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SCIENCE AND TECHNOLOGY POLICY: A SCIENTIST'S VIEW

FLOYD BLOOM, M.D.*

For the purposes of full disclosure, I am the chairman of the department neuropharmacology at the Scripps Research Institute. Since May of 1996, I have been the Editor-in-Chief at *Science Magazine*, which we like to tell people is the most widely read general scientific magazine in the world. I also consult for many biotechnology companies, as well as for the federal government and pharmaceutical companies. If you infer anything from this Article, I at least want you to know the perspective from which I am coming.

Scientists today are interested in the views expressed in this publication because we are both frustrated and under the pressures of extreme competition. There is competition between scientists for having clever ideas, and there is competition between the funders of science for who gets the rights to develop our discoveries. Last week, *Science Magazine's* news section described a new biomedical research center to be funded in San Diego by monies coming from one of the corporations within the tobacco industry.¹ We felt obliged to examine this set of issues because it raised anew the issue of whether funds from nontraditional commercial sources would in some way diminish the quality of the research being funded; and whether by putting a

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1. Jon Cohen, *Tobacco Money Lights Up a Debate: Tobacco-Industry Support of Supposedly Independent Research*, 272 *SCIENCE*, Apr. 26, 1996, at 488.

lot of money into an important molecular area of medical research, we would be in some way misleading the public as to the dangers of the product that provided the funds for the research in the institutions.

If you read that news article written by Jon Cohen, *Science's* reporter from Southern California, you will find a very balanced coverage of the degree to which fair-minded people strongly disagree on those sets of issues. Therefore, as scientists trying to exist in a highly competitive atmosphere, we must always be aware of the fact that funds from any source are not necessarily equal in their value as to what might come of them. You will also find that there were some very accomplished scientists who felt coerced into taking tobacco money because their regular research grants had dried up. Some of those scientists went on to win Nobel prizes.² So, in my view, such funding can't be completely bad.

The federal commitment for the support of the National Institutes of Health's (NIH)³ basic research budget has experienced a slow, but steady, rise over the last several years. The problem is that there has been a rapid increase in the number and the quality of investigator initiated research grants. This has strongly compromised that modestly growing NIH budget. This means that scientists spend an awful lot of their time writing grant applications and experiencing the frustration that, even though they have received scores far better than any scores they have ever received before, they are unable to secure funding for their research grants. It is difficult enough for a senior scientist to try to buck these trends, but it is extremely demoralizing for our young people. In my view, it is the young people on whom we have to rely for the future of this research field.

Over the last decade or so, Congress has tinkered with the NIH's budget, forcing first the aspect of the total numbers of grants and then another aspect, the average duration of grants (as well as a variety of other manipulations), in an effort to make research dollars stretch farther. It generally has not worked. In the face of the Republican Congress's zeal to balance the budget, the NIH supporters were very pleased that we were able, thanks to Congress-

2. Stanley Cohen, of Vanderbilt University; Baruj Benacerraf of the Dana-Farber Cancer Institute; and Harold Varmis, Director of the National Institutes of Health. *Id.* at 490-496.

3. The NIH is a federal agency that underwrites research in its own laboratories, as well as in those at private and public institutions by awarding grants and contracts.

In the area of biotechnology, NIH-supported research can be divided in two categories. The first is basic research directly related to biotechnology, which includes recombinant DNA techniques; gene mapping and DNA sequencing; isolation, separation, and detection of DNA; the creation of hybridomas; the production of monoclonal antibodies; protein engineering; production of antibody-toxin chimeras (immunotoxins); and the computer analysis of DNA and protein sequences. The second category relates to the broad research underlying biotechnology and refers to studies in the fields of genetics, cellular and molecular biology, biological chemistry, biophysics, immunology, virology, macromolecular structure, and pharmacology.

U.S. CONGRESS, OFFICE OF TECHNOLOGY ASSESSMENT, BIOTECHNOLOGY IN A GLOBAL ECONOMY 249 (1991).

man Porter's⁴ leadership, to get a modest 5.5% spending increase in the 1996 Budget. That is a very unique growth in this year's fiscal budget for science, but it is not very good. It barely allows us to maintain an adequacy with inflation—and in biomedical research, inflation is considerably higher than it is for the general public.

It is not only frustrating for scientists who have to compete, but it is frustrating for the public who wants the scientists to succeed. There are many important insoluble problems that we face today and the biological sciences offer an unprecedented opportunity for significant advances in the understanding of the molecules responsible for both health and disease. Scientists are as frustrated by their inability to proceed as they are frustrated by the intensity of the competitions that we face.

