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Publicly Funded Science and the Productivity of the Pharmaceutical Industry

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Executive Summary

U.S. taxpayers funded $14.8 billion of health related research last year, four times the amount that was spent in 1970 in real terms. In this paper we evaluate the impact of these huge expenditures on the technological performance of the pharmaceutical industry. While it is very difficult to be precise about the payoffs from publicly funded research, we conclude from a survey of a wide variety of quantitative and qualitative academic studies that the returns from this investment have been large, and may be growing even larger. Public sector science creates new knowledge and new tools, and produces large numbers of highly trained researchers, all of which are a direct and important input to private sector research. But this is not a one way street: the downstream industry is closely linked with upstream institutions, and knowledge, materials, and people flow in both directions. One important contribution of public science is that it sustains an environment in which for-profit firms can conduct their own basic research, which in turn contributes to the global pool of knowledge. Measured quite narrowly in terms of its effect on private sector R&D, the rate of return to public funding of biomedical sciences may be as high as 30% per year. Large as this figure is, these calculations are likely an underestimate, since they fail to fully capture the wider impact of pharmaceutical innovation on health and well-being. Indeed, the best may be yet to come: the revolution in molecular biology that began in publicly funded laboratories 25 years ago—and continues to be driven by the academic research—promises dramatic advances in the treatment of disease.

I. Introduction

Between 1970 and 1999, public funding in the U.S. for health related research increased over 400% in real terms, to $14.8 billion, or 38% of the non-defense Federal research budget. Worldwide, the U.S. spends more of its publicly available research funds on human health than any other nation (table 1.1). What kind of impact is this research having? Is

Table 1.1
National expenditures on academic and related research by main field, 1987

	Expenditure (1987 M$)[a]						
	U.K.	FRG	France	Neth.	U.S.	Japan	Average[b]
Engineering	436	505	359	112	1,966	809	14.3%
	15.6%	12.5%	11.2%	11.7%	13.2%	21.6%	
Physical Sciences	565	1,015	955	208	2,325	543	21.2%
	20.2%	25.1%	29.7%	21.7%	15.6%	14.5%	
Life Sciences	864	1,483	1,116	313	7,285	1,261	36.3%
	30.9%	36.7%	34.7%	32.7%	48.9%	33.7%	
Social Sciences	187	210	146	99	754	145	6.0%
	6.7%	5.2%	4.6%	10.4%	5.1%	3.9%	
Arts & Humanities	184	251	218	83	411	358	6.8%
	6.6%	6.2%	6.8%	8.6%	2.8%	9.6%	
Other	562	573	418	143	2,163	620	15.6%
	20.1%	14.2%	13.0%	14.9%	14.5%	16.6%	
Total	2,798	4,037	3,212	958	14,904	3,736	

[a]Expenditure data are based on OECD "purchasing power parities" for 1987 calculated in early 1989.
[b]This represents an unweighted average for the six countries (i.e., national figures have not been weighted to take into account the differing size of countries).
Irvine, J., B. Martin, and P. Isard 1990 p. 219.

the public getting an appropriate "bang for its buck"? This paper explores one aspect of this question by focusing on one issue in particular: the impact of publicly funded research on the productivity of the U.S. pharmaceutical industry.

The pharmaceutical industry provides a particularly interesting window through which to study the more general question of the impact of publicly funded research. The public sector probably plays a more important role in determining private sector productivity in the pharmaceutical industry than in any other industry except defense. Public sector research spending almost equals private sector spending, and publicly funded researchers generate a disproportionate share of the papers published in the relevant fields (Stephan 1996). It is also the case that scientific advances in medical practice appear to have had a very significant effect on human health. Between 1940 and 1990, average life expectancy in the U.S. increased from 63.6 to 75.1 years, and the average quality of life appears to have also increased over the same time period (Cutler and Richardson 1999). While advances in human health have many causes, advances in pharmaceutical therapies have made a very significant contribution. New drugs have revolutionized the treat-

ment of ulcers, stroke, and various psychiatric conditions. They have dramatically improved the quality of life of asthma sufferers. They have brought the symptoms of AIDS under control for a significant fraction of the infected population. Some cancers are now reliably curable by drug therapy, and new drugs for hypertension and high cholesterol are proving instrumental in the treatment of heart disease, still the largest killer of Americans. Drugs "in the pipeline" promise major advances in the treatment of arthritis, Alzheimer's disease, many kinds of cancers and a variety of other chronic conditions. Since there is general agreement among qualified observers that publicly funded science has played a major role in these advances, the industry presents a particularly salient setting in which to explore its economic impact.

This paper begins by briefly reviewing the progress that has been made in estimating the rate of return to publicly funded science in other settings. Efforts to measure the rate of return to public research in any context are dogged by a variety of difficult practical and conceptual problems (Griliches 1979; Jones and Williams 1995), and many of these problems are particularly severe in the case of the pharmaceutical industry. We outline some of the difficulties inherent in generating quantitative estimates, and summarize some key results. Although measuring the research output of the public sector and its impact on the rest of the economy presents enormous challenges, both quantitative and qualitative estimates suggest that the rate of return to basic research in general is probably quite high. Case studies of specific technologies and government programs point to the critical role of public sector research in laying the foundation for technological advances that have later had enormous impact on the civilian economy (see for example David, Mowery, and Steinmuller 1992), and direct quantitative estimates suggest that the rate of return to publicly funded research is on the order of 25–40%, (Adams 1990; Mansfield 1991; Griliches 1979, 1994).

The paper then turns to a discussion of the pharmaceutical industry. We show that publicly funded research has increased dramatically over the last 60 years, and present some evidence suggesting that its role has become increasingly important. While pharmaceutical research in the 1960s and 1970s drew upon the results of federally funded research, it typically took many years for the results of publicly funded work to have an impact on the private sector, and many firms made only limited use of publicly generated results. The revolution in molecular biology and the transition to "rational" or "mechanism driven" drug

design and then to the techniques of biotechnology have revolutionized the relationship between the public and private sectors, making immediate access to leading edge publicly funded science a key competitive advantage for leading pharmaceutical firms and stimulating the development of an entirely new segment of the industry: the small biotechnology firm. While early research in the industry followed a more traditional waterfall model, with the results of publicly funded research gradually flowing downhill to the private sector, over the last 25 years the relationship has become much more that of an equal partnership, with ideas and materials flowing upstream to the public sector as well as downstream to industry.

This is followed by a discussion of the quantitative evidence. We show that many of the problems that make the measurement of the impact of publicly funded research difficult in the wider economy operate with particular force here: it is quite difficult to measure either the "output" of publicly funded research or its impact on the private sector, there are long and variable lags between the generation of knowledge in the public sector and its impact in industry, and there are many different pathways through which the public sector shapes private sector research. The public sector generates more than just scientific papers, pure knowledge, and highly trained graduates: its existence also supports a community of "open science" that sustains high quality privately funded research in the for-profit laboratories.

While it is, therefore, very hard to precisely estimate the return to publicly funded biomedical research, we nonetheless conclude that it is quite high. On the one hand, the qualitative evidence is compelling: the U.S. pharmaceutical and biotechnology industries lead the world, and while there are a variety of plausible reasons for this, the strength of the public research base is surely among the most important. Detailed case studies have highlighted the role of the public sector in supporting the development of important new drugs, and almost universal agreement among private sector researchers that publicly funded research is vital to all that they do. There are also a number of econometric studies that, while imperfect and undoubtedly subject to improvement and revision, between them make a quite convincing case for a high rate of return to public science in this industry. It is worth noting that there are, so far as we are aware, *no* systematic quantitative studies that have found a negative impact of public science!

We conclude the paper with a brief summary and some speculations as to the future. The ongoing revolution in genetics, genomics, and

bioinformatics—all advances that have their roots squarely in federally funded research—promises to revolutionize the treatment of many diseases. If this promise is realized, the role of publicly funded research in advancing human health through the support of pharmaceutical innovation will be beyond question. This is an exciting period in which to be studying the impact of publicly funded research.

II. Measuring the Impact of Publicly Funded Research: The General Problem

Government funding for "basic" or "fundamental" research has traditionally been justified on the grounds that the *social* returns to basic research are likely to significantly exceed *private* returns, and thus that the private sector will underinvest in basic research relative to the social optimum (Nelson 1959; Arrow 1962). Private firms are unlikely to be able to capture (or "appropriate") the returns to basic research because, in general, it usually takes a very long time for the practical implications of basic research to become apparent and because these implications are often highly diffuse. A firm that is funding basic research in optics, for example, might not see any return on its investment for many years, and many of these returns might be realized by its competitors or by firms competing in entirely different industries. There is also some evidence that basic research has its greatest impact when it is funded by the public sector because publicly funded researchers are more likely to compete for prestige in their fields than for financial gain, and since prestige is gained through the rapid publication of their results, publicly funded research is likely to become more rapidly available across the economy than privately funded work (Dasgupta and David 1987, 1994; Merton 1973).

