

1983. Changes since then give larger totals but do not significantly alter the efficacy pattern described.
12. P. C. Steptoe, R. G. Edwards, J. M. Purdy, *Br. J. Obstet. Gynaecol.* **87**, 757 (1980).
 13. I. Johnston *et al.*, personal communication.
 14. A. O. Trounson *et al.*, *Science* **212**, 681 (1981).
 15. A. O. Trounson *et al.*, *J. Reprod. Fertil.* **64**, 285 (1982).
 16. H. W. Jones *et al.*, *ibid.* **38**, 14 (1982).
 17. P. Renou *et al.*, *ibid.* **35**, 409 (1981); C. Wood *et al.*, *Br. J. Obstet. Gynaecol.* **88**, 756 (1981).
 18. R. G. Edwards, *Nature (London)* **293**, 253 (1981).
 19. J. D. Biggers, paper presented at the symposium on "In Vitro Fertilization and Embryo Transfer," Carmel, Calif., October 1982.
 20. P. Ramsey, *J. Am. Med. Assoc.* **220**, 1346 (1972); L. R. Kass, *Public Interest* **26**, 18 (1972); L. Walters, *Hastings Cent. Rep.* **9**, 23 (August 1979).
 21. L. Mettler, in (10), p. 119.
 22. P. C. Steptoe and R. G. Edwards, *Lancet* **1976-I**, 880 (1976).
 23. D. H. Smith *et al.*, *Fertil. Steril.* **38**, 105 (1982).
 24. An additional seven ectopic pregnancies have been reported recently among 76 pregnancies not included in Table 1 [Committee to Consider the Social Ethical, and Legal Issues Arising from In Vitro Fertilization, Interim Report to the Attorney General, State of Victoria, Australia (April 1983)]. The resulting overall ectopic pregnancy rate (3.4 percent) is not significantly greater than normal.
 25. D. A. Edelman, *Int. Plann. Parent. Fed. Med. Bull.* **14**(3), 1 (1980).
 26. R. M. L. Winston, *Fertil. Steril.* **34**, 521 (1980).
 27. F. E. French and J. M. Bierman, *Public Health Rep.* **77**, 835 (1962); C. J. Roberts and C. R. Lowe, *Lancet* **1975-I**, 498 (1975); J. G. Boue and A. Boue, *Curr. Top. Pathol.* **62**, 193 (1976).
 28. J. J. Schlesselman, *Am. J. Obstet. Gynecol.* **135**, 135 (1979).
 29. C. Wood *et al.*, *Fertil. Steril.* **38**, 22 (1982).
 30. American Fertility Society, *Fertil. News* **16** (1982), insert.
 31. A. O. Trounson and C. Wood, *Clinics Obstet. Gynecol.* **8**, 681 (1981).
 32. H. W. Jones, personal communication.
 33. E. Mehren, *Los Angeles Times* (6 February 1983, IV-1).
 34. A. Trounson *et al.*, *Br. Med. J.* **286**, 835 (1983).
 35. A. Trounson, personal communication; *Los Angeles Times* (4 May 1983); 1-4. The pregnancy resulted in a miscarriage at 6 months.
 36. D. Shapley, *Nature (London)* **301**, 101 (1983).
 37. K. Elliott and J. Whelan, Eds., *The Freezing of Mammalian Embryos* (Elsevier/North-Holland, New York, 1977).
 38. J. W. Gordon *et al.*, *Proc. Natl. Acad. Sci. U.S.A.* **77**, 7380 (1980); E. F. Wagner, T. A. Stewart, B. Mintz, *ibid.* **78**, 5016 (1981); F. Constantini and E. Lacy, *Nature (London)* **294**, 92 (1981); J. W. Gordon and F. H. Ruddle, *Science* **214**, 1244 (1981); T. E. Wagner *et al.*, *Proc. Natl. Acad. Sci. U.S.A.* **78**, 6376 (1981); R. L. Brinster *et al.*, *Cell* **27**, 233 (1981); T. A. Stewart, E. F. Wagner, B. Mintz, *Science* **217**, 1046 (1982); R. D. Palmiter *et al.*, *Nature (London)* **300**, 611 (1982).
 39. Only after seven attempts is the probability greater than half that a particular couple will have a child ($P = 1 - 0.9^7$).
 40. There was only one clinic (Norfolk) operating in 1980. Two more began operation in 1981 and, at present, available information suggests that as many as 20 centers are operational with between 10 and 20 more in early planning stages.
 41. National Center for Health Statistics, *Vital and Health Statistics, National Center for Health Statistics* **55**, (1980).
 42. Z. S. Jones and K. Pourmond, *Fertil. Steril.* **13**, 398 (1962); A. Raymont *et al.*, *Int. J. Fertil.* **14**, 141 (1969); J. Dor *et al.*, *Fertil. Steril.* **28**, 718 (1977); K. P. Katayama *et al.*, *Am. J. Obstet. Gynecol.* **135**, 207 (1979); M. Roland, *J. Reprod. Med.* **25**, 41 (1980); R. F. Harrison, *Int. J. Fertil.* **25**, 81 (1980).
 43. C. Grobstein, M. Flower, J. Mendeloff, in preparation.
 44. A. Trounson, personal communication.
 45. President's Commission for the Study of Ethical Problems in Medicine and Biomedical and Behavioral Research, *Splicing Life* (Government Printing Office, Washington, D.C., 1982). This report was in part a response to inquiry from three major religious groups. It noted that "gene therapy could also be applied to embryos in conjunction with in vitro fertilization techniques."
 46. Mass. Ann. Laws, Ch. 112, §112J(a) IV (Michie/Law Co-op Cum. Supp. 1978); D. M. Flannery *et al.*, *Geo. Law J.* **67**, 1295 (1979).
 47. Committee to Consider the Social, Ethical, and Legal Issues Arising from In Vitro Fertilization, Interim Report to the Attorney General, State of Victoria, Australia (September 1982), p. 27.
 48. Australian National Health and Medical Research Council, *Monash Univ. Bioethics News* **2**, 25 (1982), supplementary note 4.
 49. R. G. Edwards, in (10), p. 371.
 50. British Medical Association, *Br. Med. J.* **286**, 1594 (1983); Royal College of Obstetricians and Gynaecologists, *ibid.* 1519.
 51. British Medical Research Council, *ibid.* **285**, 1480 (1982).
 52. H. W. Jones, A. A. Acosta, J. E. Garcia, B. A. Sandow, L. Veeck, *Fertil. Steril.* **39**, 241 (1983).
 53. L. Mettler *et al.*, *ibid.* **38**, 30 (1982).
 54. R. P. Marrs *et al.*, *ibid.*, p. 270.
 55. J. F. P. Kerin *et al.*, *Lancet* **1981-II** 726 (1981).
 56. A. Trounson, personal communication.
 57. Supported by NSF grant PRA-8020679.

