Public Research Funding and Private Innovation: The Case of the Pharmaceutical Industry

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Abstract

The United States has an extensive system of government funding for basic research. The traditional rationale for this policy is that due to the inappropriability of research results, the private sector provides suboptimal levels of basic research, and government subsidy will correct this underprovision. In addition, it is likely that higher levels of basic research stimulate higher levels of private applied research by increasing the stock of scientific knowledge. It is possible, however, that government-funded basic research "crowds out" private basic research by reducing its private returns. This may mitigate or even reverse the former effect, so that government funding of basic research may stimulate less, and in the extreme case may even reduce the level of private research relative to the alternative in which basic research is privately funded.

This paper uses data on public and private funding of biomedical research to study the effect of government research funding on private-sector research and development (R&D) expenditures and new product development in the pharmaceutical industry. The main finding is that increases in government research funding appear to crowd out private R&D for approximately the first four years and start to stimulate private research in the fifth year after the increase. A reasonable interpretation is that the direct effect of government funding is to crowd out private basic research in the short run and stimulate private applied research in the long run. The crowding out (substitution) is more pronounced when expenditure levels are measured in constant dollars according to the Biomedical Research and Development Price Index (BRDPI), rather than in current dollars or constant dollars according to the GDP deflator. Numerous robustness checks fail to support alternative interpretations, and anecdotal data from the development of a new class of drugs (COX-2 inhibitors) supports this interpretation. In addition, empirical results fail to show any clear effect of government funding on output in the pharmaceutical industry.

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1 Introduction

It is widely, and quite reasonably, believed that the major source of economic growth in advanced countries is technological improvement and that such technological improvement is largely due not to chance discoveries, but rather to organized research effort (Romer 1990). However, because of the uncertainty inherent in research activity and the fact that the output of research activity may be inappropriable, it is possible that in equilibrium the private sector might provide suboptimal levels of innovation, particularly in areas of "basic" research (Arrow 1962; Nelson 1959). One possible solution to this problem is for government to provide subsidies for basic research. However, it is then possible that government funding of basic research might "crowd out" private basic research, thus mitigating its effectiveness as a solution to the underprovision problem. The goal of this paper is to study the effect of government research funding on private-sector research and development (R&D) expenditures and new product development.

This paper uses data on public and private funding of biomedical research to study the effect of government research funding on private-sector research and development (R&D) expenditures and new product development in the pharmaceutical industry. The main finding is that increases in government research funding appear to crowd out private R&D for approximately the first four years and then stimulate private research starting in the fifth year after the increase. One possible interpretation is that the direct effect of government funding is to crowd out private basic research but stimulate private applied research.

The pharmaceutical industry is particularly well suited to a study of the relationship between public and private R&D, since this industry is characterized by substantial levels of both private and government funding. Research in most other R&D-intensive industries is typically funded either primarily by government (as in the case of the aerospace and other defense-related industries) or primarily by for-profit corporations (as in the case of electronics

and manufacturing industries). However, in the case of the pharmaceutical industry, both sectors have substantial shares of expenditures, with government accounting for about 40% and the drug industry for about 60% of biomedical research spending in the U.S.(National Science Foundation 1999). In addition, the division between "basic" and "applied" research is much more clearly defined in this industry, compared to other industries. Basic research into disease processes, which is funded by government grants as well as private companies and nonprofit organizations, is an input into the (applied) development of pharmaceuticals, which is funded primarily by the private sector. Unlike other government R&D efforts, such as research for defense projects that require secrecy, detailed project-level data are available for government-funded biomedical research. Furthermore, virtually all products in this industry are protected by patents (rather than, for example, as trade secrets) and are subject to technical regulation by the Food and Drug Administration (FDA),[1] which means that much more data on private R&D are available than in the case of most other research-intensive industries.

In addition, the pharmaceutical industry is a substantial sector of the economy and accounts for an even more substantial share of both public and private R&D expenditures. For example, in 1998 total U.S. private-sector pharmaceutical R&D spending was $17.2 billion, accounting for 20.1% of pharmaceutical sales (PhRMA 2000). In addition, the federal government spent over $11 billion in medical and biological research in 1998, accounting for about one-sixth of federal R&D spending (NSF, 1999). The inflation-adjusted level of federal spending has tripled since 1970 (Shadid 2001) and continues to rise; Congress increased the budget of the National Institutes of Health (NIH) by 15% in both 1998 and 1999. In the 2000 U.S. Presidential election campaign, both major-party candidates proposed doubling the NIH budget from its 1998 level ($12.9 billion) by 2003 (Brainard 2000), and this was more than achieved when Congres
billion to NIH for fiscal year 2003.