Now I work at the Scripps Research Institute. Scripps has been a leader in trying to find innovative ways of protecting our faculty against some of these rigors and variations in federal support. Thus, I write my next remarks not on behalf of any formal statement of our Scripps leadership, but really as a faculty member who was deeply involved in examining the various contracts we have implemented with our current and our future research partners. At Scripps, we view ourselves as a small, private research organization. In order for us to compete successfully for the research opportunities that our faculty face, we found alternative sources of funding to be a very desirable feature; but it bothered many of our faculty to undergo these kinds of corporate relationships. My friend, Carleton Gajdusek, the Nobel prize winner⁵ who currently has his own problems,⁶ has noted that almost all modern science requires patronage. All patronage requires wealth and power on the part of the patron, but the accumulation of wealth or power implies, to a moralist, an underlying evil. This applies whether the patron be the church, government, foundations, academic societies, or private universities. Almost certainly, the implied evil of corporate sponsorship could extend to commercial industries' involvement in academic research—but I don't really think it will.

Industry plays a very important role, and an increasingly important role, in the health sciences. Although corporate America's annual investment in research exceeds that of the NIH and biomedical research, most of those funds go into research and development and the development of the technologies. The apparent commercial potential for genetically engineered medications has attracted considerable private investment money in the general industry and it is a pleasure that San Diego has become a leader in making this common bridge between academic, scientific laboratories, and industry. It has been estimated that of the \$700 billion health-related industries (pharmaceuticals, biotech, medical devices and instruments) spend

4. John F. Porter (R-III.).

5. Nobel prize in medicine, awarded 1976.

6. See *Nobel Winner's Trial Seated for October*, WASH. TIMES, June 4, 1996, at C6.

each year little more than 10% of those research funds are actually spent outside the companies' own research labs at either universities or private research institutes such as Scripps. When the Scripps Research Institute (TSRI) ran afoul of public opinion a couple of years ago, we were trying to develop long-term relationships with a new corporate collaborator.⁷ I found it quite surprising that many of my scientific colleagues remained blissfully unaware of the federal statutes that dealt with the ownership of intellectual properties that arise from federally funded research projects.

When I began my grant-seeking research career in the mid-1960s, all patents that could have been derived from federally funded research were deemed to be owned by the government and all of us grant applicants had to forfeit our rights and relinquish our interest in anything we might discover. Although very few of us discovered anything that was able to be developed, a few things were developed. That changed in 1980, when President Carter enacted the Bayh-Dole Act or the Patent & Trademark laws amendment of 1980,⁸ which gave first preference for the licensing of federally funded inventions to non-profit organizations and small business firms. In 1983, President Reagan extended the licensing opportunity to all sizes of business, as an incentive to private industry to commercialize investments developed with federal funds.⁹ Both of these pieces of legislation extended the earlier Stevenson-Wyldler Technology Innovation Act,¹⁰ which had also attempted to facilitate the conversion of research into useful public purposes.

The Technology Innovation Act has encouraged cooperation between the academic establishment and industry, and has helped in technology transfer. It has also helped in personnel exchanges, joint research projects, and things that called for a comprehensive national policy to enhance technological innovation for commercial and public purposes. The combined effect of these pieces of legislation is that universities and research institutions are the owners of the federally funded research and the results of that research. Furthermore, they are legally bound to seek prompt development of these discoveries, and failure to do so could result in reinstatement of the government's ownership for purposes of such development.

As you know, there are at least five ways in which we in scientific academic labs can collaborate with industrial relationships in the health sciences. We can have what we think we have forming between Scripps and Sandoz,¹¹ which is an academic industry training relationship in which the industry funds trainees for academic settings. In turn, the academic settings provide educational expertise for the industrial employees. We look forward

7. See Leslie Helm, *Foreign Firms with Deep Pockets Test U.S. Labs*, L.A. TIMES, Nov. 6, 1991, at D1.

8. 35 U.S.C. § 3200 (1994) superseded by 15 U.S.C. § 3710 (1994).

9. 15 U.S.C. § 3710(a) (1994).

10. 15 U.S.C. §§ 3701-3717 (1994).

