# Letters

## Microbial Containment

The *NIH [National Institutes of Health] Guidelines for Research Involving Recombinant DNA Molecules* define two general methods to reduce the hazards that might arise from the application of this technique. The first of these is called physical containment and is, in effect, the sum of all the physical and technical barriers that are designed to keep infectious materials confined to the laboratory. The second, which is called biological containment, is not truly a containment at all. It is the selection or construction of a host-vector system which has been so modified as to minimize its chances of survival should it escape from physical containment into the environment.

The long-awaited reports by Israel, Chan, Garon, Rowe, and Martin (2 Mar., pp. 883 and 887) have demonstrated a remarkable attenuation of the infectivity of polyoma virus DNA when it has been incorporated into either plasmid or phage DNA and inserted into *Escherichia coli* $\chi$1776. These results would seem to indicate the existence of a third kind of containment, which for want of a better name is here called microbial containment. Microbial containment may be defined as the increment (or decrement) in safety which results when otherwise infectious DNA is spliced into a vector and this, in turn, is inserted into an appropriate microbial host. The studies with polyoma virus DNA reveal that this increment is large, possibly of the same order of magnitude as the increments in safety anticipated with approved physical and biological containment methods. It is suggested that, in future experimental designs, attention be paid not only to two but to three containments: physical, biological, and microbial. Only half in jest, it has been suggested that the safest way of handling infectious DNA materials in the future will be by the application of the recombinant DNA technique.

Certainly, extrapolation from these results must be cautious. As in the case of biological containment, where each candidate host-vector 2 system must be individually tested and proved, so in microbial containment each new situation must be separately tested. It is noteworthy, however, that contrary to the common experience wherein procedures deemed to be safe are found to be unsafe, in the present situation a procedure initially flagged as potentially dangerous has proved to the contrary to enhance safety. Let us rejoice!

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## Grants: The Time Factor

In his editorial on the burden of competitive grants (16 Feb., p. 607), A. Carl Leopold suggests that now might be the moment to give thought to ways of reducing the time required to prepare (and review) research proposals.

Not a bad idea. And in fact the National Institutes of Health presently would like to encourage scientists to submit shorter and more cogent proposals. Peer review groups are, likewise, encouraged not to summarily reduce the tenure of meritorious proposals, but to allow those scientists to get down to the uninterrupted business of research as planned. Leopold's observation that currently a large number of proposals fail to obtain funding is related to the politics of national priorities rather than to review mechanisms.

However, even if research funds were unrealistically boundless, a wise researcher would still invest substantial time reviewing what has gone before and reflecting on what his or her own best approach ought to be. In facing the realities of time and support, and since neither will ever be open-ended, a major and systematic effort should continue to be made to help us all realize the best return on our finite dollars and years.

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I would like to respond to Leopold's perceptive editorial. Let me propose a specific reform that should retain the present system's most essential feature—accountability—yet greatly ease its burdens.

In brief, established investigators should compete on the basis of recent (say the past 5 years) accomplishments rather than proposals. For the investigator, it should be a reasonably simple task to collect a set of reprints and preprints and prepare a summary of their import. For the panels, it should be considerably easier to review accomplishments rather than promises.

Another very important advantage of an *accomplishment grant* system would be the encouragement of innovation. The investigator, not the panels, would judge the truly new and take the risks.

Under this proposed reform, the older *proposal grant* system would continue, but on a much reduced scale. It would be generally patronized only by beginning investigators, or by older ones who somehow needed a fresh start.

In addition to its apparent practicality, the spirit of this reform should appeal to a country weary of too much bureaucracy and too much regulation. It would be a move toward freer enterprise in research.

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Leopold's editorial brought a flash of enlightenment. The Egyptians had their pyramids, Roosevelt his WPA (Work Projects Administration), and we have the writing of grants.

The country has expensively educated more scientists than it feels it can employ as research scientists. The problem is not their salaries but the expense of their research.