[1] A list of acronyms used in this paper appears on pages 99–101.

Finally, biomedical research is important because the social gains are huge: Murphy and Topel (1999) and Nordhaus (1999) estimate that the total value of gains in utility from improved health and increased life expectancy in the U.S. since the year 1900 is on the order of the increase in traditional Gross Domestic Product (GDP) over the same period. In other words, despite the fact that health-related R&D makes up only 13.8% of total R&D (and only 0.3% of GDP), if improvements in health and increased life expectancy were included in GDP, the growth rate of GDP would be doubled. Lichtenberg (1999b) estimates that a large portion of the increased life expectancy is due to new drugs; in particular, the average new drug introduced between 1970 and 1991 is estimated to have saved 11,200 life-years in 1991 alone. In other words, a substantial portion of the benefits of this research accrue to the general public through the use of pharmaceutical products, whose U.S. sales account for only about 0.94% — less than 1% — of total GDP.

Given the importance of medical research and the large roles of both government and private industry in conducting such research, it is surprising that so little work has focused on the interaction between the two. The study that comes closest to the present one in intent is that by Ward and Dranove (1995), who treat pharmaceutical innovation as a flow of information through three stages: government-funded basic research, publication in medical journals, and industry-funded drug development. Their measure of government funding is the budget of the NIH, broken down into five categories based on the constituent institutes of the NIH. For industry R&D, they use the annual survey of the Pharmaceutical Manufacturers' Association (PMA, since renamed Pharmaceutical Research and Manufacturers of America, i.e., PhRMA), which reports industry R&D expenditures broken down into seven therapeutic classes corresponding to five-digit Standard Industrial Classification (SIC) codes. Ward and Dranove report results of regressions of the logarithms of industry R&D expenditures on the logarithms of NIH expenditures (lagged 0-7 years) for the five PMA/PhRMA categories which can be linked to NIH institutes. A 1% increase in own-category NIH spend-

ing corresponds to a cumulative increase in PMA/PhRMA spending of 0.57-0.76% over seven years. Five of the seven lag coefficients are positive, and only the sixth-order lag is significant at the 5% level.

In this study, we use an updated version of the same data for industry R&D, but a much more detailed set of data for government-sponsored R&D. Since we have data at the project level rather than the NIH institute level, we are able to finely categorize projects and allocate them more precisely to the corresponding industry R&D therapeutic categories. This also allows us to include projects in those therapeutic categories (respiratory and dermatological) that do not have corresponding NIH institutes. While far from perfect, these data also avoid the problem of classifying funding in the "wrong" category when a project is funded in the "wrong" institute, as might happen for political or budgetary reasons, or when a research program has subcomponents that cut across categories.[2] In addition, we adjust expenditures to constant dollars using the Biomedical Research and Development Price Index (BRDPI), a price index specifically designed for biomedical R&D inputs, whereas previous studies adjust expenditures either using the GDP deflator or, more commonly, not at all.[3] We find more negative regression coefficients on federal R&D, mostly in the lags of the fourth order and lower, and these negative coefficients are more pronounced for BRDPI-adjusted data than for current-dollar data. We interpret the negative coefficients in lower-order lags and positive coefficients in higher-order lags as a substitution in the short run but complementarity in the long run. This is consistent with a model in which publicly-sponsored basic research "crowds out" private basic research but stimulates private applied research.

The plan of this paper is as follows. Section 2 discusses basic issues important to

[2] Dranove mentions that he has observed this in his work with NIH committees (Ward and Dranove 1995, p. 81n).

[3] One of the few exceptions is Jensen's (1987) study of the relationship between firm-level R&D expenditures, firm size, and research productivity in the drug industry. She used an *ad hoc* index consisting of a weighted average of the index of hourly labor compensation (49%) and the implicit deflator in the non-financial corporations sector (51%), as suggested by S. Jaffe (1972).

understanding the economics of innovation. Section 3 reviews prior studies of innovation in general, without specific reference to the pharmaceuticals industry. Section 4 reviews regulatory issues in the drug-development process and prior studies of the effects of regulation on drug innovation. Section 7 describes the econometric model on which the analysis is based, Section 6 describes the data used, Section 8 describes the results and their interpretation, and Section 9 concludes.

