Biotechnology Issues

I would like to clarify some points in relation to the U.S. Department of Agriculture's handling of biotechnology issues as related to Agracetus's efforts to field test tobacco plants made disease-resistant by genetic engineering (News and Comment, 16 Aug. p. 634).

The federal government is involved in a very positive manner in an almost singularly unique situation of combining all agency guidelines and regulations in biotechnology in one document. This was done by the Cabinet Council on Biotechnology through the President's Office of Science and Technology Policy (OSTP) and published as a comprehensive statement in the *Federal Register* of 31 December 1984. Comments have been received from the public on both regulation and research in biotechnology for the entire federal government. As a result, a totally coordinated effort in the review process of biotechnology is evolving that should be to the benefit of all research scientists, industry, and the users of the products of biotechnology.

The Department of Agriculture has a logical distribution of responsibilities. All regulatory aspects of biotechnology are under the purview of the Animal and Plant Health Inspection Service (APHIS). For research issues, I chair the Department of Agriculture's Agriculture Recombinant DNA Research Committee, which reviews recombinant DNA research proposals in agriculture. This committee is department-wide and located in Science and Education under assistant secretary Orville G. Bentley; it is not a part of the Agricultural Research Service. The committee has representatives from all appropriate agencies in the Department of Agriculture, including the Agricultural Research Service, the Cooperative State Research Service, the Office of Grants and Program Systems, and APHIS, as well as representatives from the National Institutes of Health and the National Science Foundation. The entire federal structure for regulation and assessment of biotechnology of which this committee is a part is evolving through the leadership of Bernadine Healy of OSTP and now David T. Kingsbury of NSF, and it promises to function well. During the early evolutionary phases of the expanded recombinant DNA responsibilities, there may be some delays; but in the end it is anticipated that there will be a well-coordinated total federal system in place to the benefit of all parties concerned. A considerable amount of time and consideration has been given to bringing this program to fruition.

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Crystals in Space

Having many years of experience growing crystals of biological macromolecules, I would like to express my skepticism about growing crystals in space (Research News, 26 July, p. 370).

The problems associated with growing crystals of biological macromolecules for diffraction studies are finding solvent conditions for the production of well-ordered single crystals of a suitable habit and a certain minimum size.

If we look at these problems in relation to the (rather meager) data (*1*) so far presented by the proponents of the space program, we might be able to decide whether it makes "scientific sense."

Each biological macromolecule is unique and, although we have certain general principles (*2*), the conditions for crystal-growing for each new system must be determined ab initio. Needle-shaped or thin-plate crystals present problems to the crystallographer who prefers "chunky" crystals. Given an undesirable habit, it is necessary to search for other conditions to produce other crystal forms, as Blundell indicates. This may require many experiments changing a number of solution variables. Since the β-galactosidase crystals shown by Littke and John (*1*) are long thin needles, one would think the first priority would be to try to obtain different crystal forms rather than larger ones of the same form.

Most of the emphasis of the space program seems to be on the size of crystals, and Bugg might be correct in that convective currents prevent the growth of large crystals; but how large should they be? More than 30 years ago Low and Richards (*3*) described the growth in gelatin gels of β-lactalbumin crystals weighing up to 50 milligrams (about 30 cubic millimeters), and Lewin (*4*) grew crystals of mercury mercaptalbumin derivatives 7 mm long. A requirement for high resolution neutron diffraction is large crystals, and for this purpose lysozyme crystals up to 20 mm^3 have been obtained (*5*). On the other hand, the advent of synchrotron x-ray sources has

meant that the x-ray crystallographer can use much smaller crystals, say 0.01 to 0.1 mm^3.

There are various problems associated with disorder in crystals of macromolecules, and what probably concerns us here are lattice defects, which have been attributed to rapid growth. So although Bugg is encouraged by the growth of large lysozyme crystals in only 5 days in space, neither he nor Littke and John (*1*) provide diffraction evidence that their crystals are better ordered.

