certainly shows that the DuPont Company believes that this is so. This means one of two things: either the people going into research are incapable of generating ideas worthy of research (from the standpoint of a return on investment), or such opportunities no longer exist in the field chosen for research. In the case of DuPont, in the field of polymers, when the cost of internal development was too high to be absorbed, it indicated that the area being searched was no longer a rich field and that perhaps one should look elsewhere. However, when a company is very rich, the field must be extremely valuable or the research will not "pay off."

The standard reply by the industry is, "we'll buy our research from somewhere else." This would indicate that the probem is neither the researchers nor the paucity of ideas, but rather is in the guidance of the research or the selection of areas chosen for research. Many times, the decision of where to search is not the choice of those doing the research, but of financial analysts who say, "We have found gold here before, keep searching." Often, when gold is searched for, silver is found and those paying for the search are not interested. They may not know how to market the silver or feel that only a market for gold exists.

Most often, large companies do not buy their research from other large companies (unless those companies are in trouble themselves), but purchase research from smaller companies or from universities. No doubt, the cost structure for research is better at smaller companies, where overheads tend to be lower. Research can often be purchased from small companies for far less than it is worth, because of the inability of the small company to bear the cost of commercialization, which tends to dwarf research costs. At universities, the cost is lower still, as proved by the tremendous rush by all major companies to align themselves with the industrial transfer folks at the best research universities. Intellectual property rights always present the biggest obstacle in all of these negotiations, because the universities and small companies want a good return for the funds invested, whereas the purchasing companies want those costs to be small in order to provide a higher return. The fact that universities are not charging full costs, that is, the cost of failed research, makes them the cheapest cost provider for purchased research. Serendipitous discovery also provides an incentive for government to fund such research, thus providing industry with research at no direct cost to the purchasing companies. Unfortunately, this opportunity is afforded to all comers, and the mark and the yen have proved to have astonishing purchasing power over the last decade. It's something like having a fire sale for certain customers who have responded by buying everything in sight.

Those of us in small companies will either find the funds to support our research from those willing to take a high risk for a commensurate return, or progress will cease. Fortunately, in the chemical and biotechnical fields with which I have been associated, there are such people. They are unwilling to pay for research in which vast sums have already been expended because they realize there is little to be found and the cost will be high. But for new and innovative chemistries, there is an amazing quantity of funds available.

Concerning the lack of need for Ph.D.'s, we should remember that in the early days of genetic engineering, 5 to 7 years of postdoctoral experience was the norm. Shortly after the discovery of the value of genetic engineering, these postdocs were commanding a salary 30% higher than other scientists in the area. The universities quickly responded, and salaries became more moderate. Whereas DuPont was reducing its hiring of technically trained people, the biotechnology and pharmaceutical industries quickly took up the output of our universities. It reminds me of the swings in petroleum engineering students and salaries. In 1982, R. L. Whiting of Texas A&M University told me that there were 600 graduates, only two of whom had jobs in petroleum engineering, and two freshman students. Our students have never been slow to determine whether they should enter a field if they have good information about the field. When there are no jobs or the pay is poor, the students will evaporate like the morning dew.

To those who bemoan the poor students, my reply is to tell them that chemical research is rewarding for those who have a new idea of where or how to search. For those who don't, latch on to someone who does. If you can't do one of these, get ready to be frustrated by the lack of jobs in research.

Gary Calton
Chairman and Chief Executive Officer,
SRCHEM, Inc.,
5331 Landing Road,
Elkridge, MD 21227, USA

■

Predicting Protein Crystal Structures

We write to call attention to a passage in a figure legend of a recent research article by David Barford *et al.* (*1*). The article reports the crystal structure of human protein ty-

rosine phosphatase 1B; the legend for figure 3 notes that most of the core secondary structural elements were predicted correctly by Livingston and Barton *before* the experimental structure was published (*2*).