2 Basic Issues in the Economics of Innovation

Technology is defined as the knowledge necessary to produce goods, and as such constitutes information. Information is traditionally viewed as a public good: once information (or technology) is produced, perhaps at great cost, it can be transmitted to and used by many people and organizations at relatively low marginal cost. In particular, unlike physical goods or money, when technology is given by one party to another, the original party still possesses it, and his or her ability to use the technology to produce goods is not reduced by virtue of having transmitted the technology.

While ability to make *use* of technology is unaffected by transmission of information, ability to *profit* from the technology may be greatly reduced. Indeed, an individual or firm may go to great lengths and expend substantial resources in research to produce technology, only to find that it can no longer profit from the technology once others copy it. Without some means of protecting rights to information, there would be no way to profit from producing information, thus very little would be produced.

One of the main incentives for research in the private sector is the existence of patent systems, which grant to innovators monopoly rights to their discoveries for substantial (but limited) periods of time. Of course, the main problem with patents is that they are *ex post* inefficient, due to monopoly pricing. On the other hand, eliminating patents might well be

even worse: in exchange for eliminating deadweight loss due to monopoly, we might also give up much of the gains, since the lack of *ex ante* profit opportunity would result in fewer new technologies. In short, we might eliminate the possibility of deadweight loss in some markets by eliminating those markets — and all their remaining surplus — in their entirety.

There have been many attempts to balance the countervailing forces acting in favor of and against patent protection. There is an extensive literature on optimal patent length and scope, most of which finds solutions that would be difficult to implement in practice due to the heterogeneity of new technologies and *ex ante* uncertainty as to their value. For example, Nordhaus (1969) notes that, "In general it is not possible to determine the exact value of the optimal [patent] life without knowing the parameters" such as elasticities of demand and invention productivity and the social discount rate. More recently, Wright (1999) notes that, "[the] optimal patent design may be broad and short-lived or narrow and infinitely-lived depending on the market structure assumed and the properties of the demand function." Since these properties are different for every product and not usually known in advance, it is virtually impossible to use these findings as a basis for policy.

There have also been attempts to stimulate innovation without any patent protection by giving prizes for successful innovations known in advance to be useful to society (see Sobel (1995) for an intriguing example and **?**) for a theoretical model), or by providing government subsidies, in the form of either tax credits or direct grants, to innovators. The idea is that the government will pay the costs of innovation, the results of which will be available to everyone at marginal cost. While this solves the problem of *ex post* monopoly inefficiency, it introduces other problems, the most serious of which are how to determine what types of research the government should subsidize and how subsidies should be allocated among potential researchers. This type of system may be particularly useful in cases where a specific innovation is desired, and in cases in which the innovation is a pure-information public (i.e., non-appropriable) good. Even in this case, if prizes are available for some

specified innovations and patents available more generally, the results may not be what one would expect, since innovators will choose to work on projects with prizes or projects with patents, whichever they believe will be more profitable in the long run.

In addition, many governments provide some form of subsidy directly to private firms that conduct R&D. This can take the form of direct cash subsidies to favored businesses, as in the case of the U.S. Small Business Innovation Research Program (SBIR), or favored fields of innovation, as in the case of the Advanced Technology Program (ATP) of the National Institute of Standards and Technology (NIST). It can also take the form of tax credits, such as the Research and Experimentation (R&E) Tax Credit, which provides firms with tax credits for 6.5-13% of the amount by which a firm's annual expenditure on certain R&D-related items causes the firm's R&D-to-sales ratio to exceed the average ratio in certain preceding years.[4] In the U.S., when research by for-profit firms is subsidized, patent protection is generally still available, even in the case of direct cash subsidies for research. See Tassey (1997) for a comprehensive summary of current and recent U.S. government programs and Tassey (1996) for a comparison of the effects of tax incentives with those of direct subsidies.

Furthermore, for numerous fields in which innovative effort is thought to be underprovided by the private sector — particularly in areas designated as "basic" as opposed to "applied" research — subsidies are granted to academic and other not-for-profit researchers, the results of which are to some extent publicly available at marginal cost. In most cases, however, patent rights to derivative innovations may be available to the same researchers who were given subsidies. This was not always the case; prior to 1980, there was no federal government-wide policy on derivative patent rights, and most funding agencies either retained rights to patents based on discoveries by contractors and grantees or insisted on receiving a share of resulting revenue. The U.S. Patent and Trademark Amendments Act

[4] Being a tax matter, of course, it is not quite that simple. For details, see Sections 41 and 280C(c)(3) of the Internal Revenue Code of 1986.

of 1980 (the "Bayh-Dole Act") and subsequent amendments in 1984 prohibited the federal government from retaining such rights in most cases and explicitly permitted universities the right to obtain patents based on government-sponsored research. The result was a huge increase in university patenting, documented and detailed by Henderson, Jaffe, and Trajtenberg (1998), the economic-theoretic underpinning of which has since been explained by Jensen and Thursby (2001). In fiscal 1997, universities earned over $446 million in patent royalties and were awarded 2,239 new patents (Basinger 1999).