Improving R&D Productivity: The Federal Role

Lewis M. Branscomb

Today more than ever, now that everyone is focusing on productivity improvement, we should not forget the need for increased R&D productivity, especially in the billions invested by the private sector to use knowledge created by scientists. With the government spending some \$47 billion a year on R&D, it seems to me penny-wise and pound-foolish not also to invest in evaluation, integration, and end user packaging of this knowledge produced at federal expense so that it can and will be put to use by the private sector. More effort in this area would greatly enhance the leverage of economic benefits from the federal government's investment.

Data and access to data are critical to every R&D project. Recently, in checking our own experience, I discovered that, in one typical IBM laboratory and

plant library, 25 percent of the reference collection is primarily concerned with scientific and technical data. Some 15 percent of the volumes in circulation and over a third of the journals deal heavily with numeric data. This is a very heavily used collection.

When accurate, pertinent data are available, work can proceed. When they are not, work must stop while a researcher invents a different approach, develops (or redevelops) missing data, or experimentally verifies unevaluated data reported in the literature before daring to commit another period of time and effort on a project that is heading down a critical path.

Progress is not made by stopping work, or by shifting the goal away from the one you must achieve toward the one you can achieve. That is a good practice

in research but a terrible way to do business. There is no way to measure this loss in R&D productivity—the cost in problems not pursued because they are unpursuable, or in new knowledge delayed—but the cost of the present policy is obviously high.

As materials science and process technologies mix with piece-parts assembly in high-technology manufacturing, we will see a whole new wave of industry requirements for basic scientific data. In this case, the requirements read directly on manufacturing effectiveness and productivity, as well as on the R&D process that most people associate with science and technology data.

Getting a product out the door is no longer a simple linear process, if indeed it ever was. Ideas do not necessarily originate in research and flow to development, to manufacturing engineering, to production, and to marketing. The relationship we now confront is a triangular one among partners in research, development, and manufacturing. It is not unusual today in my company to find

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large numbers of research scientists—Ph.D.'s from our corporate laboratory—working side by side with manufacturing and development engineers. We are often preparing to manufacture with processes that deal with phenomena science has not yet fully mastered. Here, instead of scientific knowledge at risk because of missing data, it might be a whole new product line; it might be several billion dollars in revenue.