How, then, can one occupy the time of these elegant intellectual athletes without permanently crippling their research abilities? How can they be kept in the "ready reserve," prepared to move into the breach if the nation decides it must catch up with Sputnik Russia or the war on cancer?

The solution is simple—let them write grant applications. They can think about research even if they can't actually perform it. It's a little like the draftees before World War II drilling with wooden rifles; but it is better than no drill at all.

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## Szent-Györgyi's Research

In order to create a more complete picture of the situation described in the article "Albert Szent-Györgyi, electrons, and cancer" (News and Comment, 9 Feb., p. 522), I offer some additional information pertaining to this important problem. The author states that "nothing so far has been published about it [Szent-

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Györgyi's theory] in the scientific literature other than one or two papers in the *Proceedings of the National Academy of Sciences*." Some 30 years ago Szent-Györgyi published in *Nature* his prediction that proteins are semiconductors (*1*). Since then, a number of papers published in scientific journals indicate that charge transfer reactions occur in biological systems. Semiconductor properties have been demonstrated for collagen (*2*), deoxyribonucleic acid (*3*), and certain metalloproteins (*4*). Bone and tendon have been shown to exhibit photoconductivity, reflecting their electronic properties (*5*). Moreover, amide bond, the backbone of proteins, is a transmitter of electronic effect (*6*). Finally, most biopolymers, including proteins, nucleic acids, and mucopolysaccharides, are capable of mechanoelectrical transduction (piezoelectricity) (*7*).

In view of these facts indicating the potential importance of bioelectricity for controlling the growth of cells, to state that ". . . there are no data indicating that it [Szent-Györgyi's theory] might have validity" seems difficult to justify.

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Constance Holden's article on Albert Szent-Györgyi contains almost as an aside a statement of much that is wrong with American science. She says, "scientists connected with the NFCR [National Foundation for Cancer Research] agree with others that this is not a theory that is exactly ripe for government support. It is exceedingly unconventional, a leap into the unknown."

I could not disagree with these sentiments more strongly. Great discoveries in all fields from the sciences to the humanities have nearly always been the result of imaginative and innovative approaches to old problems. In the process of becoming the principal source of research funding, the federal government has exercised a subtle but pervasive control over the kinds of research that are performed. As one member of a funding agency remarked to me, "We admire innovation, but we don't trust it. And we fund what we trust."

American preeminence in science has historically been based on the willingness of past researchers to take imaginative leaps. Today, support for this kind of thinking is extraordinarily difficult to come by, even for persons with strong reputations (witness Linus Pauling and Albert Szent-Györgyi). For those with equally fertile imaginations but of less repute, the truly creative art of scientific research is an unreachable dream. Federal funding agencies would do well to mark out a portion of their budgets specifically for the researching of a few wild ideas. Otherwise, we may find ourselves lagging progressively farther behind those places "further East" which Holden says are more in sympathy with fantastic ideas.

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## Cancer Incidence

Luther J. Carter, in his excellent article on cancer policy (News and Comment, 9 Feb., p. 525), misses an important consequence of assuming a proportional relationship between cancer incidence and dose—that the total number of cancers tend to stay constant if the pollutant is spread more widely in the population. Carter says, "With the current popularity of self-service pumps at gasoline stations, exposure to this chemical [the additive ethylene dibromide] is presumed to have been increasing." This is probably wrong.

Replacement of gas station attendants by self-service pumps will increase the number of persons exposed, but if the exposure per car filling remains the same, so will the total exposure—it is merely spread over more persons. There will be fewer cancers among the attendants but more among the customers. The decrease in one will be matched by an increase in the other to within statistical error.

If, as some people believe, there is a threshold exposure below which no cancer appears, then the customer may get no cancers at all, and the total number of cancers will go down.

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***Erratum:*** **Because of a printer's error, a line was dropped from the letter by Robert W. Berliner (16 Mar., p. 1066). The third sentence in the third paragraph should have read, "Schools of medicine have large fixed costs that do not vary with the number of students. . . ."**