In addition to correcting the under-provision, another rationale for the policy of providing government grants for basic research is the belief that more basic research not only brings benefits of its own, but in addition stimulates private-sector applied research, both of which produce economic growth. This rationale is often explicitly cited by policy makers to justify government spending,[5] and there is some empirical evidence indicating that government-funded scientific research is an important input into patentable applied research.[6]

Of course, this policy is not without its costs either. With government funding of basic research, the results of which are to be publicly available at marginal cost,[7] the private returns to basic research are reduced. There are two reasons for this. First, if the government is funding research and making the results available for free, there is little benefit to a

[5] For example, Rep. Vernon Ehlers, Ph.D. (R-MI), speaking on the House floor on May 14, 1999, explicitly invoked this rationale to advocate continued funding of basic research. After pointing out that he is the first physicist ever elected to Congress, he cited the example of how the basic physics research aimed at measuring the magnetic moment of the nucleus eventually lead to the development of the medical diagnostic tool known as magnetic resonance imaging (MRI). He concluded, "Basic research drives the engine of medicine, it drives the engine of our economy, and it is high time we recognize that investing in basic science is a good investment for the future, with a very good rate of return." He did not give any empirical estimates of the rate of return. (Ehlers 1999)

[6] See, for example, Narin, Hamilton, and Olivastro (1997) and the discussion on page 14.

[7] Notwithstanding the provisions of the Bayh-Dole Act mentioned above, government research grants generally result in publication of results. Bayh-Dole Act provisions have the effect of applying to inventions derived from federal basic research, rather than basic research results themselves. For example, a mathematician with an National Science Foundation (NSF) grant for research on linear programming methods would have to report his theorems and algorithms publicly, but the Bayh-Dole Act would permit him to retain copyright and other rights to software implementing the algorithms. Likewise, a medical researcher would have to report publicly on the nature of a disease process discovered using a federal grant, but would be permitted to obtain a patent on a drug designed to block that disease process.

private firm's doing research in the same field that might produce similar results. Second, and more important, since government-funded research is publicly available, there is little opportunity to appropriate the results of any research in that particular field, either by means of secrecy or patents, since a private firm's research might well be replicated by publicly-subsidized researchers working in the same field. Thus, the overall incentives to private firms for conducting basic research are substantially reduced. Government expenditures undertaken to increase the total quantity of basic research (and thereby stimulate private applied research) might in fact "crowd out" private basic research. This would, in turn, reduce the stimulatory effect on applied research. Indeed, if the crowd-out effect is strong enough, or if inappropriability of basic research extends far enough, it might even be the case that increased government basic research decreases private applied research.

The idea here is as follows: suppose a government-subsidized "basic" researcher makes a new discovery about a disease, which is likely to be useful for developing a drug to treat that disease. The discovery is published, and it is common knowledge that by incurring a positive cost, any of several firms could do the research to develop a drug based on this discovery. It might be that a monopolist in this type of treatment could recover the cost and make a profit, but if two or more firms incur the cost, develop the drug, and compete, none will recover their costs. In a sort of reverse prisoners' dilemma, the equilibrium outcome might be that no firm develops the drug. (This outcome would not be a Nash equilibrium.) In most cases, however, there will be enough uncertainty in the rate and likelihood of successfully developing the drug that this situation will not occur.

On the other hand, in cases where the the goal is well-defined and the probability of success is sufficiently high, socially wasteful "patent races" may occur. That is, many firms may engage in research attempting to meet the same technical goal or consumer need. This is potentially wasteful to the extent that they duplicate each other's production of knowledge and also partly to the extent that they find different solutions to the same problem. If

patent protections are sufficiently narrow, both firms may be able to sell their products as monopolists in narrow sectors. In a related vein, Davidson and Segerstrom (1998) present an endogenous growth model in which "imitative R&D" — that is, R&D by firms for the purpose of producing equivalent goods without infringing existing patents — actually retards economic growth, even as non-imitative R&D leads to faster growth.

The question of whether government sponsorship of basic research crowds out (substitutes) or stimulates (complements) private basic and applied research must be answered empirically. There have been surprisingly few attempts to do so, despite the fact that the federal government has been funding scientific research for over half a century, and that the issue has been discussed by policy makers for even longer. This paper presents one attempt to address this question.