Unfortunately exactly the same characteristics that make it economically desirable for the government to fund basic research—the long lags between research and impact and its wide diffusion across firms and industries—also make it very difficult to measure its effects. Two techniques have been widely used: case studies and econometric production function based analysis. The available case studies are suggestive, and most of them suggest that government funded research has indeed had a significant effect on private sector productivity (see, for example, David, Mowery, and Steinmuller 1992; Mansfield 1991; and the NSF 1968), but it is always difficult to know how far one can generalize from the results of case study research. Broad-based statistical

estimates of the relationships between upstream funding and downstream performance could place this case study evidence on sounder footing, but these too have their problems.

III. Productivity Measurement

Productivity is a natural way to assess the performance of firms and industries. High levels of productivity and rapid growth in productivity are unambiguous indicators of the technological progress which public sector research is intended to support. Productivity relates output to input, and publicly funded research affects this relationship in a number of ways. Research results, experimental materials, and the human capital of highly trained researchers are "free" inputs to the production of drugs. At the same time basic research improves the efficiency with which these inputs are utilized as it identifies productive areas for investigation or provides new, more effective research tools.

There are good reasons to expect to see an important impact of publicly funded research in the productivity statistics for the pharmaceutical industry. The problem is that productivity measurement is beset by a number of difficult problems, which are exacerbated in knowledge-intensive industries with a high rate of new product development. To frame our subsequent discussion, we first review these difficulties.

Measuring Output

Productivity is the ratio of inputs to output.[1] We begin with the numerator. Measuring output is difficult in any research-driven industry for two closely related reasons. In the first place, output is conventionally measured by the sales of the level of the firm that produces it. There are good reasons to believe that this underestimates the social value of output. If there are significant externalities, or "spillovers," these will not be captured in the price charged to consumers. Vaccines provide a good example: purchasing the product provides private benefits to the individual who is vaccinated, but also society benefits from the impact that vaccination has on lowering the prevalence of the disease—or in the case of smallpox, wiping it out altogether.

The second problem is that research tends to improve the quality of output, and quality improvement may or may not be reflected in the price of output. The computer industry provides the classic example of

this problem: the price of a standard PC has remained more or less constant over the last 5 years, but the power and capabilities of the standard package has consistently increased over time. Statistical methods for addressing this problem have revealed that the "true" quality- adjusted price of a PC has been falling at a very rapid rate: 20% per year or more. The same may be true for pharmaceutical products. New drugs tend to be more effective, have fewer side effects, and can be taken in much more convenient dosages (once per day instead of four times per day). But efforts to apply quality adjustments to reflect these benefits to the consumer have had limited success. While the quality attributes of a car or a PC are relatively straightforward to measure (fuel efficiency, weight, processor speed, storage capacity, etc.) those of pharmaceutical products are more difficult to define and measure. (See for example Berndt et al. 2000; and Cockburn and Anis 2000.)

For pharmaceuticals, an additional complication is introduced by the tangled web of economic relationships between patients, physicians, pharmacists, and insurers. In some industries, prices are a reasonably good measure of consumers' willingness to pay. Here, the link between expenditures on drugs and the value to the consumer is harder to draw. In some cases, the value of a drug to the patient who receives it may be considerably greater than the price received by the pharmaceutical company which produces it. (It is also possible that some pharmaceuticals are worth less to patients than the price that is charged for them.)

Some researchers have used measures of output such as quality adjusted life years (QUALYs) to correct for these problems, but any such attempt must inevitably rest on a series of assumptions and judgments that will always be open to question (Cutler and Richardson 1999).

Measuring Inputs

Measuring inputs to the production of pharmaceuticals raises similar problems. To produce pharmaceuticals requires not just person hours, capital, energy, materials and so forth, but also "knowledge capital" or know-how. Measuring knowledge capital is particularly difficult since the impact of knowledge is felt over an extended period of time. Labor generates output today: but scientific explorations often only produce tangible output after many years. For example in a study of the impact

of scientific research across the entire economy, Adams (1990) found evidence that *on average* it takes 20 years for basic research to produce tangible economic results! In the context of the pharmaceutical industry this problem is particularly acute. Not only is it the case that the lags between the publication of any particular piece of publicly funded research and its impact on the discovery of a new drug are long and highly variable, but on average it takes 12–14 years to translate any given private sector discovery into a drug that can be given to patients. This problem is particularly concrete in the case of federal funding for molecular biology in general and genetics in particular. While this funding has had some immediate impact on industry productivity, there is widespread (even universal) agreement that in this case the best is yet to come. The interpretation of the human genome, for example, is not expected to have a direct effect on human health for many years.

The measurement of knowledge inputs in pharmaceuticals—and of the effect of publicly funded research in particular—is further complicated by the fact that there are a multitude of mechanisms through which publicly funded research shapes and supports private sector productivity. The most straightforward is through the development of new scientific knowledge. Figure 1.1 presents a much simplified diagram of the process of drug discovery and development.

In general, fundamental research (the discovery of fundamental scientific knowledge) precedes "drug discovery" (the search for compounds that seem to work in test tubes and/or in animals), which is followed by "drug development" (the process by which one makes sure that seemingly useful compounds actually work safely in humans). But while it is certainly the case that publicly funded research has been responsible for generating an enormous amount of fundamental science that has supported major breakthroughs in the industry, this is by no means the only way in which public investment in biomedical research has shaped the industry.

The public sector supports private sector research through a variety of other mechanisms. One of the most important of these is the provision of trained scientists, but the impact of others should not be overlooked: public sector science also includes discovery of new research tools, direct investment in a small amount of drug discovery work, and funding of leading edge work in clinical development.

Studies of the relationship between universities and the private sector in general have suggested that one of the most important outputs of

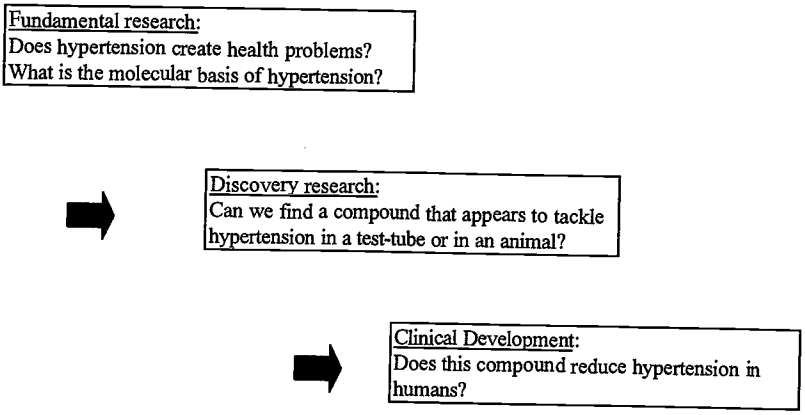

Figure 1.1
A simple model of drug discovery

the university sector is trained personnel (see for example Agarwal 2000). This is likely to be particularly true in the pharmaceutical industry, where research is conducted by battalions of skilled scientists, many of them with doctorates and postgraduate educations funded in large part through NSF and NIH grants. As industry hires these graduates it benefits not only from their general training and skills but also from the leading edge access it gives them to research being conducted within the public sector. Another important publicly funded input to the private sector is not new knowledge, per se (how do viruses metabolize?) but new *tools*. Cohen and Boyer's discovery of one of the most fundamental tools of genetic engineering is one prominent example of this phenomenon.

Figure 1.1 suggests that the process of drug discovery is an almost entirely linear one, with scientific knowledge feeding directly into drug discovery. In reality, however, the interaction between the public and private sectors is much more iterative and complex. In *Networks of Innovation*, for example, Galambos and Sewell (1995) show that the development of vaccines was characterized by the continual exchange of information between researchers working at Merck and researchers working in the public sector. On several occasions the development of novel therapies by the private sector or advances made in clinical treatment have *preceded* major advances in fundamental knowledge. Brown and Goldstein's Nobel Prize winning work on the structure of the LDL receptor, for example, occurred simultaneously with the discovery of the first effective HMG CoAse reductase inhibitors; and the recognition

that stomach ulcers are bacterial in origin flowed from the pioneering work of physicians working in the clinic rather than from basic scientific research. Even apparently straightforward cases such as the discovery of AZT appear, on closer examination, to have a fine grained structure that reflects a bidirectional flow of knowledge rather than the simple transmission of research results or new ideas from the public to private sectors (Cockburn and Henderson 1998).