11. Sandoz will soon become Novartis, as it has now merged with the Ciba-Geigy Corporation.

to this kind of exchange of personnel. We can have grants or contracts from industry to members of a university lab. We can have what many in the industry have already experienced: consultancies by individual faculty members to advise specific companies in their areas of interest. We can sell or license our academic patents to the industry, and we can participate, either the institution or individual faculty members, in establishing and owning new companies. That is what CONNECT¹² is really all about in this area.

In the views of many medical economists,¹³ academic industrial relationships can have many potential benefits for the academic institutions who choose this route to supplement their research funding base. For example, TSRI is a private, self-standing research institution. Income from our endowment amounts to less than 10% of our annual operating budget. So for our leadership, our corporate agreements are our means to strengthen the economic stability of our institution, buffer ourselves against the increasing pressures on federal support for health sciences research, and provide a means to renew our infrastructure and faculty recruitment.

There are also substantial perceived risks to such relationships. Among the most frequently listed potential problems are the possible compromise to the institution and their faculty in the selection of their research directions, and the potential for investigator bias in the interpretation of research results resulting from projects in which the institution or the faculty member might have a proprietary interest. Potential conflicts of interest, to a certain extent, contaminate or shroud many of these relationships. There is no easy way to eliminate them completely, but through candid disclosures of all our relationships when we sit down at a table to enter into agreements, I think we can eliminate some of the anticipated onerousness of such disclosing actions, even though it may have prevented many other scientists and their institutions from getting into this particular kind of relationship.

Given the need for a dependable funding base that can sustain the institution and nurture its growth, we looked at all the opportunities that were available to us and recognized two of them. On the one hand, we could take the course followed by many academic institutions and simply spin-off each patentable discovery of potential, practical marketability into a subsidiary that could be funded by venture or industrial capital, in which we or our elite scientists might then play significant ownership and management roles. There is potential for the individuals involved to reap sizable financial rewards but it neglects to provide any support for the broader institutional community or the institution that contributed to the environment in which the discoveries were made. On the other hand, as Richard Lerner (President of TSRI) reasoned, we could establish exclusive relationships with a single company and work with them to maximize the potential of our discoveries in the

12. CONNECT is the Program on Technology and Entrepreneurship at the University of California at San Diego Extension.

13. See Robert Bohrer, Address to the 1994 Mid-Winter Institute Thursday Luncheon (Jan. 27, 1994), in *AIPLA BULL.*, Mar.-Apr. 1994, at 309.

ultimate commercial marketplaces. This was the course that we originally adopted 13 years ago, when Dr. Frank Dixon (founding Director of Scripps Research) negotiated the agreement with Johnson & Johnson, and that is the course that we will be taking with Sandoz starting in January of 1997.

Our agreement with Sandoz recognizes at the outset that our purpose in establishing this relationship is to cooperate in making available to the public the benefits of discoveries, inventions, and research of TSRI applicable to the fields in which the company and its affiliates have business interests. In the current period of our relationship with Johnson & Johnson, and in our future relationship with Sandoz, there are going to be faculty members who feel that their discoveries are not being covered by these agreements. And, in fact, when we were able to sit down with Bernadine Healy's¹⁴ lawyers and then Dr. Varmus' lawyers, we were able to carve out areas to which Sandoz could not have rights. In those areas, our faculty members can still go out and establish relationships in terms of CONNECT.

Ray Kahn¹⁵ was our first liaison trying to find venture capitalists who might be interested in starting these companies. These new approaches that you have now will facilitate those types of arrangements. They have to be there; there is always going to be someone who does not recognize what the scientist thinks is the greatest thing since sliced bread or vine-ripened tomatoes. The problem is that it takes an awful lot of the scientists' time to do that and if they are as committed to their original research discovery as they are to getting the new company funded, they cannot do them both. So, having an organization such as CONNECT is an irreplaceable resource that allows us to proceed.

It is awfully hit-or-miss, and certainly something that could help young scientists understand the business side of their discoveries' exploitations. This is a critical element in making real what we all perceive to be the possibilities of the kind of research that we are doing. Obviously, what is good for TSRI is not necessarily good for everybody. Institutions with extensive endowments, or with dependable budgets provided by state legislatures, might logically have other ways in which to carry their future.