Institutions end up delegating the job back to individuals. In most company situations, an individual who confronts a data problem in the middle of a piece of committed work, with a committed schedule, has no choice but to try to get around it empirically. The knowledge environment is assumed by most companies to be something they cannot affect, at least not in first approximation or in the near term.

Summary. Despite widespread concern about lagging productivity growth rates and renewed interest in research, federal support for the review and packaging of hard-won new knowledge continues to languish. Yet accurate, accessible data are critical, not only in every R&D project but also in the most advanced manufacturing processes. Ensuring reliable, retrievable data is not a function that can be left to the professional societies, the publishing industry, or the private sector. In this article a six-point national science and technology data policy is proposed, and it is suggested that progress ultimately will depend on an overall science and technology policy, the first priority of which is to make available existing knowledge.

None of this is new news. The famous Weinberg Report of the President's Science Advisory Committee, which was, in some sense, the starting point for this whole debate, is now more than 20 years old. The National Bureau of Standards' National Standard Reference Data System is also 20 years old. It is still healthy, I understand, but it has had flat funding for the last decade, and it certainly does not represent a growing segment of our national technical activity.

From the point of view of the dedicated scholars in the data evaluation and review literature field, no doubt progress has been made. They certainly have done yeoman service for the technical community and for the country. But from the point of view of engineers and scientists in a company that employs over 20,000 of them in the United States, the general perception is that you cannot, in general, expect to find existing reliable, evaluated data, even on matters you know have been subjected to scientific research and publication. Handbooks are generally out of date and incomplete; caveat emptor governs the application of results from the primary literature.

That very perception damages progress. I think that, as a nation, we are so far from doing the job properly that there is little demand pressure to get it done, simply because expectations are so low. Another reason, of course, is that the job is not as simple as many people make it out to be. They erroneously focus their attention on access and distribution, rather than on the scholarship required to put data in a form in which users will dare rely upon them.

Government today depends on professional societies to sustain the journals for both the primary and secondary literature. Yet there is coming into being a commercial capability to provide science and technology data collections through computer networks in a form attractive to users. Remote computer services companies operate some of the biggest networks in the world, and they are providing access to information and to computing capability, in a business running close to \$5 billion a year.

The fall 1982 *Directory of Online Databases*—itself an old-fashioned book, I might point out—describes 1350 databases, up 40 percent from the year before. The publishers anticipated that their spring 1983 edition would show 20 percent additional growth. Mind you, those are not all science and technology databases; they represent the whole panoply of information for sale via networks and other electronic access methods.

These capabilities can be a vehicle for private sector access to science and technology data, but ensuring reliable, retrievable data is not a function we should leave exclusively to professional societies, the publishing industry, or the private sector. The cost of the scientific expertise required to evaluate the data and put them in a form attractive to end users is small compared to the cost of the original research, but it represents a large, high-risk front-end investment for a potential data vendor.

Thus, while it seems to me very appropriate for the private sector to provide access to knowledge and as much of the analysis as can be justified from a business viewpoint, government should ac-

cept the premise that funding the review literature and data evaluation is a responsibility integral to funding research activities. Government research agencies should fund both the generation and the evaluation and user-packaging of the knowledge.

A national science and technology data policy might have six elements:

1) Concern with productivity of the R&D process, half of which is sustained with federal funds. Agencies sustaining the science and technology infrastructure should be held accountable for increasing R&D productivity.

2) Responsibility for ensuring not only publication of results but also evaluation and preparation of data in a form suitable for application and provision of public access to these data at reasonable cost. Again, all agencies funding research should be held accountable.

3) Financial support of the scholarship required for data analysis and evaluation. The private sector should be encouraged to take an increasing, but not exclusive, role in the provision of access to evaluated data, but commercial companies cannot be expected to finance the depth of scholarship needed to analyze and evaluate the data. That must be viewed as the obligation of the sponsor of the original research. User fees for the allocated cost of access are appropriate for government-provided information systems.

4) Provision of unrestricted access to unclassified data generated at public expense. This is a cardinal requirement for a dynamic, high-technology economy. The desire to frustrate technical progress by hostile nations must not be allowed to impede the competitiveness of our own economy in its dependence on available scientific and technical data.

5) Initiation of agreements with other nations to share the costs and scarce skills for data evaluation and access. We should take the lead in this worldwide cooperative effort as, indeed, we have done in the past. As the nation with the most innovative economy, most dependent upon being innovative in the future, we have the most to gain from global cooperation.