This bidirectional structure not only complicates the problem of imposing a time structure on the estimation of the effect of public research (see below). It also hints at another important role of public research: the maintenance of a community of researchers, or a public rank hierarchy in which private sector researchers can be evaluated and promoted on the basis of their standing in the public community of science. As the techniques of drug discovery evolved and it became increasingly important to be able to take advantage of the findings of public science, the most productive pharmaceutical firms began to reward their researchers on the basis of their standing in the eyes of their peers (Henderson and Cockburn 1994; Cockburn, Henderson, and Stern 2000). To some degree the adoption of this incentive mechanism undoubtedly reflects the fact that it encourages a firm's scientist to publish and to engage with the community of public scientists, and this in turn facilitates the firm's ability to take advantage of publicly generated knowledge. But its adoption also probably solves a difficult problem for managers: evaluating the effort and performance of scientific professionals whose work is becoming increasingly complex and increasingly difficult to monitor. To the degree that these practices increase the flexibility and creativity of the private sector, the maintenance of a public community of science acts as an input (of a particularly subtle kind) to the private sector.

Arguably, the presence of the community of open science also provides an implicit subsidy to the industry in that it provides important nonmonetary rewards. Scott Stern (Stern 1999) has shown that researchers are willing to trade salary for the opportunity to work on scientifically interesting projects. Since salaries are a large fraction of total research costs, to the extent that this phenomenon drives down the wages demanded by scientists, the industry benefits.

The public sector also invests in the actual discovery of new drugs through its support of screening programs such as that conducted by the National Institute for Cancer. While this program has generated one important new drug—Taxol—its overall impact appears to be min-

imal. Last, but by no means least, the public sector supports private sector productivity through the support of clinical development and clinical research. There is some evidence that this type of research provides a critically important stimulus to the discovery of new drugs (Wurtman and Bettiker 1994, 1996).

The measurement of knowledge capital is further complicated by the problem of "spillovers," or the fact that knowledge generated in one place or firm is often useful elsewhere. At the level of the entire economy this effect is unproblematic, but when one is trying to measure the impact of spillovers from publicly funded research on a particular firm, for example, it raises serious problems. Where should one look for spillovers? One important source may be a firm's competitors. In the case of pharmaceuticals, for example, we showed that private sector research productivity was directly and significantly affected by competitive research activity (Henderson and Cockburn 1996). Then there is the question of whether to treat all federally funded entities equally, or to trace spillovers only to those that are geographically or technically "close." And while the U.S. government accounts for a substantial fraction of worldwide public sector research, science is a global enterprise. Contributions from significant publicly funded research activity in Europe and elsewhere ought not to be ignored.

Despite these problems, a number of researchers have attempted to use productivity measures to estimate the rate of return to publicly funded research. Studies at the aggregate level, or at the level of the entire economy, generate numbers in the 20–40% range, as described above. As an illustration of these results, table 1.2 reproduced from Griliches 1995, summarizes the results from a number of studies of industry productivity. The results vary widely, but seem to suggest that the rate of return to public research is likely to be quite high.[2]

IV. The Role of Publicly Funded Research in the Pharmaceutical Industry

Attempts to measure the role of publicly funded research in the context of the pharmaceutical industry must not only grapple with these issues, but must also take account of an environment in which the relationship between the public and private sector has changed dramatically over the last 50 years.

Public funding for health related research is largely a product of the Second World War. Before the war the pharmaceutical industry was

Table 1.2
Selected estimates of returns to R&D and R&D spillovers

Agriculture	Rate of return to public R&D
Griliches (1958) Hybrid corn	35–40
Hybrid sorghum	20
Peterson (1967) Poultry	21–25
Schmitz-Secker (1970) Tomato harvester	37–46
Griliches (1964) Aggregate	35–40
Evenson (1968) Aggregate	41–50
Knutson-Tweeten (1979) Aggregate	28–47
Huffman-Evenson (1993) Crops	45–62
Livestock	11–83
Aggregate	43–67
Industry	Rate of return to all R&D
Case studies	
Mansfield et al. (1977)	25–56
I-O Weighted	
Terleckyj (1974): Total	28–48
Private	29–78
Sveikausakas (1981)	10–50
Goto-Suzuki (1989)	26–80
R&D Weighted (patent flows)	
Griliches-Lichtenberg (1984)	46–69
Mohnen-Lepine (1988)	28–56
Cost Functions	
Bernstein-Nadiri (1988, 1989)	
Differs by industry	9–160
Bernstein-Nadiri (1991)	14–28

Table 3.4 from Griliches, 1995.

not tightly linked to formal science. Until the 1930s, when sulfonamide was discovered, drug companies undertook little formal research. Most new drugs were based on existing organic chemicals or were derived from natural sources (e.g., herbs) and little formal testing was done to ensure either safety or efficacy. Harold Clymer, who joined SmithKline (a major American pharmaceutical company) in 1939, noted:

> [Y]ou can judge the magnitude of [SmithKline's] R&D at that time by the fact I was told I would have to consider the position temporary since they had already hired two people within the previous year for their laboratory and were not sure that the business would warrant the continued expenditure. (Clymer, 1975)

World War II and wartime needs for antibiotics marked the drug industry's transition to an R&D intensive business. Penicillin and its antibiotic properties were discovered by Alexander Fleming in 1928.

However, throughout the 1930s, it was produced only in laboratory scale quantities and was used almost exclusively for experimental purposes. With the outbreak of World War II, the U.S. government organized a massive research and production effort that focused on commercial production techniques and chemical structure analysis. More than 20 companies, several universities, and the Department of Agriculture took part.

The commercialization of penicillin marked a watershed in the industry's development. Due partially to the technical experience and organizational capabilities accumulated through the intense wartime effort to develop penicillin, as well as to the recognition that drug development could be highly profitable, pharmaceutical companies embarked on a period of massive investment in R&D and built large-scale internal R&D capabilities. At the same time there was a very significant shift in the institutional structure surrounding the industry. Whereas before the war public support for health related research had been quite modest, after the war it boomed to unprecedented levels. The period from 1950 to 1990 was a golden age for the pharmaceutical industry, as for industry in general, and particularly the major U.S. players—firms such as Merck, Eli Lilly, Bristol-Myers, and Pfizer—grew rapidly and profitably. R&D spending exploded and with this came a steady flow of new drugs. (Figure 1.2 shows publicly funded spending on health related research and total U.S. R&D spending by U.S. pharmaceutical firms.[3])

A number of factors supported the industry's high level of innovation. One was the sheer magnitude of both the research opportunities and the unmet needs. In the early postwar years, there were many diseases for which no drugs existed. In every major therapeutic category—from painkillers and anti-inflammatories to cardiovascular and central nervous system products—pharmaceutical companies faced an almost completely open field (before the discovery of penicillin, very few drugs effectively *cured* diseases).

Faced with such a target rich environment but very little detailed knowledge of the biological underpinnings of specific diseases, pharmaceutical companies invented an approach to research now referred to as "random screening." Under this approach, natural and chemically derived compounds are randomly screened in test tube experiments and laboratory animals for potential therapeutic activity. Pharmaceutical companies maintained enormous libraries of chemical compounds, and added to their collections by searching for new compounds in places such as swamps, streams, and soil samples.

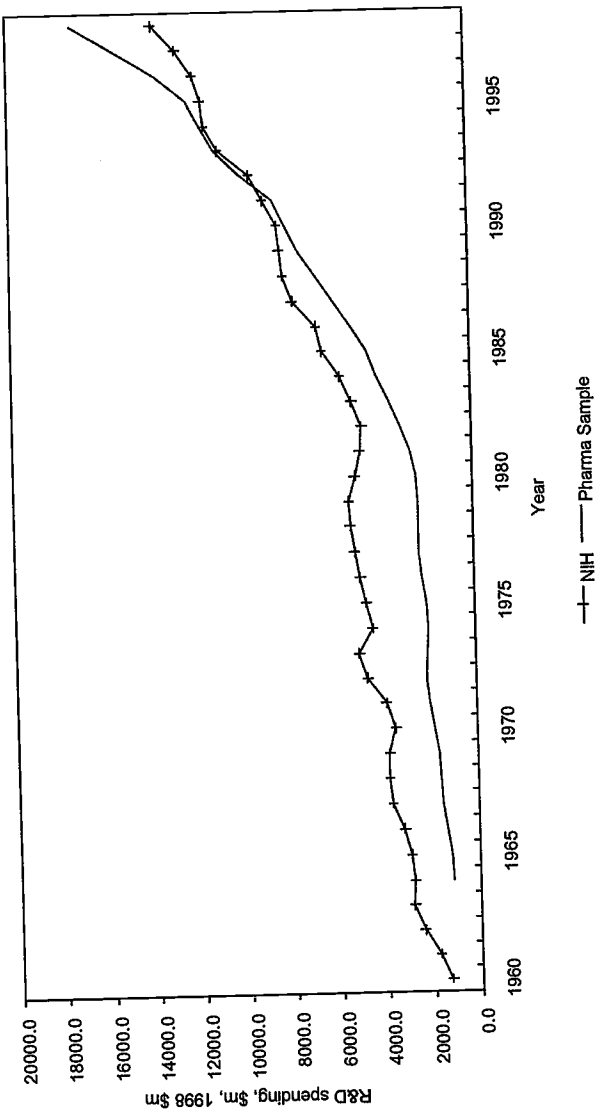

Figure 1.2
Changes in R&D spending over time

Thousands, if not tens of thousands, of compounds might be subjected to multiple screens before researchers honed in on a promising substance. Serendipity played a key role since in general the "mechanism of action" of most drugs—the specific biochemical and molecular pathways that were responsible for their therapeutic effect—were not well understood. Researchers were generally forced to rely on the use of animal models as screens. For example researchers injected compounds into hypertensive rats or dogs to explore the degree to which they reduced blood pressure. Under this regime it was not uncommon for companies to discover a drug to treat one disease while searching for a treatment for another. Although random screening may seem inefficient, it worked extremely well for many years, and continues to be widely employed. Several hundred chemical entities were brought to the market in the 1950s and 1960s and several important classes of drug were discovered in this way, including a number of important diuretics, all of the early vasodilators, and a number of centrally acting agents including reserpine and guanethidine.