Steven Paul, who is a friend of mine, was formerly the director of Intramural Research for the National Institutes of Mental Health (NIMH), where I spent many of my own formative years "growing up" in research. He left the NIMH intramural program about three years ago to become the director of CNS research for the Eli Lilly Company of Indianapolis (sometimes referred to as the house of Prozac). Just before he left the federal government, he wrote an editorial for *The Wall Street Journal*, in which he declared that government-sponsored basic research cannot produce the new medications needed to treat diseases, such as AIDS, Alzheimer's, cancer, and schizophrenia—diseases which require costly long-term hospitalizations, but

14. Dr. Bernadine Healy is a former director of NIH.

15. Ray Kahn oversees technology transfer at Scripps Institute and Research Clinic.

are essentially untreatable. He said that the skills and personnel required to convert basic scientific discoveries on the nature of these diseases into medication or preventive measures are not well represented in the pool of basic research scientists. He then felt compelled to go to private industry, where he could work on exactly that, and he felt that such treatments to treat these devastating illnesses could be found and developed only through private entrepreneurship. That is a very strong statement, but if you recognize the history of the medication represented by Prozac, you will find perhaps ironic, and perhaps poignant, the fact that the action for this class of drugs, which are amine re-uptake inhibitors,¹⁶ was in fact discovered in the intramural program at the NIMH in 1965 by Julius Axelrod, about 5 years before he won the Nobel prize for completely different reasons.¹⁷

It took many drug companies years to recognize what their goal was in developing Prozac. To the Eli Lilly company's credit, in order to eliminate the perceived side effects of this class of compounds (you may have heard of them referred to as tricyclic antidepressants) which have significant cardiovascular effects,¹⁸ they decided from their in-house research to focus on simply blocking the re-uptake of serotonin. To achieve a thousand-fold increase in specificity on the amine transporter for serotonin, well before this molecule had ever been cloned, they used classic pharmacological development techniques, structure activity relationships, and came up with a compound that today has the majority of the market of tricyclic antidepressants. Thanks in part to its specificity of action, and the consequences of that combined with a highly specific drug, you have very few serious side effects.¹⁹ That required of them at least 15 years of research after they recognized what their target was. Today, they have about four years of patent protection left and I can tell you from a recent visit, they are avidly pursuing the sons and daughters of Prozac even as we speak.

To give you another anecdote from my experience at *Science*, on the 28th of July last year, we reported three separate research papers on a newly discovered peptide hormone that has been named Leptin.²⁰ Leptin has the capacity to reduce the weight of genetically obese rodents and is thought to be a possible new pathway to control obesity in human beings.

16. Amine Re-uptake Inhibitors are an older type of antidepressant that use an amine instead of serotonin.

17. Julius Axelrod won the Nobel Prize for medicine and physiology for research on neuronal transmission in 1970.

18. The Cardiovascular side effects from antidepressant drugs include significant blood pressure changes, conduction disturbances, and arrhythmias. *Cardiovascular Safety in Depressed Patients: Focus on Venlafaxine*, 56 J. CLIN. PSYCHIATRY 574 (1995).

19. Typical side effects for this class of drugs include headache, nausea, and sexual dysfunction. J.M. Andrews & C.B. Nemeroff, *Contemporary Management of Depression*, 97 AM. J. MED. 24S-32S (1994).

20. Arthur L. Campfield, et al., *Recombinant Mouse OB Protein: Evidence for a Peripheral Signal Linking Adiposity and Central Neural Networks*, 269 SCIENCE, July 28, 1995, at 546.

At *Science*, we normally operate under an embargo rule: We inform the press of the contents of an issue, eight days before we release the forthcoming issue. We give them this opportunity in advance so that the reporters, regardless of the media in which they work, will have the time to do the diligent background that is required for them to file their own independent scientific reports on these discoveries. That occurred in this case; however, in complete disregard of our press embargo, a biotechnology analyst with a large New York brokerage company, who had been asked by one of the reporters for the financial implications of this new discovery, sent out alerts to thousands of the firm's customers alerting them of the possible financial benefit of these new papers. This triggered a small run-up in the stock prices of one of the three companies, each of which had patents pending on the applications of this new natural hormone.

In my view, these customers who bought in on the news of our *Science* report were not well served by this extremely enthusiastic, overrated recommendation. The Leptin's payoff, should it ever come, is likely to be years, if not decades, into the future. Leaking advance information some forty-eight hours before the rest of the scientific public knew about it, provided only an illusory and quite modest financial gain.

Most of the scientists active today are really only interested in pursuing their curiosity. I think that if you ask people if they would rather have a lifetime of grant support or win a million dollars in their own company, most of them would opt for having consistent, continuous research support to fuel their ability to pursue curiosity. A vital research environment, and that is what we sought to protect with our corporate relationship, makes an environment where there is a large number of curiosity-driven investigators—and it is their skills that create the innovative technologies and precedent-breaking rules through which the operations of living organisms are being understood at the molecular level.