3 Prior Studies of Research and Innovation

3.1 Basic Science and Product Innovation

According to Kealey (1995), the first influential person to advocate government funding of science was Francis Bacon (1561-1626). Kealey also claims that Bacon was the first to propose a "linear" model of technological progress, starting with (government-funded) basic research producing pure scientific knowledge, which in turn becomes an input into applied research to produce technology and eventually economic growth.

In the United States, there was little public support of pure science until after World War II. In 1945, Vannevar Bush, who had headed the wartime Office of Scientific Research and Development, proposed an extensive program of government-sponsored research (Bush 1945; reprinted 1960 by NSF), which was eventually implemented with the establishment of the National Science Foundation in 1950. By 1953, federal funding of basic science had

overtaken private funding (Kealey 1995).

The importance of technological innovation to economic progress has been well-established among economists for decades. Nelson (1959) first raised the issue of the economically optimal level of basic research. Arrow (1962) applied the classic reasons for market failure — "indivisibilities, inappropriability, and uncertainty" — to explain why we should expect under-provision of research, particularly basic research.

Nevertheless, the linkage between basic science and technological improvement has been difficult to establish empirically. First, there are "spillover" studies that attempt to link research institutions, such as universities or government laboratories, to firms that are geographically nearby and that appear to benefit from having the scientists nearby (Jaffe, Trajtenberg, and Henderson 1993) or that can be shown to have some sort of link through which information flows. For example, Adams, Chiang, and Jensen (2000) study the Cooperative Research and Development Agreements (CRADAs) between national laboratories and private firms, formal agreements one goal of which is the economic exploitation by the firm of knowledge developed at the lab. Jaffe, Fogarty, and Banks (1998) measure spillovers by examining patents issued to federal labs and measuring their impact by the number of citations of those patents in other patents issued to private inventors.

Second, there are studies that link patents to basic science based on the scientific articles cited on patent applications. The main legal requirements for a patent are (1) the innovation must be new, (2) it must not be "obvious" to someone skilled in the relevant field, and (3) it must be potentially useful.[8] To establish that an innovation meets these requirements, applicants often refer to previous patents and/or scientific publications in the relevant field. In addition, as a patent examiner studies the patent application and previous work in the field to determine whether the proposed innovation is "novel," "non-obvious"

[8] The basic requirements are set forth in Title 35, United States Code, Part II, Chapter 10. The patent examiners in the U.S. Patent and Trademark Office have considerable latitude to exercise judgment in deciding whether a proposed patent meets the requirements.

and "useful," he or she often adds relevant references to both patents and other literature. If a patent is granted, these references are listed on the front page of the official patent document and are often used in bibliometric studies.

In a study based on citations of published scientific articles in U.S. patent applications, Narin and Olivastro (1992) found that the average number of science articles cited more than tripled from 1975 to 1989, from an average less of than one-third of a citation per patent in 1975 to more than one citation per patent in 1989. Pharmaceutical patents cited more science articles than did patents in any other field, averaging 4.5 articles per patent. In a subsequent study, Narin, Hamilton, and Olivastro (1997) found that a significant and increasing fraction of patents cite government-funded scientific research, including research conducted at both government and academic laboratories. For example, of all scientific papers cited in U.S. patent applications in 1993-1994, 73% were authored at academic or government institutions, and a substantial majority of the academic papers acknowledged a government funding source. Taking this a step further, Deng, Lev, and Narin (1999) use several measures of a firm's "patent portfolio" to try to predict the firm's stock performance. They find that, within industries, the average number of "non-patent references" (generally presumed to be scientific articles) listed on the first page of the firm's patents was strongly associated with the firm's stock performance.[9]

There are, of course, some problems with bibliometric studies based on patent citations. For one thing, it is not clear what a patent citation means. Patent applications are drafted to meet legal requirements and designed to increase the probability of success and perhaps the scope of the granted patent. Applications are often drafted by patent specialists (specialized "patent attorneys" and licensed "patent agents") rather than by inventors. The goal of the application in general and the citations in particular is to show how the

[9] They also found that stock performance is strongly associated with an index of how frequently the firm's patents are cited in later patents (the "patent impact"), and weakly associated with the number of patents received and the median age of patents cited (the "technology cycle time"). These factors are important but outside the scope of the present study.