In general, this early form of random screening made only delayed and indirect use of the results of publicly funded research. Beginning in the early 1970s, the industry began to benefit more directly from the explosion in public funding for health related research that followed the war. Publicly funded research had always been important to the industry's health, but initially it was probably most important as a source of knowledge about the etiology of disease. For example it was the publicly funded Framingham heart study that showed that elevated blood pressure (hypertension) was associated with a greater risk of heart disease and death, and thus encouraged the industry to search for drugs that might tackle it.

From the middle 1970s on, however, substantial advances in physiology, pharmacology, enzymology, and cell biology—the vast majority stemming from publicly funded research—led to enormous progress in the ability to understand the mechanism of action of some existing drugs and the biochemical and molecular roots of many diseases. This new knowledge made it possible to design significantly more sophisticated screens. By 1972, for example, the structure of the renin angiotensive cascade, one of the systems within the body responsible for the regulation of blood pressure, had been clarified by the work of Laragh and his collaborators (Laragh et al. 1972) and by 1975 several companies had drawn on this research in designing screens for hypertensive drugs (Henderson and Cockburn 1994). These firms could

replace ranks of hypertensive rats with precisely defined chemical reactions. In place of the request "find me something that will lower blood pressure in rats" pharmacologists could make the request "find me something that inhibits the action of the angiotensin 2 converting enzyme."

The more sensitive screens in turn made it possible to screen a wider range of compounds. Prior to the late 1970s, for example, it was difficult to screen the natural products of fermentation (a potent source of new antibiotics) in whole animal models. The compounds were available in such small quantities, or triggered such complex mixtures of reactions in living animals, that it was difficult to evaluate their effectiveness. The use of enzyme systems as screens made it much easier to screen these kinds of compounds. It also triggered a virtual cycle in that the availability of drugs whose mechanisms of action were well known made possible significant advances in the medical understanding of the natural history of a number of key diseases, which in turn opened up new targets and opportunities for drug therapy.

Both "random" and "guided" or "science driven" drug discovery continue to be important tools in the search for new drugs,[4] but the most important development in the pharmaceutical industry is the advent of the science and techniques of biotechnology—and in this field the role of publicly funded research is even more pronounced. Historically, most drugs have been derived from natural sources or synthesized through organic chemistry. Although traditional production methods (including chemical synthesis and fermentation) enabled the development of a wide range of new chemical entities and many antibiotics, they were not suitable for the production of most proteins. Proteins, or molecules composed of long interlocking chains of amino acids, are simply too large and complex to synthesize feasibly through traditional synthetic chemical methods. Those proteins that were used as therapeutic agents—notably insulin—were extracted from natural sources or produced through traditional fermentation methods. However, since these processes (which were used to produce many antibiotics) could only utilize naturally occurring strains of bacteria, yeast, or fungi, they were not capable of producing the vast majority of proteins. Cohen and Boyer's (publicly funded) key contribution was the invention of a method for manipulating the genetics of a cell so that it could be induced to produce a specific protein. This invention made it possible for the first time to produce a wide range of proteins synthetically and thus opened up an entirely new domain of search for new

drugs—the vast store of more than 500,000 proteins that the body uses to carry out a wide range of biological functions.

In principle these new techniques of genetic engineering thus opened up an enormous new arena for research. However the precise function of the majority of these proteins is still not well understood, and the first firms to exploit the new technology chose to focus on proteins such as insulin, human growth hormone, tPA, and Factor VIII —for which scientists had a relatively clear understanding of the biological processes in which they were involved and of their probable therapeutic effect. This knowledge greatly simplified both the process of research for the first biotechnology-based drugs and the process of gaining regulatory approval. It also made it much easier to market the drugs since their effects were well known and a preliminary patient population was already in place.

As firms and researchers gain experience with the new science, however, it has had increasingly dramatic impacts on the ways in which new drugs are discovered. For example the techniques of genetic engineering allow researchers to clone target receptors, so that firms can screen against a pure target rather than against, for example, a solution of pulverized rat brains that probably contain the receptor. They can also allow for the breeding of rats or mice that have been genetically altered to make them particularly sensitive to interference with a particular enzymatic pathway. Both of these techniques allow for the design of greatly improved "screens" against which compounds can be tested for therapeutic activity.

A second strategy has been to focus on a specific disease or condition and to attempt to find a protein that might have therapeutic effects. Here detailed knowledge of the biology of specific diseases is an essential foundation for an effective search. For example researchers working in cancer, AIDS, and autoimmune diseases have focused on trying to discover the proteins responsible for modulating the human immune system. A third strategy is to focus on genomics—the use of knowledge of the human genetic code to uncover new treatments for disease. This strategy is only at the most preliminary stage, but it promises to revolutionize the treatment of many diseases.

Taken together, these events have moved public research from an important but distant foundation for drug discovery to a critically important source of immediately useful knowledge and techniques that is actively engaged by the private sector. Table 1.3 and figures 1.3 and 1.4 graphically illustrate this transition. Table 1.3 summarizes detailed case

