Editorial & Letters

EDITORIAL

Science Roadmaps

Technology roadmaps are gaining acceptance in industry and government laboratories, and now there are signs that the application of roadmapping to the sciences may grow even faster. A "roadmap" is an extended look at the future of a chosen field of inquiry composed from the collective knowledge and imagination of the brightest drivers of change in that field. Roadmaps can comprise statements of theories and trends, the formulation of models, identification of linkages among and within sciences, identification of discontinuities and knowledge voids, and interpretation of investigations and experiments. Roadmaps can also include the identification of instruments needed to solve problems, as well as graphs, charts, and showstoppers.

The optimal process for gathering and selecting the content of roadmaps is to include as many practicing professionals as possible in workshops periodically in order to allow all suggestions to be considered and to objectively evaluate the consensuses that will more often than not emerge. Equal treatment should be given to minority views and individual advocacies.

Roadmaps communicate visions, attract resources from business and government, stimulate investigations, and monitor progress. They become *the* inventory of possibilities for a particular field, thus stimulating earlier, more targeted investigations. They facilitate more interdisciplinary networking and teamed pursuit. Even "white spaces" can conjure promising investigations. In engineering, the roadmapping process has so positively influenced public and industry officials that their questioning of support for fundamental technology support is muted.

Motorola has prolifically used sophisticated engineering roadmaps to great advantage over several decades. Other corporations such as Intel have also benefited.

In the early 1990s, U.S. semiconductor competitors decided to work together to solve some of the more basic, confounding, but precompetitive, technical barriers whose impact was a concern to our companies over a 15-year time horizon. The solution to many of these problems was likely to be beyond one company's affordability. Most competitors assigned their brightest engineers to meet in common, in committees, and in ad hoc specialist reviews. Over a few weekends, 150 to 175 of them convened to flesh out the broadest agendas. A Roadmap Coordinating Group was formed to oversee the process of determining target values for device and circuit specifications. Technology working group teams were then assigned to flesh out tasks more fully. The result was a 200-page roadmap, now in its third edition. This dynamic document is the basis for assigning various initiatives to certain companies or institutions. Self-forming alliances tackle others. These alliances include Sematech, a consortium specializing in developing the most productive, quality driver manufacturing equipment, and Semiconductor Research Corporation, through which the industry pools funding for advanced research to centers of excellence in university science laboratories.

Roadmaps allow our industry leaders to communicate convincingly with those in government and business regarding their support of our goals. I believe a similar use of roadmaps in the sciences would allow a fresh, positive approach to science to emerge among public officials. Similarly business leaders would have a renewed interest in financially supporting science.

The roadmap process as used by industry reveals that industry is "idea limited." For example, industry roadmaps do not answer questions such as what increments of, or breakthroughs in, the fundamentals of nature can we learn from? This is where science roadmaps can play a key role. Fortunately, examples of science roadmaps are blossoming.

NASA has used roadmaps built on basic themes for years and encourages others to do the same. The leadership of the National Science Foundation encourages experiments with roadmapping in science and engineering, while cautioning that history tells us that the most important discoveries cannot be predicted. The Department of Energy is launching science roadmaps and the Electric Power Research Institute has committed to them as well. The Santa Fe Institute has given its unqualified support to science roadmapping and is preparing a Novel Computational Roadmap to synthesize and guide the research needed now to create the computing technologies needed 15 years hence.

Roadmaps are working now in industry and they are beginning to gain a stronghold in science. Just as engineers first scoffed at them, so will some scientists. But who better than scientists to experiment with an experiment that can strengthen sciences' support and accelerate its generation of knowledge.

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LETTERS

Protection?

More than 75 top U.S. AIDS researchers urge that the government effort to develop an AIDS vaccine should remain the responsibility of the U.S. National Institutes of Health. French AIDS czar Jean-Paul Lévy expresses his doubts that an efficacious AIDS vaccine is ready for testing. A social science method for analyzing complex behavior is endorsed. The nature of drug addiction is discussed. And an economic plan to preserve biodiversity in Korea's DMZ is suggested.