It is clear that we need to know how to crystallize and grow diffraction-quality crystals of biological macromolecules. The amount of data now available provides no justification for the enormous costs of a space program to acquire this knowledge. The funds (or a fraction thereof) would be better invested in supporting programs aimed at the determination of the mechanics of crystal growth of biological macromolecules on Earth.

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We would like to put the protein crystal growth experiment described in Kolata's article "The great crystal caper" in perspective. We agree with Blundell that "there have been very, very few advancements (in the art of making crystals) over the past 20 years. We need a concerted approach." This is precisely why this project was undertaken. A team including fluid physicists, physical chemists, and protein chemists from the Marshall Space Flight Center and the University of Alabama in Huntsville with considerable experience in growing small molecule crystals, both on Earth and in space, has been combined with protein crystallographers from the University of Alabama at Birmingham and other leading institutions in this field to mount an interdisciplinary attack on this important problem.

At present, there are fewer than a dozen papers in the literature that deal with the processes involved in the growth of macromolecular crystals. Our ground-based research and the few papers in the literature strongly suggest that the growth of most macromolecular systems is controlled by surface kinetics. Calculations indicate that transport of solute to the growth interface of a typical protein crystal in Earth's gravity is dominated by solutal convection after the crystal becomes larger than a few tens of microns. It can also be shown that such transport is sufficient to maintain an excess of solute at the growth interface so that growth is limited by the rate at which the solute can be incorporated into the lattice. By taking away gravity this convective transport can be eliminated, and the growth rate will eventually be controlled by diffusive transport instead of surface kinetics. We conjecture that this should result in a slower growth rate for a given solute concentration, which usually improves the degree of perfection, and a more compact growth habit because of the spherical symmetry of the diffusion field. There are also other advantages of growth in a microgravity environment. The growing crystal can remain suspended in a liquid droplet, which provides a more uniform growth environment that should improve its quality. Also, fewer nucleation events seem to occur in a quiescent supersaturated fluid than in one that is stirred by convection. The larger crystals grown in space by Littke and John (*1*) at least partially resulted from the fact that fewer crystals nucleated in the flight samples, which meant less competition for solute among the growing crystals.

The description of the experiment in Kolata's article leaves the impression that liquid diffusion is the only growth technique being considered. Our primary emphasis is on the vapor diffusion method, which is a space version of the widely used hanging drop technique. However, we are also exploring the dialysis method along with liquid diffusion.

The experiment performed on shuttle flight 51-D was a simple test of the concept of growing crystals in droplets suspended from syringes under microgravity conditions. One of the major issues was the proper design of the syringe tips to maintain such droplets under the combined effects of interfacial forces and low-level transient accelerations. The unscheduled pursuit of the errant Syncom satellite involved firing of the primary thrusters, which resulted in far greater accelerations than were anticipated. We believe most of the droplets were lost during these maneuvers. We have used what was learned in this flight to redesign the syringe tips to provide for a more stable droplet configuration. Small, inexpensive experiments such as

this are indispensable for working out the details before attempting more sophisticated experiments with precision control of temperature and other variables.

With regard to the large crystal lysozyme that was recovered, the quote to the effect that no one has grown a crystal that size in 5 days was unclear. What was meant was that we had never seen a crystal grow this large using microcrystalline techniques in our control experiments.

We find it difficult to understand the reservations that were expressed about doing such experiments on the shuttle. The shuttle gives us access to a different environment in which growth conditions can be systematically varied in a controlled manner. Given the broad agreement that little progress has been made in the growth of protein crystals in the last 20 years, shouldn't this prospect be explored? The least that can happen is that we will obtain a better insight to improve growth techniques used here on Earth.

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The Granting System and Healthy Research

I am responding to Daniel E. Koshland, Jr.'s, editorial "Modest proposals for the granting system" (19 July, p. 231) from the perspective gained as member, and now chair, of a committee that has debated these topics with federal agency staff since 1982. The Forum on Research Management was founded by the Federation of Behavioral, Psychological, and Cognitive Sciences to improve communication between scientists and federal managers (*1*). Peer review, priority score inflation, indirect costs, simplified applications, and the role of funding agencies in salary support have been discussed, sometimes with final agreement.