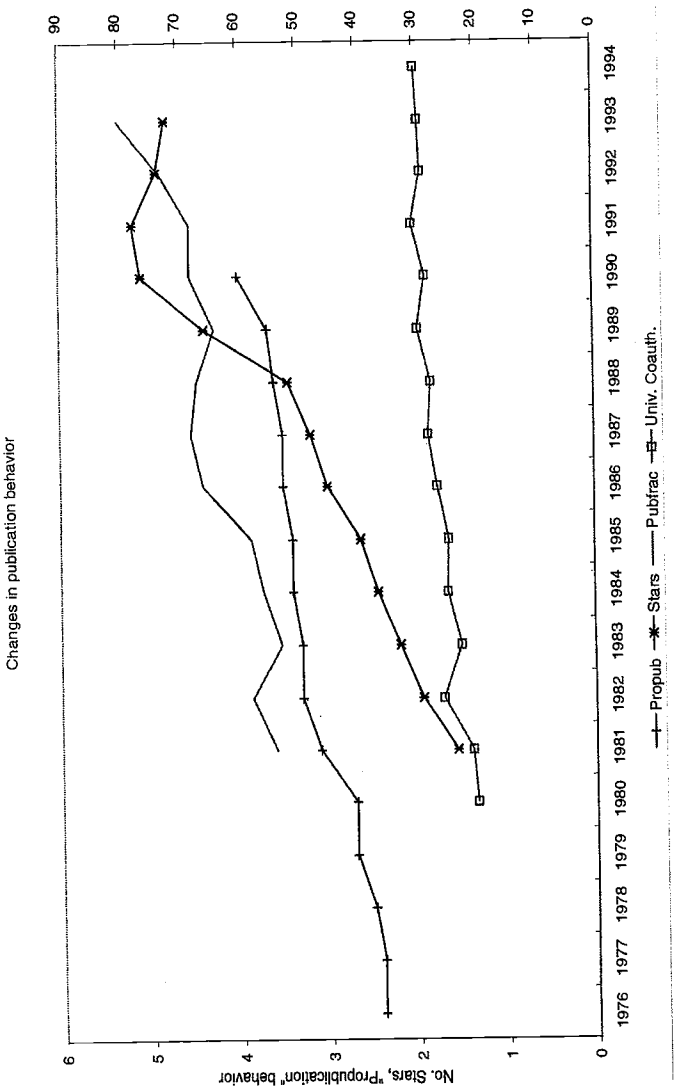

Figure 1.3
The changing relationship between the public and private sector

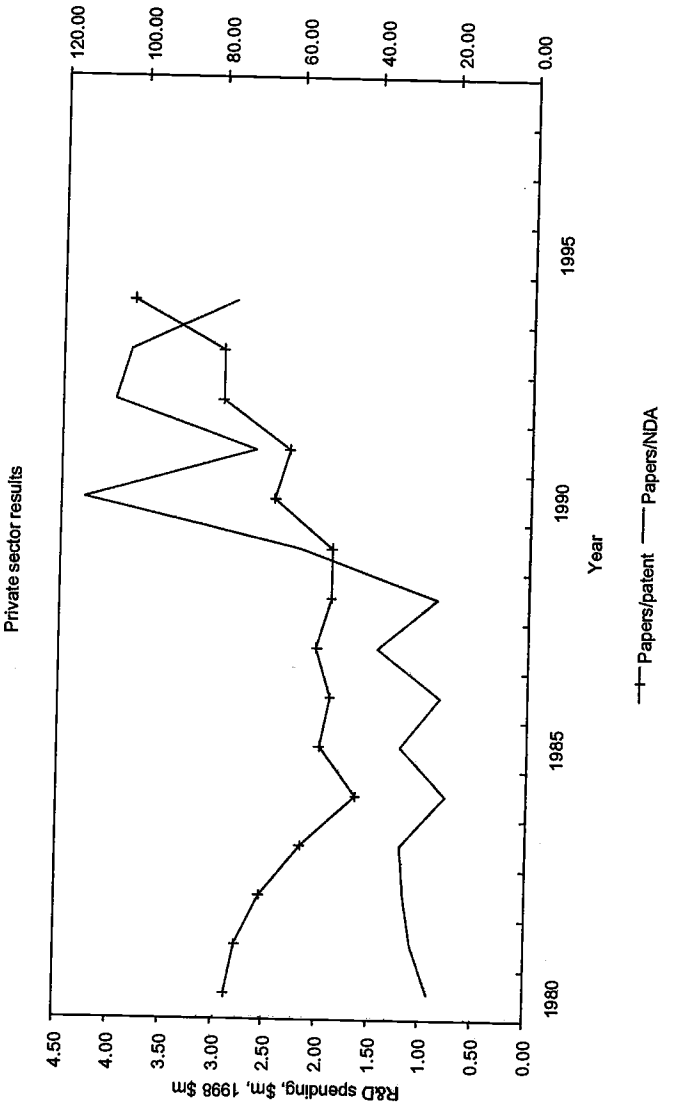

Figure 1.4
The increasing importance of publications

Table 1.3
History of the development of the 21 drugs with highest therapeutic impact introduced between 1965 and 1992

Generic name	Trade name	Indication	Date of key enabling discovery	Public?	Date of synthesis of compound	Public?	Date of market introduction	Lag from enabling discovery to market introduction
Old Fashioned or "random" drug discovery: screening of compounds in whole or partial animal screens								
Cyclosporine	Sandimmune	Immune suppression	NA		1972	N	1983	
Fluconazole	Diflucan	Anti-fungal	1978	N	1982	N	1985?	7
Foscarnet	Foscavir	CMV Infection	1924	Y	1978	Y	1991	67
Gemfibrozil	Lopid	Hyperlipidemia	1962	N	1968	N	1981	19
Ketoconazole	Nizoral	Anti-fungal	1965	N	1977?	N	1981	16
Nifedipine	Procardia	Hypertension	1969	N	1971	N	1981	12
Tamoxifen	Nolvadex	Ovarian cancer	1971	Y	NA		1992	21
"Mechanism driven" research: screening of compounds against a very specific known or suspected mechanism								
AZT	Retrovir	HIV	Contentious	Y	1963	Y	1987	
Catopril	Capoten	Hypertension	1965	Y	1977	N	1981	16
Cimetidine	Tagamet	Peptic Ulcer	1948	Y	1975	N	1977	29
Finasteride	Proscar	BPH	1974	Y	1986	N	1992	18
Fluoxetine	Prozac	Depression	1957	Y	1970	N	1987	30
Lovastatin	Mevacor	Hyperlipedimia	1959	Y	1980	N	1987	28
Omeprazole	Prilosec	Peptic Ulcers	1978	N	1982		1989	11
Ondansetron	Zofran	Nausea	1957	Y	1983	N	1991	34
Propranolol	Inderol	Hypertension	1948	Y	1964	N	1967	19
Sumatriptan	Imitrex	Migraine	1957	Y	1988	N	1992	35
Drugs discovered through fundamental science								
Acyclovir	Zovirax	Herpes	—		—		1982	
Cisplatin	Platinol	Cancer	1965	Y	1967	Y	1978	13
Erythropoietin	Epogen	Anemia	1950	Y	1985	N	1989	39
Interferon beta	Betaseron	Cancer, others	1950	Y	Various	N	Various	

Authors' compilations.

histories of the discovery and development of 21 drugs identified by two leading industry experts as "having had the most impact upon therapeutic practice" between 1965 and 1992. The table confirms the important role that the public sector plays in providing fundamental insights in basic knowledge as a basis for drug discovery.[5] Only five of these drugs, or 24%, were developed with essentially no input from the public sector. (This contrasts with Maxwell and Eckhardt's finding (Maxwell and Eckhardt 1990) that 38% of their sample of older drugs were developed with no public sector input.) In the second place, these data are consistent with the hypothesis that public sector research has become more important to the private sector over time. The table groups the drugs into three classes according to the research strategy by which they were discovered: those discovered by random screening, those discovered by mechanism-based screening, and those discovered through fundamental scientific advances. Broadly speaking, the degree of reliance on the public sector for the initial insight increases across the three groups, and as the industry has moved to a greater reliance on the second and third approaches, so the role of the public sector has increased. In the first group of therapies—those discovered through "random screening"—public sector researchers made the key enabling discovery in only two of the five drugs. In the two more recent groups public sector researchers made the key discovery in all but two of the cases. The very long lags apparent in the table between fundamental advances in science and their incorporation in marketed products may be shortening as the public and private sectors draw closer together, but it is difficult to draw strong conclusions from this small sample.

One way to capture interaction between the public sector and industry is via the paper trail of publications by pharmaceutical company researchers in the open literature. Publication is a key indicator of participation in the wider scientific community, and in our studies of the management of research in a sample of major pharmaceutical firms, we found evidence from analysis of these "bibliometric" data that this participation has become more and more significant over time. Figure 1.3 shows four key measures of this dimension of the relationship between the public and private sector in the industry, and tracks their evolution over time. *"Propub"* is a measure of the degree to which the firm relies on its scientists' standing in relationship to public science as a key criteria in promotion decisions (Henderson and Cockburn 1994).[6] *"Stars"* is the average number of scientists at each

firm who publish more than 25 papers within any given three year period. *"Pubfrac"* is the percentage of all those scientists whose names appear on a patent in any given year whose name also appears on scientific publication.[7] *"Univ-coauth"* is the average percentage of the firm's papers that are coauthored with university authors.[8] All of these measures increase significantly over the period, illustrating graphically the private sector's increasing engagement with the world of publicly available (and largely publicly funded) research. Figure 1.4 illustrates one result of this dynamic: the number of papers per patent and papers per NDA (New Drug Application) has also steadily increased over the period.

V. What, then, can we say?

The estimation of the effect of publicly funded research on the productivity of the pharmaceutical industry thus presents formidable challenges. It is very difficult to accurately measure either inputs or outputs: there are very long and highly variable lags in the relationship between inputs and outputs, and furthermore the nature of this relationship has likely changed dramatically over time.

Research in this area has thus proceeded along three lines. The first is the broad brush comparison of the United States with the rest of the world. The second, perhaps not surprisingly, is the detailed case study. The third is econometric or statistical. All three suffer from limitations, but taken together they suggest that publicly funded research has a very significant impact on the generation of new drugs.

Regional Comparisons

One of the intriguing aspects of the revolution in molecular biology is that despite the fact that it is global in nature, and despite the fact that scientific advances are normally thought of as creating a "free good," or as being instantaneously available worldwide, it has resulted in quite different changes in industry structure in different parts of the world. In the U.S., it has spawned both the emergence of radically new actors—the new specialized biotechnology firms—and the gradual creation of biotechnology programs within established firms. In Europe, responses have differed dramatically from country to country. Despite a strong research tradition in molecular biology, in general Europe has not witnessed the creation of a specialized biotechnology sector. Several of the leading Swiss and British "Big Pharma" incumbent firms

have attempted to build strong biotechnology capabilities through a combination of internal development and an aggressive program of external acquisition, but the French, German, and Italian firms have been much slower to adopt the new techniques. In Japan, where historically the pharmaceutical industry has been somewhat less innovative than its Western rivals, most substantial investments in biotechnology have been made by firms with historical strengths in fermentation based industries, and the large pharmaceutical companies have been particularly slow to embrace the new technology.