6) Formation of a national body to monitor the adequacy of the science and technology information system and provide policy guidance to the federal agencies and recommendations to the private sector. The task of evaluating and preparing for application published scientific and technical data of general utility is a joint responsibility of user institutions in the private sector, private information vendors, professional associa-

tions and societies, and agencies funding, producing, and using research. A national body to monitor this information system should be constituted with federal and private participation.

I have not provided a "recipe" for how to bring this or whatever policy is correct into being. In truth, I am not even very optimistic. My recommendation number 6, for example, was in place in the 1950's and 1960's when the Committee on Scientific and Technical Information (COSATI) was in the Office of Science and Technology Policy. The ex-

ecutive coordinating function for science and technology information policy has been moved and downgraded ever since.

We will not make much progress in this area until the government takes a very pragmatic view of its whole science and technology policy—not just a data policy. I have long advocated such an overall policy, but I do it with a certain amount of concern.

The science and technology policy I suggest would expend federal funds on assuring that those solving problems in the interest of our society—whether they

be in the public or private sector—have the best and most appropriate, most available technical means for doing so.

Now, if that were our federal science policy, the number one priority would be to make available existing knowledge. Most existing knowledge is very badly underutilized. If users benefited greatly from information services, there would be an increased demand for new knowledge to fill in the gaps—because massive gaps there are—and we would have a driving force for the basic research investment.

RESEARCH ARTICLE

Differential Gene Expression in the Gastrula of *Xenopus laevis*

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One of the fundamental ideas of molecular embryology is that the process of development is controlled, directly or indirectly, by changes in the patterns of expression of nuclear genes. The spectrum of messenger RNA (mRNA) molecules synthesized, processed, and exported to the cytoplasm differs among tissue types, and in many cases is correlated directly, in the form of specific protein products, with a particular cellular phenotype. Many developmentally regulated genes whose expression is limited to certain terminally differentiated tissues or cell types have been isolated and studied (1). While much has been learned about eukaryotic gene expression from such work, genes whose expression is associated with the final stages of cellular differentiation seem unlikely to be involved in the initial processes of determination. Thus, it is of interest to isolate and study genes whose expression is regulated in the earliest stages of development, before any terminally differentiated tissues have appeared. In this article, we summarize the results of such a study.

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We chose as an experimental system the gastrula stage of *Xenopus laevis* because in this animal, as in others, gastrulation is the first event in embryogenesis that involves overt differentiation, leading to the elaboration of endoderm, me-

la stage of development, and mechanisms apparently exist for selective utilization of various mRNA sequences (4). There is no detectable transcription of the *Xenopus* embryonic genome until after the 12th cleavage (the "midblastula transition") at which time transcription begins suddenly (5). Synthesis of pA+ RNA (6) proceeds at a rate sufficient to replace up to 30 percent of the maternal pA+ RNA mass by gastrula, with complete turnover attained as early as the neurula stage (7). While this synthetic activity demonstrates considerable gene activation in the early embryo, an earlier study has suggested that most of this newly synthesized RNA is homologous in sequence to RNA molecules present in the egg (8). Replacement of inherited RNA molecules with identical or similar

Summary. A modified cloning method designed to produce differential complementary DNA libraries permits the isolation of sequences that are present in the RNA population of any developmental stage or tissue, but are not present or are much less abundant in another stage or tissue. Selective complementary DNA cloning is especially useful when the differentially expressed RNA's are of low to moderate abundance in the cells in which they occur. A class of cytoplasmic polyadenylated RNA's differentially expressed in gastrula embryos of *Xenopus laevis* (DG RNA's) has been isolated. These DG RNA's occur very rarely or not at all in unfertilized eggs and blastulae, accumulate as the result of transcription before and during gastrulation, and, with some exceptions, decline in abundance as development proceeds. Many of these RNA molecules appear to be translated at the gastrula stage. Thus, DG RNA's may encode proteins that are important in the process of gastrulation.

soderm, and ectoderm (2). Furthermore, the eggs and embryos of *Xenopus* can be obtained easily, and considerable data on molecular aspects of genome organization, transcriptional, and translational activities and the composition of RNA populations in the embryos of this vertebrate are available (3). The unfertilized egg of *X. laevis*, like those of most animals, contains a sufficiently large supply of maternal mRNA to support protein synthesis at least through the blastu-

transcripts rather than mobilization of previously unexpressed genetic information thus appears to be the primary function of early RNA synthesis in *Xenopus*. Nevertheless, the observation that interference with transcription during cleavage results in the arrest of gastrulation (9) suggests that some of the RNA sequences that are expressed by the gastrula are not included in maternal RNA. Such new RNA's would represent the earliest examples of developmentally