Those who are equally interested in applying this technology to important health-related opportunities recognize that innovative science is the best starting point for innovative therapeutic developments. Since one cannot legislate or plan discoveries, we at Scripps feel that a funding partnership with biotech to maximize the new applications that may emerge from our work can best be served by a system of funding support that can nurture individuals, refine their discoveries, and then at the proper time hand them over to equally skilled colleagues who can carry them forward into the marketplace. Academic scientists are frustrated in this current environment because of the extremely competitive funding times. The reason for this is that we are at just that point in the scientific evolution of our research when the knowledge from our distributed intelligence, whether it is molecular genetics, cell biology, combinatorial chemistry, or even the linkages between genetics and epidemiology and preventive medicine, are at their peak of

potential—the fruits of the mind that Commissioner Lehman addresses in his article.²¹

This frustration over being unable, in a timely manner, to harvest the fruits of our past investments in research makes me want to ask if there is no better way to do this. Are we so unimaginative that we accept meekly the idea that the only way to balance past budgetary deficits is to cut-off the small wedges of discretionary funding that sustain our research enterprise? The San Diego community may have recalled the article written by the Commissioner of the Port District in the Sunday paper about three Sundays ago,²² in which he noticed that when he came here, everything was in decline and he decided he could cut his budget back to live within the budget they had given him or take a chance and try some adventures that would create new jobs and new skills. I think he has done a remarkable job in restoring the shipbuilding industry to this area, bringing tourism back, and creating job opportunities. And that is what I think biotechnology and science can do together.

It is failure to understand the nature of fundamental research within the federal government that really puts us in the position that we are in today. My experiences in Washington so far, as editor of *Science*, tell me that we are scarcely distinguished from other subsidies to other so-called “public needs” seen by Congress in their attempts to maintain reelection. We are no different to them from supporting gasoline prices or controlling them, or from the falling costs of beef which require the government to buy \$50 million worth of beef to maintain the beef industry because the cost of grain is at the highest it has ever been because we paid farmers not to plant the grain that would have gone to feed the cattle. And when the cattle industry got their \$50 million relief, the pork, lamb, chicken and turkey industries rose, saying that they had to buy that same grain too and shouldn't they have relief, which then caused the salmon farmers of Alaska to note that they still have most of last year's salmon crop frozen in their fisheries, and if the government doesn't buy that up, the fishermen won't go out, which will cause lots of unemployment, not to say ecological benefits somehow sinisterly perceived that will affect future generations of salmon now breeding in the ocean.

We are no different to Congress than these industries who are asking for artificial supports to maintain their livelihood. If our research momentum is able to continue, I do not think that any single corporate sponsor or any federal patron can absorb all of the opportunities that are available today. I do not think that knowledge is a commodity whose supply and demand should determine its value. And I do not think the role of the government in fundamental research is simply to buffer the ups and downs of the supply and demand in the pursuit of knowledge. I think that as Americans, we ought to

21. Bruce Lehman, *Major Biotechnology Issues for the U.S. Patent & Trademark Office*, 33 CAL. W. L. REV. 49, 60 (1996) (this volume).

22. Lawrence M. Killeen, *Opportunities Abound on San Diego's Waterfront*, SAN DIEGO UNION TRIB., Apr. 28, 1996, at G1.

be able to ask who is to determine how healthy we should be and when we should achieve that state of healthfulness. If we do not ask that, then we are not going to spend our money on something that we as individuals and as a society would consider the best appropriation of those funds.

We not only need to support basic scientific research, but also that intermediate critical area that pushes the basic understanding closer to the point at which privately funded research can convert basic knowledge into drugs, diagnostics, or even preventive strategies into products for improved health. In this political campaign season, some open-minded thinking could well be investigated on why we must continue to invest in, and not subsidize, health from basic research science through the chemistry and physics that provide the diagnostics and the research instruments all the way to the delivery of the products to our society.

Subsidies, not investments, to the health care insurance industry in the form of non-taxable contributions amount to nearly \$50 billion each year. These subsidies contribute not at all to the investment in health research. The industry needs to bear its share of continuing to provide funding for basic scientific discovery. Scientists want to harvest and replant the fruits of the human mind. Industry is a natural partner, and funding of technological development has to remain a high priority to national good, at least in the view of this scientist.