The question of why the phenomenon of the small, independently funded biotechnology startup was initially an American one is an old and much discussed question. One of the reasons that it cannot be answered definitively is that the answer is to a large degree over determined. In the United States a combination of factors made it possible for small, newly founded firms to take advantage of the opportunities created by biotechnology.

On the one hand, the majority of the American biotechnology startups were tightly linked to university departments, and the very strong state of American academic molecular biology clearly played an important role in facilitating the wave of startups that characterized the eighties (Zucker, Darby, and Brewer 1997). The strength of the local science base may also be responsible, within Europe, for the relative British advantage and the relative German and French delay. Similarly the weakness of Japanese industry may partially reflect weakness of Japanese science. There seems to be little question as to the superiority of the American and British scientific systems in the field of molecular biology, and it is tempting to suggest that the strength of the local science base provides an easy explanation for regional differences in the speed with which molecular biology was exploited as a tool for the production of large molecular weight drugs.

On the other hand, a number of other important factors supported the new firms' growth. These factors included a favorable financial climate, strong intellectual property protection, a scientific and medical establishment that could supplement the necessarily limited competencies of small newly founded firms, a regulatory climate that did not restrict genetic experimentation, and, perhaps most importantly, a combination of a very strong local scientific base with academic and cultural norms that permitted the rapid translation of academic results into competitive enterprises. Nelson (1993) has labeled this a "national system of innovation," and it appears to have been particularly conducive to innovation in biotechnology. In Europe (although to a

lesser extent in the U.K.) and in Japan many of these factors were not in place. For example, for many years the patentability of various aspects of biotechnology was uncertain in Europe, and until recently there was a relatively small local venture capital industry. In general, it was left to larger firms to exploit the new technology in these countries.

Case Study Research There have also been a significant number of careful case studies of this issue, most focused on the development of detailed histories of the discovery of new drugs. See for example Borel, Kis, and Beveridge 1995, Comroe and Dripps 1976, Penan 1996, Raiten and Berman 1993, Richardson et al. 1990, and Rittmaster 1994. By tracing the involvement of particular individuals or laboratories in the discovery of a particular drug it is possible, at least in principle, to identify and evaluate the relative importance of privately funded versus publicly funded research. Of course, the exercise can be very difficult in practice, and is unlikely to produce unambiguous conclusions.

Consider the case of AZT, the first drug to approved by the FDA for use in treatment of HIV infection. AZT was first synthesized in the early 1960s by a public sector researcher looking for activity against cancer. It then languished for many years in the library of compounds maintained by antiviral researchers at Burroughs Wellcome. Its value in prolonging the life of some AIDS patients only became apparent when BW sent it, along with a dozen other candidate compounds, for testing against a screen developed at NIH. BW then took the lead in conducting clinical trials and obtaining FDA approval. "Who discovered what and when" was an integral part of the intense controversy surrounding this case, with the U.S. Supreme Court eventually ruling against claims that NIH scientists should have been listed as inventors on BW's patents on the use of AZT in treatment of AIDS.

Legal claims aside, debates about priority in discovery are an integral part of science, and different observers may place more or less weight on different contributions. In many instances, it is simply impossible to definitively assign credit for the invention of a drug to a specific individual or institution. Furthermore, many of these case histories overlook the subtler influences of the public sector in providing "infrastructure," graduate training, and so forth. But between them these studies—and others like them—make a compelling quantitative case for the importance of publicly funded research. All of them suggest that publicly funded research made critical contributions to the discovery of an important therapeutic advance.

Econometric or Statistical Studies Econometric studies of the impact of publicly funded research on private sector productivity supplement the particularity of case studies with more general results, but are subject to all of the problems that we outlined above. Figures 1.5 and 1.6 hint at some of the issues that must be dealt with in interpreting the raw quantitative data. Both figures show that several key measures of the output of the industry—papers, patents, and NDAs, or New Drug Approvals—have been increasing over time.[9] But all three measures involve considerable error,[10] all three measures trend up quite smoothly over time, and all three are only loosely related to social impact. Presumably we care about patient health, not papers, patents, or NDAs *per se*, and while there is almost certainly *some* link between the two, at any general level it is impossible to be precise about what it might be. Similarly there are the long lags to consider: the NDAs approved tomorrow will rest on research that was performed anywhere from 5 to 15 years ago, and since both private and public research trends up over time it is very difficult to separately identify their effects.

Despite these difficulties, a number of researchers have attempted to measure the effects of public sector research directly. Zucker, Darby, and Brewer (1997) show that biotechnology startups tend to co-locate with public sector researchers, an intriguing and suggestive result. Zucker, Darby, and Armstrong (1998) show further that collaborations between these new firms and university stars is correlated with some measures of success. For an average firm, five articles coauthored by academic stars and the firm's scientists imply about five more products in development, 3.5 more products on the market, and 860 more employees. These results are consistent with the hypothesis that university research has a powerful effect on the private sector, though they should be interpreted carefully—the authors were not able to fully control for the level of R&D spending by the firms or the quality of their other scientists.

Two studies have explored another indirect measure of public sector impact: the relationship between a firm's ability to take advantage of knowledge generated in the public sector and its own productivity. Gambardella (1995) showed that in the 1970s and 1980s those pharmaceutical firms that published more scientific papers were relatively more productive than their rivals. In a similar vein, in Cockburn and Henderson (1998) we explored the relationship between a firm's research productivity and its "connectedness" to the public sector, using data on coauthorship of scientific papers across institutional