Many complaints about peer review would vanish if agency research budgets doubled (a futile hope), but some complaints are common to funded and unfunded alike. For example, the process takes too long. Simple paperwork consumes most of the time and would be reduced if the Division of Research Grants at the National Institutes of Health, for example, could accept and distribute applications directly from laboratory computers. In addition, many agencies must fund basic science through their procurement system. Financial managers, naive about research, are imposed between scientist and project manager and often delay funding, discourage scientists from modifying their protocols as the project develops, and prevent them from treating several projects as one related task. Much would be saved if these agencies could reorient their procedures towards providing the support for basic research rather than its purchase.

Peer review appears to discourage innovative research because controversial projects that generate strong but differing opinions seem to be rarely funded: one dissent dooms an idea that excites most reviewers. Science may benefit from schemes using medians rather than means, lopping off extreme votes, or requiring public votes, for example, proposed to counter the blackball. Priority scores at NIH are now problematical, although simple inflation is not the real problem. If they improve uniformly across sections, then, with coordinate advances in the payline, normal funding patterns are maintained. Study sections bias funding decisions only when they assign idiosyncratic meanings to the scales: percentages and normalized scores strike at bias, not inflation. Furthermore, the increased competition for funds has likely improved the quality of the proposals, and better priority scores may well be deserved. This is not entirely to the good: "grant writing" consumes ever more time and effort, leading, unfortunately, to an increase in overhead costs and a decrease in research productivity. Because preparing applications competes too successfully with real research, Koshland and others reasonably argue that previously successful grantees and the well published be given special consideration. However, this aids the senior worker and perhaps routine research. A seemingly radical proposal is to award an entitlement grant with the Ph.D., with federal money sufficient for an initial project. This scheme would provide young scientists with a painless first grant and help to balance their chances for the next. This proposal is not so radical in fact, because research departments do set up the new Ph.D. with salary, facilities, and often a graduate assistant—in effect, a research grant.

In many universities this "seed money" derives from indirect cost revenues, one of their many general and valuable contributions. Discussions about indirect costs typically focus on their recent expansion and how they must be reduced, rather than on their value to the university as unrestricted income. But the industrial benchmark for overhead is at 150 percent of direct costs, compared to the 50 percent academic rate, which reveals that universities underrecover their costs. The remainder is subsidized by state taxpayers, by endowment income, and by student tuition. Indirect costs vary over time and place because of differences in labor and utility costs and the age and quality of the facilities; because state legislatures and university administrators variously push for more complete recovery; and because of the changing mix of disciplines. (The space needs for theoretical physics are different from those of the biomedical sciences, for example). The political turmoil within our universities set off by a common national rate is not difficult to imagine, as administrators would be pressured to give up valuable programs, including certain of the sciences, as too expensive. Indirect cost recovery, like the other issues, including the impact of academic salaries on research funds, merits continued discussion in an overall context of national science policy and the purpose of the federal government in supporting a healthy research establishment.

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Erratum: The last sentence of the fourth paragraph of Philip H. Abelson's editorial "Use of and research on pheromones" (27 Sept., p. 1343) contained an error. It should have read, "As a result, the amount of pesticides used has been decreased by about 70 percent, and costs of control have dropped."

Erratum: In the article "String as a theory of everything" by M. Mitchell Waldrop (Research News, 20 Sept., p. 1251), the last line of the first column was inadvertantly omitted. The affected sentence should have read, "Not only were the strong interactions far more complex than predicted by field theory, but the particles that participated in the strong interactions—the *hadrons*, a group that includes protons, neutrons, pi mesons, and many others—seemed to be relatively large, extended objects as much as 1 Fermi across (10^{-13} centimeter)." In the next-to-the-last line of the second full paragraph in column 2 on page 1252, 10^{-19} should have been 10^{+19}. Finally, the words "quandary" (page 1251, column 1, paragraph 6, line 2) and "quark" (page 1252, column 3, last paragraph, line 18) were misspelled.