AIDS Vaccine Development

In recent months, the U.S. National Institutes of Health (NIH) human immunodeficency virus (HIV) vaccine research program has been criticized by a few activists and public health figures who serve on, or have provided testimony to, the President's Advisory Committee on HIV/AIDS (PACHA) (M. Balter, News, 30 Jan., p. 650). It has been proposed that responsibility for the development of an HIV vaccine should be removed from NIH and transferred to other federal agencies. It has been suggested that an effective HIV vaccine would be available much sooner if only NIH would support efficacy trials of currently available candidates, notably of glycoprotein 120 (gp120) subunits, on an empirical ("trial-and-error") basis.

We are concerned about these criticisms. We believe that NIH exercised appropriate judgment in 1994 when declining to support efficacy trials of the present generation of gp120 subunit vaccines. Clinical and laboratory studies during the past 4 years clearly reinforce the wisdom of that decision. The gp120 proteins do not induce relevant antibody or cell-mediated immune responses of significant potency. Their performance in Phase I/II trials has been disappointing, judging by careful evaluation of individuals who became infected with HIV-1 despite previous vaccination with gp120. Traditionally, the trial-and-error approach has been successful in vaccine development, but empiricism has not delivered an HIV vaccine despite much effort over the past 15 years. This is because HIV has properties not possessed by other pathogens for which

vaccines were created empirically. These characteristics include the poor immunogenicity of the HIV envelope glycoproteins and their resistance to neutralizing antibodies, the extensive variation in the viral genome, and the ability of the virus to become integrated in the host genome of immune cells. To overcome these unprecedented scientific obstacles requires a more sophisticated strategy than has been successful previously. We need to acquire fundamental information about the workings of the human immune system and its interactions with HIV. More and different vaccine concepts must be tested in Phase I clinical trials, aimed at optimizing immunogenicity.

In his testimony to PACHA and in a subsequent article in *Nature* (*1*), Jonathan Mann described the failure to proceed with large-scale phase III vaccine trials as a "human rights violation," and he complained that David Baltimore, Harold Varmus, and the scientific community are holding a "monopoly lock"on the process of developing an HIV vaccine. The scale of the worldwide AIDS epidemic creates a compelling urgency for developing an effective vaccine. Slow progress is frustrating to all concerned, but attacking NIH and the scientists who are working on the problem serves no useful purpose. There are no quick fixes to the scientific problems of HIV vaccine development. It may be many years before an effective HIV vaccine is finally created. NIH has been, and will continue to be, the federal agency most suited to supporting the development of this vaccine. It has been only a little more than a year since the AIDS Vaccine Research Committee was established to provide strategic advice to NIH. The performance of this committee must be judged over a period measured in years, not months.

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Recently, AIDS vaccine research has become the subject of impassioned debates. Some highly dubious trials in human subjects have been announced. Scientifically, it is impossible to say whether we will be capable of making a suitable vaccine. It is clear, however, that vaccine research is of the highest priority. We must accelerate both phase I trials in human subjects and experiments in animal models that are truly relevant to human infection, if we wish to obtain useful results by the beginning of the next century.