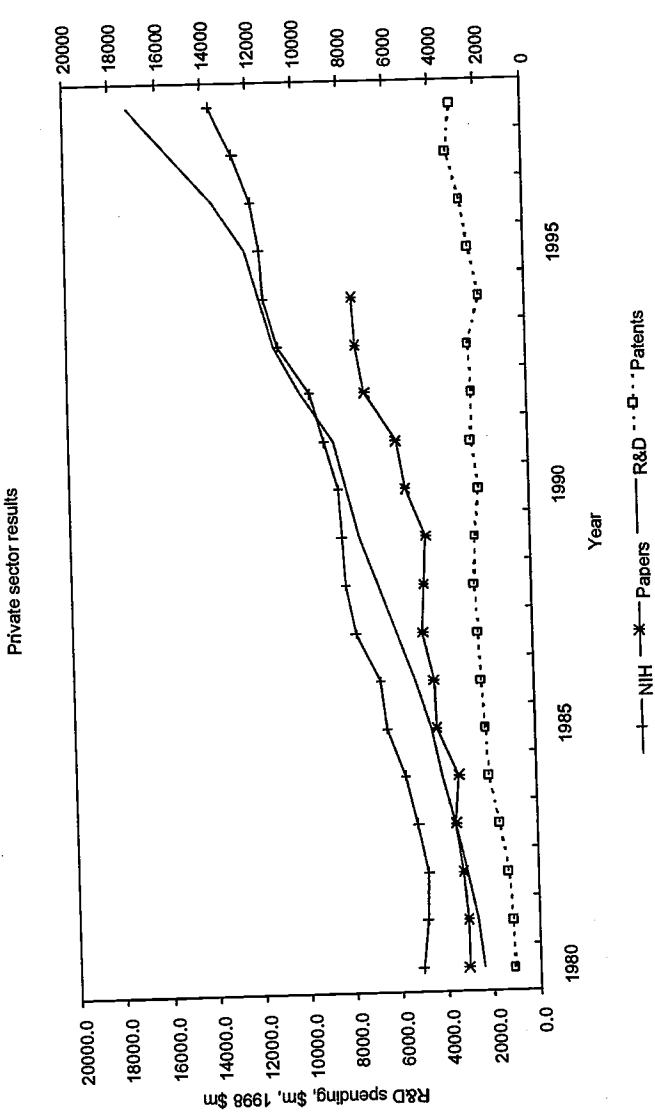

Figure 1.5
Patents and papers as the output of pharmaceutical research

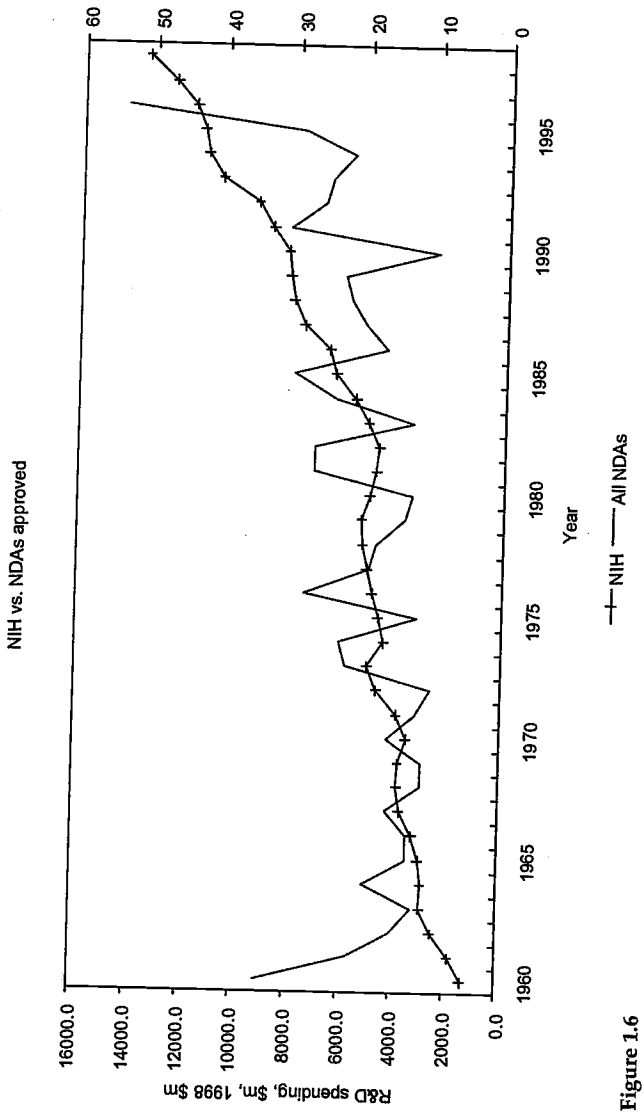

Figure 1.6
NDA output over time

boundaries. "Connectedness" in this sense is closely related to a number of other factors that also increase the productivity of privately funded pharmaceutical research, including the number of star scientists employed by the firm and the degree to which the firm uses standing in the public rank hierarchy as a criterion for promotion. Linking these data with measures of research productivity we found that "connectedness" and research performance are correlated across firms and over time. While any estimate of this type must be treated with great caution, our results also suggested that differences in the effectiveness with which a firm was accessing the upstream pool of knowledge corresponded to differences in the research productivity of firms in our sample of as much as 30%.

One interpretation of this result is that it represents a lower bound estimate of the impact of public sector research, since by definition it excludes the impact of any publicly generated knowledge that can be costlessly accessed across the industry. However the fact that "connectedness" is likely to be correlated with other hard-to-observe organizational practices that improve research productivity, as well as other important sources of unobserved heterogeneity across firms (such as the quality of human capital) made us hesitate to assign the result too much weight. Rather we suggested that our results were consistent with the hypothesis that the ability to take advantage of knowledge generated in the public sector requires investment in a complex set of activities that taken together change the nature of private sector research. They thus raise the possibility that the *ways* in which public research is conducted may be as important as the *level* of public funding. To the extent that efforts to realize a direct return on public investments in research lead to a weakening of the culture and incentives of "open science," our results are consistent with the hypothesis that the productivity of the whole system of biomedical research may suffer.

In a study at a more aggregate level, Ward and Dranove (1995) showed that a 1% increase in research funding by the National Institutes of Health leads to an estimated 0.6–0.7% increase in spending by members of the Pharmaceutical Manufacturers of America (PMA), after a lag of 6 to 10 years. This result is also consistent with the hypothesis that the private return to publicly funded research is quite high, since if increases in public sector research fuel private sector increases, then presumably the presence of public sector research is raising the marginal productivity of private sector work.

The most recent paper in this stream of research is by Andrew Toole (1999). Toole uses data at the level of the therapeutic class to obtain estimates of the rate of return to publicly funded research. His (unpublished) estimates imply that a 1% increase in the stock of public basic research ultimately leads to a 2.0% to a 2.4% increase in the number of commercially available new compounds, and that industry firms appropriate a return on public science investment in the range of 11% to 32%. He notes that this result suggests that the returns to public science are actually rather larger since these estimates are based on conservative estimates of firm profits from an average compound and since they ignore any consumer surplus that may be created by the introduction of a new therapy.

Conclusions We have suggested that there are a number of factors that make it difficult to estimate precisely the impact of publicly funded research. Such estimation is always difficult, but in the case of the pharmaceutical industry it is a notably difficult task since the public sector provides inputs to industry research in so many different and subtle ways, and spillovers are likely to be so large that the social returns to innovation are substantially different from the measurable private returns.

Nevertheless, a considerable body of both qualitative and quantitative evidence indicates that the public sector has had a profoundly positive impact on the industry, and that this appears to have increased significantly over time. Qualitative evidence suggests that public sector research has made possible fundamental advances in the ways in which new drugs are discovered and has opened up doors that may revolutionize the treatment of disease. The quantitative evidence suggests that the rate of return to public sector research *as measured by its effect on the private sector,* may be as high as 30%.

There are a number of reasons for believing that this figure is in fact a quite conservative estimate of the overall social return to publicly funded research in this sector of the economy. First, it is highly unlikely that private sector firms capture all of the benefits to public sector research in their own output. When drugs come off patent, to take one example, their price tends to fall considerably, but the benefit to consumers in terms of QUALYs or other measures of health status remains constant. Thus "true" output is likely to be seriously undercounted, and economic estimates of the bang for the buck from publicly funded research will therefore, if anything, be lower bounds to the real value.

Second, the lag between when basic scientific advances are made and when their impact becomes visible in marketed products is particularly long in this industry. Despite intense commercial competition and the dedicated effort of many thousands of individuals, it can take 10 years or more for promising discoveries to be turned into approved drugs. Today's improvements in treatment of many diseases reflect public research expenditures made in the 1960s and 1970s. The bulk of the impact of the investments made in the 1980s and 1990s has probably not yet been felt. Arguably, we have yet to benefit from the most important contribution of modern publicly funded science: the breakthrough in our understanding of genetics and molecular biology that is summarized under the name "the biotechnology revolution." There are hundreds of new compounds in development that draw upon this knowledge, and surely thousands more yet to be discovered. Econometric studies conducted 10 or 20 years from now are likely to find even higher rates of return to publicly funded research.

Over the past 50 years, the pharmaceutical industry and the publicly funded biomedical research establishment have grown hand in hand in their size and economic significance. Ever larger investments in research on both sides have resulted in new drugs and vaccines that are responsible for very significant improvements in health and well-being. This remarkable innovative performance is unlikely to have been realized without substantial public support of basic research, along with the development of close linkages between private sector and public sector institutions.

The relationships between the NIH, government labs, universities, and the private sector continue to evolve, and areas of conflict have inevitably arisen. In genome research, for example, private firms have been seeking proprietary rights over some of the results of decades of publicly funded work on DNA sequencing. Equally, universities have become increasingly aggressive and effective in realizing licensing revenue from their discoveries. These changes are altering the delicate balance between nonprofit and for-profit institutions which appears to have been so effective in the past at generating scientific advances and bringing them to market, and are surely a cause for some concern.

Nonetheless, absent any evidence of exhaustion of scientific opportunities, there is a compelling case for continued substantial public support of the biomedical sciences. As today's taxpayers reach retire-

ment age they will enjoy a generous return from these investments, but if the experience of the past five decades is any guide it will be their children and their children's children who will benefit the most.

Notes

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1. The preferred embodiment of this idea expresses productivity in terms of a production function which models output as a function of inputs. These functions can be quite elaborate, allowing for returns to scale, substitution between inputs, etc. Estimation of these functions raises a further set of problems, see, e.g., Griliches, 1979, 1994, 1995.

2. The vagueness of this statement reflects the very considerable methodological problems inherent in these types of studies. To give a taste of these, consider the statistical problems inherent in trying to econometrically estimate production functions in which measures of publicly funded knowledge capital appear as an input. Even if accurate measures of inputs and outputs can be found, getting accurate estimates of the parameter values which tell us about the rate of return to public research is very difficult. For example, in general, measures of outputs and inputs tend to be correlated with each other and to move together over time. This makes it hard to determine the direction of causality: does research cause sales or do sales cause research? Even if there is sufficient independent variation in these variables, it is far from clear what the appropriate functional form of the production function might be.

3. Most major pharmaceuticals are multinational, performing R&D in more than one country. These figures do not include an additional 10–20% of overseas R&D spending by U.S.-headquartered firms, or expenditures in the U.S. by foreign-based firms.

4. Indeed the development of "combinatorial chemistry" coupled with the techniques of "high throughput screening" have given a new lease of life to random drug discovery.

5. For purposes of general comparison we list a date of key enabling discovery for each drug. The choice of any particular event as the key enabling discovery is bound to be contentious, since in pharmaceuticals, as in many fields, discovery usually rests on a complex chain of interrelated events. In the case of drugs discovered through screening we give the date of first indication of activity in a screen. In the case of mechanism based drugs, we give the date of the first clear description of the mechanism. Dates for the third class are only broadly indicative, and all should be used carefully.