proposed invention is *different* from previous work in the area ("prior art"), *not* to show how the proposed invention is *derived* from prior art. Furthermore, citations are often added by the patent examiner (in addition to the applicant) in the course of his or her research to determine whether the proposed innovation is "novel." In this case, the cited work is likely completely irrelevant to the inventor's development process, rather than being an input into it; the inventor may even have been unaware of the prior work cited. Meyer (2000) addresses many of these issues by interviewing patent attorneys, examiners, and inventors, and includes detailed case studies of ten particular patents. In five of the ten cases studied, the inventors interviewed reported that, while scientific research was important for background information about the subject, in only one of ten cases was a citation on the patent an antecedent to the innovation patented. In many cases, the inventors were unfamiliar with articles and even authors in citations added by patent examiners; in other cases the connection was rather that the same inventor was active in both academic publishing and industrial research, and his own papers were cited in the application.

Indeed, allowing publication of internal research can itself be profitable for firms for two main reasons. First, in order to make use of basic scientific research produced by university and publicly-funded researchers, industrial researchers must maintain active links with academic and government researchers. Such relationships are often easier to maintain if the firm allows publication, since there are opportunities for coauthored research (Cockburn and Henderson 1998; Kealey 1995) and other forms of non-monetary exchange. Second, many scientists prefer having the opportunity to publish in the scientific literature; Stern (1999) finds that firms that allow publication can command an average wage discount of about 25% in the scientific labor market.

Furthermore, science-based firms often have close relationships with academic scientists, and firms often provide funding for academic research in areas of interest to the firm or hire academic scientists as consultants. Blumenthal et al. (1996) surveyed over 200 firms

in the life sciences and found that almost 90% of such firms hire academics on a consulting basis, almost 60% sponsor academic research projects directly, and over a third support students with grants, fellowships, or scholarships. Most pharmaceutical firms conduct clinical trials through academic hospitals, but only 2% of firms in the sample sponsor no research other than clinical trials. All told, Blumenthal et al. estimate that firms provided about $1.5 billion, or about 11.7%, of the funds supporting academic research in the life sciences in 1994. Furthermore, they estimate that firm returns (measured by patent counts, product counts, or sales) per dollar invested in academic research are similar to returns on research conducted elsewhere. It is therefore likely that, consistent with traditional economic theory, firm-sponsored academic research and firm-conducted research are about equally productive at the margin, and firms have chosen a profit-maximizing level of sponsorship of academic research. The authors also conclude, since the dollar amount of firm-sponsored academic research is much less than the dollar amount of government-sponsored research, that industry could not make up the difference in the case of federal cutbacks. However, there is no evidence given for this except the levels of funding themselves. On the contrary, it is possible that if government-sponsored research projects are infra-marginal from the point of view of industry, then industry might well find it worthwhile to make up the entire amount. A rational case for government funding must be made on the basis of the public-good nature of research, excessive risk aversion, or some other economic factor, rather than simply a desire to maintain the current, possibly arbitrary, level of funding.

David, Hall, and Toole (2000) specifically address the question of complementarity and substitution. They survey 30 previous studies of the question, of which 21 found at least some evidence of complementarity, seven found at least some evidence of substitutability, but seven of which found mixed or insignificant results. Still, of the 30 studies, only five dealt with government research grants (as opposed to direct-to-firm contracts or subsidies). Of these, four found complementarity and one had mixed results. All of these are cross-industry

or cross-country studies; none deal specifically with biomedical research or pharmaceuticals.

David and Hall (1999) construct a theoretical model of interaction between public and private R&D which predicts that whenever the supply of inputs to the R&D process is less than infinitely elastic (which is probably always true in the short run), increased public spending on R&D, whether through grants, contracts, or subsidies, must necessarily raise prices and "crowd out" private R&D spending — unless the public spending has stimulatory effects that increase the demand for private R&D inputs by enough to compensate. This is consistent with Goolsbee's (1998) finding that a large portion of federal R&D spending accrues to increased salaries for scientists and engineers rather than to more research.

3.2 Direct Subsidies of R&D

Most previous work related to the effect of government R&D spending focuses, not on government research programs as such, but rather on the effect of government research contracts, R&D subsidies, or tax credits awarded to for-profit firms.