What can we hope for in the near future? Some people advocate moving to phase III trials. It is difficult even to imagine what the rationale could be for initiating such trials now, with the existing results. We cannot as yet provide a valid reason for supposing that the available vectors will protect against the viruses we are interested in. At best we could perhaps protect against a very small number of neutralization-sensitive viruses for a short period of time, but not against the predominant strains almost exclusively involved in human infections. Even the "Prime-boost" protocols are unsatisfactory in that strong cellular responses, especially multiepitopic responses, are not frequent enough in vaccinees. It is true that Jenner in 1796 or those who prepared the polio vaccine in the 1950s were successful without applying the criteria we demand today. Let us remember, however, that had they been able to check, clearly positive responses would likely have been found. The empirical, quasi-religious approach, neglecting half a century of science or more, could be dangerous. First, because phase III trials might actually be detrimental for prevention. The high frequency of infection found in some series of U.S. phase I volunteers (up to 3%) confirms that running a vaccination trial presupposes in the minds of many that the vaccine is likely to protect. The problem would be even greater in developing countries. In addition, we cannot ignore the question of enhancing antibodies. They exist in a significant proportion of vaccinee samples of serum when tested against a field isolate. If a panel of such isolates were tested, the proportion of donors with positive results would inevitably be greater. It must be recognized that we do not understand the biological significance of these antibodies, but it would be unethical to enroll exposed volunteers in useless trials neglecting this phenomenon, if at the same time strong arguments in favor of protection do not exist. We would do well to remember that in animals vaccinated with envelope proteins of feline immunodeficiency virus or of equine infectious anemia virus, viral infection has frequently been accelerated or the disease aggravated. We must also think in terms of a possible lowering of the viral infectivity threshold, making vaccinees more susceptible to at least some viruses. There is a fundamental right involved, that is, to be spared from enrollment in a useless and possibly dangerous trial. The problem is that scientists are faced with, on the one hand, a void of supporting arguments and, on the other, with potential danger. The cardinal rule must therefore apply: Do no harm. What experiments are necessary now? We must verify whether or not neutralizing antibodies that are effective against field isolates, broadly cross-reactive, and associated with a good memory response, might be obtained with vectors that have not as yet been sufficiently tested, like trimeric envelope proteins from field isolates, pseudovirions, and DNA vaccines. The goal would be to induce neutralizing, cross-reactive antibodies directed against B12, 2GI29, 2F5, or similar epitopes and not against the highly variable and poorly accessible V3 dominant epitope. However, knowing that they are poorly immunogenic and that experiments in vitro and in vivo in SCID-hu mice have shown that enormous concentrations of these antibodies would be necessary for in vivo projection, it appears that the chance of succeeding in this way is probably low. The prospects are better in the field of cellular immunity, and the bet must be placed on a vaccine based on these responses. We must accelerate trials for each new vector, which, in reference to macaque experiments, might improve, for example, CD8 and CD4 responses, new viral recombinants, new lipopeptides, DNA vaccines, and combinations of these. The goal would be to induce strong CD4 responses of the TH1 type, as well as strong, multiepitopic and long-lasting CD8 responses. If we succeed, and especially if protection is obtained by the same approach in macaques, it would be logical to launch a phase III trial based purely on the induction of virus-specific, cell-mediated responses. Nevertheless, we also have to multiply parallel trials designed to induce mucosal immunity. The chance of protection would be weak with a mucosal response alone, but in association with systemic cell-mediated responses, at least a partial protection might be reasonably expected. We could obtain responses in 3 to 4 years if enough trials were done and then we would be able to say whether or not a phase

III trial is justified.

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Ecological Science and Statistical Paradigms

In his excellent research commentary "Ecological science and statistical paradigms: At the threshold" (*Science*'s Compass, 23 Jan., p. 502), Brian A. Maurer calls for more testable models in analyzing ecosystem behavior, given the complexity and causal uncertainty associated with such ecosystems. Others, including me, would take his recommendation one step further. One major social science approach to analyzing highly complex and uncertain behavior is triangulation, the use of very different (indeed, orthogonal) theories, methods, or databases to converge on points for follow-up (*1*). By using such different but formal approaches to address an issue, we do not so much reduce the issue's uncertainty or complexity (although that is one aim) as we increase our confidence about how to proceed. Triangulation has recently been applied to the debate over sustainable development and ecosystem management (*2*) initiated by Ludwig, Hilborn, and Walters' 1993 *Science* Policy Forum (*3*).

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On "The Science of Substance Abuse"

The series of papers entitled "Frontiers in neuroscience: The science of substance abuse" (3 Oct. 1997, p. 45) provides a thoughtful review of recent research on how addictive drugs alter brain function. Several of the papers present the conventional view that addiction is a chronic and relapsing disorder; however, according to epidemiological research, addiction is the psychiatric disorder with the highest recovery rates and the shortest duration (*1*, *2*). Experimental and clinical studies show that the factors that influence voluntary behavior, such as economic and social costs, persuade many addicts to quit using drugs (*3*, *4*). Not mentioned is the fact that voluntary behavior is mediated by the brain and the extensive findings on relapse rates and recovery.

It has long been acknowledged that changes in brain function alter voluntary behavior, and in the last 20 years or so, laboratory research has revealed many of the details of these relations. Thus, neuroadaptation could just as likely influence preference as preclude it. The difference is important. An addict who takes drugs voluntarily can be persuaded by contingencies or new information to stop using them. An addict who takes drugs involuntarily cannot be persuaded by costs and incentives to stop using them. To determine whether drug-induced brain changes lead to involuntary drug use, we must turn to the re-