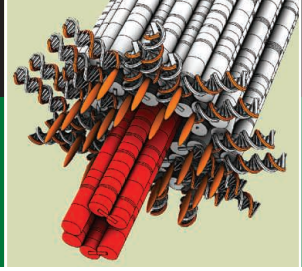

LETTERS

edited by Jennifer Sills

Small Science: Radical Innovation

B. ALBERTS' RECENT EDITORIAL, "THE END OF 'SMALL SCIENCE'?" (28 September, p. 1583), resonated with me. I think many of his conclusions apply not only to biology, but to other fields of science and engineering.

One example from the late 1960s was Multics, a joint effort of MIT and Bell Labs to create a new generation of operating systems (*1*). This was originally planned as a coordinated effort for dozens of researchers collaborating on what was then a big computer. It was preempted by an offshoot called Unix, a project on which nearly all of Multics' goals were achieved much more quickly by a single pair of researchers on a much smaller minicomputer. Unix soon became widely recognized as a big success; its present-day descendants include Linux. Multics eventually stumbled under its own weight and died.

Grand Challenge course.

Another example is the development of fully autonomous ground vehicles and human-sized robots. Starting in 2005, the Defense Advanced Research Projects Agency (DARPA) began offering "Grand Challenge" prizes for the development of fully autonomous ground vehicles capable of completing tasks formerly achieved only by vehicles with human drivers (*2*). In 2005 to 2006, the goal was to drive across a challenging 150-mile off-road course in the Mohave Desert from Barstow, California, to Primm, Nevada. In 2007, the goal was extended to drive autonomously in a mock urban environment including heavy traffic. All totaled, these competitions have attracted over 100 competing teams, each of which typically consists of only about a dozen individuals. This research and development strategy has arguably produced better results faster and with much less expense than the more traditional big-scale strategy of deploying hundreds of people in a single focused effort managed through a standard organization chart.

Of course, there are situations for which the more traditional management strategy may fare better. But when the primary goals are new understanding or radical innovation, rather than incremental improvements, smaller is often better than bigger. In more abstract theoretical subjects such as mathematics, most important research publications have only a single author, and papers with more than three coauthors are extremely rare.

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Small Science: View from Developing Nations

IN THE EDITORIAL "THE END OF 'SMALL science'?" (28 September, p. 1583), B. Alberts asks whether the era of "small-science" projects is coming to an end. He hopes not. I share this sentiment, from the perspective of developing countries where science budgets are small.

It seems clear, however, that big, headline-grabbing projects will likely continue to increase. Thus, the leaders of these projects should seize the opportunity to enable and inspire the next generation of scientists in developing countries. Developing countries do not have the budgets to initiate such "big-science" projects, but they do have ample talent to contribute. Unfortunately, ENCODE—just like the Human Genome Project and others—included scientists from only one developing nation (China).

An exceptional example of integrating developing countries into big-science projects is the decision to award the Square Kilometre Array radio telescope to Africa (*1*). The ripple effects in the media, government, and rest of society are noticeable in South Africa and promising for public support for science. Such support is critical if we are to bridge the gap between science in developed and developing countries, in order to address inequality and the interconnected sustainability problems facing the world.

The scientific community often points a finger at the failure of governments to address these issues. The scientific community, however, also needs to take care of its responsibility and opportunities to help bridge that divide. Big-science projects have the power to make a substantial difference in this regard.

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Small Science: Big Science Will Prevail

IN CANADA, I HAVE ALSO RECOGNIZED THE escalation of big science (not only ENCODE) as an increasingly dominant aspect of modern science culture, perhaps indirectly cata-

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lyzed by the Manhattan project as well as the Human Genome project ("The end of 'small science'?," B. Albert, Editorial, 28 September, p. 1583).

I attribute the situation to our academic culture. We encourage growth and renewal, but impose no limits (except money) on the size of the enterprise devoted to a specific project.

In my view, big science will prevail. The positions big science makes available provide a safety net for the plethora of well-trained Ph.D.'s, who are finding careers in academia increasingly rare, and big-science projects and successes are much more visible to politicians and the many others who are ignorant of science culture.

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Small Science: High Stakes

IN HIS EDITORIAL "THE END OF 'SMALL science'?" (28 September, p. 1583), B. Alberts perceptively highlights the threat of erosion in support for small, fundamental investigations on which a deeper understanding of the complexity of biological phenomena rests. There are other potentially insidious dangers.

The displacement of small science is also likely to have repercussions on science pedagogy. In biomedical fields, small science has historically provided the training ground on which budding scientists develop the technical and creative mastery of their craft. The curtailment of small science thus calls for a critical reevaluation of, and perhaps a transformative new approach to, the biomedical curriculum. Aside from the impact on the training of future investigators, to what extent big science may be integrated into a liberal arts curriculum (and the consequences for a scientifically literate citizenry) (*1*) requires thoughtful collective consideration.

The primacy of big science creates incentive structures that may further impinge on the work of innovative small science. These incentive structures may be reproduced in, or refracted through, funding bodies, academic promotion committees, and journal editorial boards. The diversity of scale in research may thus come to be under siege from all quarters.

Finally, big science and small science have different practices, norms, and infrastructures (*2*). Does big science facilitate successful collaborative work at the expense of substantially reduced heterogeneity in research approaches? Does big science guide scientific advance toward its own perpetuation and away from certain lines of inquiry? No less than a vision for the future of biomedical research is at stake.

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Disease Prevention: Experiments in Nature

THE SPECIAL SECTION ON DISEASE PREVENTION (21 September, p. 1466) reminded me of the late E. L. Wynder's key role in the development of this field. Wynder developed the idea of using "experiments in nature" as clues to the role of the environment in understanding disease causation and prevention. For example, he and his coauthors pointed to the fact that gastric cancer, a common cancer in the United States at the turn of the century, was relatively rare during the latter half of the century. They attributed the decline not to medical intervention but to the introduction of refrigeration and the ensuing decline in the use of nitrates for food preservation. Bolstering this view was the finding that nitrates are readily converted into carcinogenic nitrosamines in the acidic environment of the stomach (*1*). Wynder thus provided an interesting example of how a disease could be suppressed (but not cured) by a technological innovation rather than a medical intervention.

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Disease Prevention: Vitamin D Trials

ALTHOUGH THERE IS A DEBATE ON CUT-OFFS for appropriate vitamin D supplementation ("Uncertain verdict as vitamin D goes on trial," K. Kupferschmidt, News, special section on Disease Prevention, 21 September, p. 1476), clinicians universally agree that vitamin D deficiency is detrimental for bone health (*1*). We also know that vitamin D overdosing can be toxic. What quantity will prevent both deficiency and toxicity?

To find the ultimate vitamin D dose and to evaluate its effectiveness, researchers should learn from randomized controlled trials (RCTs) of drugs for diabetic or hypertensive patients, who were usually treated with the goal of achieving well-defined targets, such as certain HbA1c or blood pressure levels. In the case of vitamin D, this would mean performing RCTs in individuals with overt vitamin D deficiency and using doses to achieve optimal vitamin D levels.

Instead of performing these kinds of RCTs, the design of the ongoing vitamin D trials resembles previous (disappointing) vitamin trials, which attempted to establish a dose that should fit for the entire population (*2*). If the current vitamin D trials fail, we will ask ourselves why we did not perform RCTs exclusively in vitamin D–deficient patients rather than attempting to base conclusions on a heterogeneous population. Subgroup analyses of existing trials will not satisfy health authorities.

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