The prediction (*2*), although not perfect, marks a milestone in the development and testing of a new generation of prediction methods that start from an alignment of homologous protein sequences. There are now a dozen examples where most or all of the core secondary structural elements have been successfully predicted for a protein family with the use of (i) methods that extract secondary and tertiary structural information from an analysis of patterns of conservation and variation between homologous protein sequences (*3*, *4*) or (ii) methods that average predictions made by classical methods over a set of aligned homologous sequences (*5*).

The list of protein secondary structures predicted using the first method includes the protein kinases (*4*), the Src homology 2 domain (*6*), the Src homology 3 domain (*7*), MoFe nitrogenase (*8*), hemorrhagic metalloproteinase (*9*), and the extracellular segment of the asparate receptor of *Escherichia coli* (*10*), together with protein tyrosine phosphatase (*2*). In several of these cases, in particular for the first domain of protein kinase (*11*), the hemorrhagic metalloproteinases (*12*), the Src homology 2 domain (*13*), and the pleckstrin homology domain (see below), the predictions were accurate enough that they were plausibly useful as the starting point for modeling tertiary structure. Further, although the prediction tools do not rely exclusively on automated methods, the fact that these tools are now generating predictions in at least four different laboratories suggests that they are transferable from laboratory to laboratory (*14*).

Predictions made with the use of the second method have been less consistent in their accuracy. Nevertheless, outstanding results have been obtained with interferon (*15*), tryptophan synthase (*16*), and annexin (*17*). Averaging of classical predictions with some conservation analysis yielded the secondary structure prediction that was used to model the zinc finger domain from transcription factor IIIA (*18*). Finally, a very good model of the secondary structure of the cytokine receptor was built by combining the second method with a more complete conservation analysis reminiscent of the first method (*19*).

No finite number of secondary structure predictions can prove a method, of course. Because many bona fide predictions are now in the literature, however, prediction verifications have become monthly events. For example, since this letter was first pre-

pared, two nuclear magnetic resource structures appeared for members of the pleckstrin homology domain family (*20*). The secondary structure predictions (*21*) proved to be essentially perfect. These successes should encourage still more groups to try their hand at structure prediction.

Steven A. Benner
Dietlind L. Gerloff
Thomas F. Jenny
Department of Chemistry,
E.T.H. Zürich, CH-8092 Switzerland

References

1. D. Barford, A. J. Flint, N. K. Tonks, *Science* **263**, 1397 (1994).
2. C. D. Livingston and G. J. Barton, *Int. J. Pept. Protein Res.*, in press.
3. S. A. Benner, *Adv. Enzyme Regul.* **28**, 219 (1989).
4. S. A. Benner and D. Gerloff, *ibid.* **31**, 121 (1991).
5. J. A. Lenstra, J. Hofsteenge, J. J. Beintema, *J. Mol. Biol.* **109**, 185 (1977); J. Garnier, D. J. Osguthorpe, B. Robson, *ibid.* **120**, 97 (1978); F. R. Maxfield and H. A. Scheraga, *Biochemistry* **18**, 697 (1979).
6. R. B. Russell, J. Breed, G. J. Barton, *FEBS Lett.* **304**, 15 (1992); G. Pananoyotou *et al.*, *EMBO J.* **11**, 4261 (1992).
7. A. Musacchio, T. Gibson, V.-P. Lehto, M. Saraste, *FEBS Lett.* **307**, 55 (1992); S. A. Benner, M. A. Cohen, D. L. Gerloff, *J. Mol. Biol.* **229**, 295 (1993).
8. D. L. Gerloff, T. F. Jenny, L. J. Knecht, G. H. Gonnet, S. A. Benner, *FEBS Lett.* **318**, 118 (1993).
9. D. L. Gerloff, T. F. Jenny, L. J. Knecht, S. A. Benner, *Biochem. Biophys. Res. Commun.* **194**, 560 (1993).
10. G. R. Moe and D. E. Koshland Jr., in *Microbial Energy Transduction: Genetics, Structure, and Function of Membrane Proteins*, D. C. Youvan and F. Daldal, Eds. (Cold Spring Harbor Laboratory, Cold Spring Harbor, NY, 1986), p. 163.
11. D. R. Knighton *et al.*, *Science* **253**, 407 (1991).
12. F.-X. Gomis-Rüth, L. F. Kress, W. Bode, *EMBO J.* **12**, 4151 (1993).
13. G. Waksman *et al.*, *Nature* **358**, 646 (1992).
14. B. Robson and J. Garnier, *ibid.*, **361**, 506 (1993).
15. M. J. E. Sternberg and F. E. Cohen, *Int. J. Biol. Macromol.* **4**, 137 (1982).
16. I. P. Crawford, T. Niermann, K. Kirschner, *Proteins Struct. Funct. Genet.* **2**, 118 (1987).
17. W. R. Taylor and M. J. Geisow, *Protein Eng.* **1**, 183 (1987); G. J. Barton, R. H. Newman, P. S. Freemont, M. J. Crumpton, *Eur. J. Biochem.* **198**, 749 (1991).
18. T. J. Gibson, J. P. M. Postma, R. S. Brown, P. Argos, *Protein Eng.* **2**, 209 (1988).
19. J. F. Bazan, *Proc. Natl. Acad. Sci. U.S.A.* **87**, 6934 (1990).
20. H. S. Yoon *et al.*, *Nature* **369**, 672 (1994); M. J. Macias *et al.*, *ibid.*, p. 675.
21. A Musacchio, T. Gibson, P. Rice, J. Thompson, M. Saraste, *Trends Biochem. Sci.* **18**, 343 (1993); T. F. Jenny and S. A. Benner, *Proteins Struct. Funct. Genet.* **20**, 1 (1994).