6. "Propub" was constructed using detailed qualitative data at 10 major pharmaceutical firms. For details, see Henderson and Cockburn 1994.

7. "Stars" and "Pubfrac" were constructed using publicly available data from 19 large pharmaceutical firms. For details, see Cockburn, Henderson, and Stern 2000.

8. This variable is constructed for the same sample of 10 major firms for which "Propub" was constructed, using publicly available data. See Cockburn and Henderson 1998.

9. Industry sales have also been increasing, at roughly the same rate as private R&D spending. Recall, however, that the lag between R&D spending and the generation of sales is a very long one!

10. We show here only NDAs that warrant Class 1 or Class 2 ranking by the FDA—entirely new therapies of considerable merit and therapies that are essentially equivalent to existing therapies.

References

Adams, J. 1990. "Fundamental Stocks of Knowledge and Productivity Growth." *Journal of Political Economy* 98(4): 673–702.

Agarwal, A. 2000. "The Diffusion of Knowledge from University to Industry: A Study at MIT." Forthcoming Ph.D. Dissertation, University of British Columbia.

Arrow, K. 1962. "Economic Welfare and the Allocation of Resources for Invention." In R. Nelson, ed., *The Rate and Direction of Inventive Activity.* Princeton, NJ: Princeton University Press: 609–19.

Berndt, E. R., D. Cutler, R. G. Frank, Z. Griliches, J. P. Newhouse and J. E. Triplett. 2000. "Price Indexes for Medical Care Goods and Services: An Overview of Measurement Issues." Forthcoming in David Cutler and Ernst R. Berndt, Eds., *Medical Care Output and Productivity,* Chicago: University of Chicago Press for the National Bureau of Economic Research.

Borel, J. F., Z. L. Kis, and T. Beveridge. 1995. "The History of the Discovery and Development of Cyclosporine." In V. J. Merluzzi and J. Adams, eds., *The Search for Anti-Inflammatory Drugs.* Boston: Birkhauser.

Clymer, H. A. 1975. "The Economic and Regulatory Climate: U.S. and Overseas Trends." In R. B. Helms, ed., *Drug Development and Marketing.* Washington, DC: American Enterprise Institute.

Cockburn, I., and R. Henderson. 1998, June. "Absorptive Capacity, Coauthoring Behavior, and the Organization of Research in Drug Discovery." *Journal of Industrial Economics* XLVI(2): 157–82.

Cockburn, I. and A. Anis. 2000. "Hedonic Analysis of Arthritis Drugs." Forthcoming in David Cutler and Ernst R. Berndt, Eds., *Medical Care Output and Productivity,* Chicago: University of Chicago Press for the National Bureau of Economic Research.

Cockburn, I., R. Henderson, and S. Stern. 1999, January. "Balancing Incentives: The Tension between Basic and Applied Research." Working Paper no. 6882, National Bureau of Economic Research, Cambridge, MA.

Cockburn, I., Henderson, R. and S. Stern. Fall 2000. "Untangling the Origins of Competitive Advantage," *Strategic Management Journal,* 21: 1123–1145.

Comroe, J., and R. Dripps. 1976. "Scientific Basis for the Support of Biomedical Research." *Science* 192: 105.

Cutler, D., and E. Richardson. 1999. "Your Money and Your Life: The Value of Health and What Affects It." A. Garber, ed. *Frontiers in Health Policy Research.* National Bureau of Economic Research, vol. 2, Cambridge, MA: MIT Press.

Dasgupta, P., and P. A. David. 1987. "Information Disclosure and the Economics of Science and Technology." In G. R. Feiwel, ed., *Arrow and the Ascent of Modern Economic Theory*. New York: NYU Press.

Dasgupta, P., and P. A. David. 1994. "Towards a New Economics of Science." *Research Policy* 23: 487–521.

David, P. A., D. Mowery, and E. Steinmuller. 1992. "Analyzing the Economic Payoffs from Basic Research." *Economics of Innovation and New Technologies* 2(4): 73–90.

Galambos, L., and J. E. Sewell. 1996. *Networks of Innovation: Vaccine Development at Merck, Sharp and Dohme, and Mulford, 1895–1995*. Cambridge: Cambridge University Press.

Gambardella, A. 1995. *Science and Innovation: The US Pharmaceutical Industry in the 1980s*. Cambridge, U.K.: Cambridge University Press.

Griliches, Z. 1979. "Issues in Assessing the Contribution of Research and Development to Productivity Growth." *Bell Journal of Economics* 10(1): 92–116.

Griliches, Z. 1994. "Productivity, R&D and the Data Constraint." *American Economic Review* 84(1): 1–23.

Griliches, Z. 1995. "R&D and Productivity: Econometric Results and Measurement Issues." In P. Stoneman, ed., *Handbook of the Economics of Innovation and Technical Change*. Oxford, U.K.: Blackwell: ch 3, pp 52–71.

Henderson, R., and I. M. Cockburn. 1994. "Measuring Competence? Exploring Firm Effects in Pharmaceutical Research." *Strategic Management Journal* 15: 63–84.

Henderson, R., and I. M. Cockburn. 1996. "Scale, Scope and Spillovers: The Determinants of Research Productivity in Drug Discovery." *RAND Journal of Economics* 27(1): 32–59.

Irvine, J., B. Martin, and P. Isard. 1990. *Investing in the Future: An International Comparison of Government Funding of Academic and Related Research*. Aldershot, England: Edward Elgar Publishers.

Jones, C., and J. Williams. 1995. "Too Much of a Good Thing? The Economics of Investment in R&D." Working Paper no. 96-005, Stanford University Department of Economics. Stanford, CA.

Laragh, J. H., et al. 1972. "Renin, Angiotensin and Aldosterone System in Pathogenesis and Management of Hypertensive Vascular Disease." *American Journal of Medicine* 52: 644–52.

Mansfield, E. 1991. "Academic Research and Industrial Innovation." *Research Policy* 20(1): 1–12.

Maxwell, R. A., and S. B. Eckhardt. 1990. *Drug Discovery: A Case Book and Analysis*. Clifton, NJ: Humana Press.

Merton, D. 1973. "On the Sociology of Science." In N. W. Starer, ed., *The Sociology of Science: Theoretical and Empirical Investigation*, Chicago: University of Chicago Press.

National Science Foundation. 1968, December. "Technology in Retrospect and Critical Events in Science" Unpublished manuscript prepared by IIT Research Institute. NSF C535.

Nelson, R. R. 1959. "The Simple Economics of Basic Scientific Research." *Journal of Political Economy* 67(2): 297–306.

Nelson, R. R. ed. 1993. *National Innovation Systems: A Comparative Analysis.* Oxford, U.K.: Oxford University Press.

Penan, H. 1996. "R&D Strategy in a Techno-Economic Network: Alzheimer's Disease Therapeutic Strategies." *Research Policy* 25: 337–58.

Raiten, D., and S. Berman. 1993. "Can the Impact of Basic Biomedical Research be Measured? A Case Study Approach." Working Paper, Life Sciences Research Office, Federation of American Societies for Experimental Biology. Washington, D.C.

Richardson, K., K. Cooper, M. S. Marriott, M. H. Tarbit, P. F. Troke, and P. J. Whittle. 1990. "Discovery of Fluconazole, a Novel Antifungal Agent." *Review of Infectious Diseases* 12(3): S267–71.

Rittmaster, R. 1994, January 13. "Finasteride." *New England Journal of Medicine* 120–5.

Stephan, P. 1996, September. "The Economics of Science." *Journal of Economic Literature* 34: 1199–235.

Stern, S. 1999, October. "Do Scientists Pay To Be Scientists?" Working Paper no. 7410, National Bureau of Economic Research, Cambridge, MA.

Toole, A. 1999, November. "The Contribution of Public Science to Industrial Innovation: An Application to the Pharmaceutical Industry." Discussion Paper no. 98-6, Stanford Institute for Economic Policy Research. Stanford, CA.

Ward, M., and D. Dranove. 1995. "The Vertical Chain of R&D in the Pharmaceutical Industry." *Economic Inquiry* 33: 1–18.

Wurtman, R. J., and R. L. Bettiker. 1994. "How to Find a Treatment for Alzheimer's Disease." *Neurobiology of Aging* 15: S1–3.

Wurtman, R. J., and R. L. Bettiker. 1996, Spring. "Training the Students Who Will Discover Treatments for Psychiatric Diseases." *Psychiatric Research Report.*

Zucker, L., M. Darby, and M. Brewer. 1997. "Intellectual Human Capital and the Birth of U.S. Biotechnology Enterprises." *American Economic Review* 88(1): 290–306.

Zucker, L., M. Darby, and J. Armstrong. 1998. "Geographically Localized Knowledge: Spillovers or Markets?" *Economic Inquiry* 36: 65–86.