Joglekar and Hamburg (1983, 1986) point out that the overall share of basic research performed by private industry has fallen substantially during a period when the amount of government-funded basic research has been increasing. Therefore, effectiveness of government spending in stimulating private spending appears to be limited at best. That is, the elasticity of private research spending with respect to government basic research spending is certainly less than one. It may even be less than zero (which would indicate crowding-out), but we cannot conclude this merely from the fact that private research constitutes a smaller share of a larger total. Joglekar and Hamburg (1983) construct a theoretical model of an industry with many risk-averse firms that divide their resources between appropriable ("applied") and inappropriable ("basic") research. They find that the unaided level of private basic research is socially suboptimal, but government provision of additional basic research

spending is counterproductive in the sense that it causes firms to reduce their spending on basic research and increase spending on (appropriable) applied research. They find that if the government provides matching funds for basic research, the firms do spend more on basic research, but only slightly more. Joglekar and Hamburg (1986) also find, consistent with the "free-rider" problem associated with basic research, that deviation from the optimal level of basic research increases with the number of firms in the industry. Furthermore, they find that, contrary to intuition, increasing firms' risk aversion brings the industry *closer* to the socially optimal level of basic research (thus decreasing the need for government support).

Levin and Reiss (1984) used National Science Foundation (NSF) data on R&D in twenty manufacturing industries in three Census of Manufactures survey years (1963, 1967, and 1972) to estimate both the effect of the ratio of government R&D to sales in an industry on the private R&D-to-sales ratio and the elasticity of unit cost with respect to a firm's R&D expenditures. They find that an increase in the government-R&D-to-sales ratio is associated with a small increase in the private-R&D-to-sales ratio in the same year and a small decrease in the elasticity of unit cost in the same year. In their data, "government R&D" includes not only government grants and subsidies, but also R&D done by private firms under government contract, in which R&D is essentially a good purchased by the government or an essential input to such a good. Also, since they use data available only at three five-year intervals, they do not include any lagged effects at all. This is an important issue, since it is not unreasonable to expect that R&D expenditures in one year might not have an effect until several years into the future.

Mansfield and Switzer (1984) surveyed "senior R and D officials" of twenty-five firms in the eastern United States and asked them how they would respond to a reduction in the amount of government R&D funding going to their firms. Specifically, the officials were asked to estimate the change in their firm's company-financed energy-related R&D in each of two years following a hypothetical 10% reduction and a hypothetical 10% increase in their

firm's receipts of energy-related government R&D funding. Not surprisingly, the officials reported an average decrease in their own R&D following a decrease in federal funding (of 25 cents per $1.00 of federal cut) and an increase in company-financed R&D in the event of an increase in federal funding (of 6 cents per $1.00 of federal increase).

Leyden and Link (1991) consider the question of crowding-out to be a closed one. They title their article, "Why are governmental R&D and private R&D complements?" and proceed to develop a theoretical model to explain the complementarity through something called "infratechnology" which "is used to facilitate the R&D process ... [It] may be embodied in such things as structures used for R&D activities, equipment, or pre-existing knowledge used to understand, characterize, or interpret the R&D process." In other words, "infratechnology" is used to produce technology; the products of government-funded and privately-funded R&D are complements in production in the sense that "infratechnology" used for one can then be used for the other.

Irwin and Klenow (1996a, 1996b) examine in some detail an example of a U.S. government program specifically designed to use public funds to increase the level of R&D above the (presumably suboptimal) equilibrium level and reduce duplication of research effort in a specific industry. In 1987, fourteen U.S. semiconductor firms and the federal government formed an R&D consortium called Sematech, to conduct research to improve semiconductor manufacturing technology. The idea was for the government to fund half the cost of the consortium to increase the level of R&D funding, and for firms to share their knowledge with each other in order to reduce wasteful duplication of effort. The authors find that under this regime, member firms did in fact reduce their total R&D expenditures (including contributions to the consortium) relative to those of non-member semiconductor firms, consistent with the hypothesis that firms can share costs that would otherwise be duplicated across firms. Although three firms left the consortium at various times, the fact that the remaining firms continued to fund Sematech after the U.S. government ended its subsidy

in 1996 indicates that elimination of cost-duplication was believed sufficient to justify the consortium even without subsidization.

Wallsten (2000) investigates the effects of the U.S. Small Business Innovation Research Program (SBIR) program. The SBIR program is intended to fund research by small firms that may face capital constraints that render them unable to exploit socially and privately profitable research opportunities, and thereby to increase total R&D effort by small firms. Wallsten finds that there is a positive correlation between SBIR grants and firm employment, but his model cannot determine whether firms that receive grants have more researchers or whether firms that have more researchers receive more grants. Furthermore, he finds that both the number and magnitude of SBIR grants are negatively correlated with firm-financed R&D. In a regression with firm-financed R&D expenditures as the dependent variable, his estimate of the coefficient of SBIR research dollars is -0.82, indicating nearly dollar-for-dollar crowding out of private expenditures by government grants. In fact, he finds that we cannot reject the hypothesis that the true coefficient is -1.00, that is, that SBIR grants "crowd out" firm R&D expenditures dollar-for-dollar.