■

Glioblastoma Treatment

In Faye Flam's News & Comment article about opportunities for treatment of brain cancer, "Will history repeat for boron capture therapy?" (22 July, p. 468), I was misquoted as having said, "a small number of glioblastoma patients do survive without treatment." I am not aware of such cases, although a few percent do survive with standard treatments. My identification as a neurosurgeon was also incorrect.

Daniel N. Slatkin
Pathologist,
Clinical Research Center,
Brookhaven National Laboratory,
Post Office Box 5000,
Upton, NY 11973–5000, USA

■

Correction: Incorrect References

In our report (*1*) "Rearrangements of synaptic connections in visual cortex revealed by laser photostimulation" (8 July, p. 255), two errors were made in citing papers from the group of T. Tsumoto.

The first error is in reference 6 on page 258 [Y. Hata, T. Tsumoto, H. Sato, K. Hagihara, H. Tamura, *J. Neurophysiol.* **69**, 40 (1993)], which was described as being published in *Neurophysiology* (*USSR*). This error seems to have occurred when we left the "*J.*" out of the citation, resulting in a change to "*Neurophysiology* (*USSR*)."

The second error is in reference 17 on page 258. Here the reference that we meant to give was "T. Tsumoto, K. Hagihara, H. Sato, Y. Hata, *Nature* **327**, 513 (1987)."

Tadaharu Tsumoto was kind enough to bring these errors to our attention.

Matthew B. Dalva
Lawrence C. Katz
Department of Neurobiology,
Duke University Medical Center,
Durham, NC 27710, USA

References

1. M. B. Dalva and L. C. Katz, *Science* **265**, 255 (1994).

Corrections and Clarifications

In the 12 August Random Samples item "Fields medal honorees announced" (p. 871), Efim Zelmanov was incorrectly said to be at the University of Chicago. His permanent affiliation is the University of Wisconsin, Madison.

In the abstract of the report "Fullerenes in the 1.85-billion-year-old Sudbury impact structure" by L. Becker *et al.* (29 July, p. 642), the second sentence should have read, "The C_{60} content is estimated at a few parts per million."

Daniel E. Koshland Jr.'s editorial of 8 July, "Paradise gained" (p. 167) incorrectly implied that the world's current human population is 4 billion. It is 5.65 billion.