Gans and Stern (2000) also investigate the effects of the SBIR program. They find that the performance of projects funded by SBIR is highest in industries that also have the highest level of venture capital financing. This may indicate that the SBIR program is probably funding infra-marginal projects, perhaps because program administrators have incentives to fund projects that appear likely to produce successful innovations and therefore fund projects that also happen to have higher expected private returns. These projects, of course, are those most likely to be able to attract funding from the private sector, precisely because they have higher expected private returns. Thus, the incentives faced by SBIR program administrators have the effect of minimizing the actual impact of the SBIR program on R&D expenditures, since they induce funding decisions that selectively crowd out, rather than complement, private investment.

On a more optimistic (for proponents of R&D subsidies, that is) note, Lach (2000) studies the effects of an R&D matching-fund subsidy program in Israel and reports that a marginal dollar of government R&D funding increases private R&D expenditures by an average of 41 cents. While this is less than half the "one-for-one" matching that is the nominal requirement of the subsidy program, at least the subsidy does appear to complement rather than crowd out private funding.

3.3 Government Research Grants

The studies cited above generally concentrate on effects of direct subsidies to firms or, in some cases, R&D conducted by firms under contract to the federal government. In this paper, the primary concern is how private research is affected by research conducted directly by government agencies or funded by the government and conducted by non-profit organizations such as universities. There are far fewer previous studies on this topic.

Levy and Terleckyj (1983) examine effects of both aggregate federal contract R&D spending and aggregate federal basic research grants through organizations such as the National Science Foundation and the National Institutes of Health on the levels of aggregate privately-funded R&D. They find that while contract spending has a large and statistically significant complementarity with privately-funded R&D (increasing contract R&D by $1.00 increases private R&D by 27 cents), the effect of grant R&D on private R&D has a regression coefficient that is negative, small and statistically insignificant, indicating a lack of complementarity and possibly a small substitutability. While their data does not allow for precise estimation of the lag structure, they did find a small positive effect of grant R&D after a lag of three years.

Diamond (1999) finds a positive relationship between aggregate federal basic research spending and aggregate private R&D spending in all subject areas reported by the National

Science Foundation; however, he uses only first differences, does not control for any other variables, and (since the unit of observation is research in a subject area) does not consider that different levels of funding may lead to different outcomes in different fields of research.

In one of the few empirical attempts to measure the effects of the government funding on R&D markets, Goolsbee (1998) pointed out that about two-thirds of R&D expenditures go to wages for scientists and engineers. Because of the long training period required to enter the research labor market, he notes that the supply of research scientists and engineers is rather inelastic, so increases in government R&D spending will increase the salaries of the researchers. This means that observed increases in expenditures reflect an increase not only in the quantity but also in the price of innovation. Using wage data from the Current Population Survey, Goolsbee estimates that a 10% increase in R&D spending results in about a 3% increase in income for researchers. Depending on the distribution of federal subsidies among scientific fields, as much as 30-50% of federal R&D spending may accrue to increased salaries for scientists and engineers rather than to a higher quantity of research. In addition, since privately- and publicly-funded researchers are hired in the same market, federal research spending increases the price of R&D for private firms, thus directly crowding out private R&D.

4 Research and Regulation in the Drug Industry

Research in the biomedical and pharmaceutical fields differs from research in other fields in several important ways, First, pharmaceutical innovation in the U.S. is subject not only to the regulations of the patent system, but also to the much more detailed and stringent regulations of the Food and Drug Administration (FDA). In order to implement their regulations, the FDA collects a lot of scientific data, which become public once a drug is approved. Furthermore, biomedical research is one of the few fields in which private and government

R&D expenditures are both large and of approximately the same order of magnitude, and the government component consists almost exclusively of grants to researchers at non-profit institutions (such as universities), as opposed to contract research or research aimed at a product of which the government will be a consumer, as is the case, for example, in aerospace and other defense-related industries.[10]

4.1 Regulation of Drug Research in the U.S.

Prior to 1962, drug development was regulated by the FDA according to the Food, Drug, and Cosmetic Act of 1938.[11] A firm wishing to market a new drug would submit a New Drug Application (NDA) to the FDA. The FDA had a statutory maximum of 180 days to evaluate the application and determine whether the application demonstrated that the drug was safe for use according to the proposed labeling. If the FDA did not act to block a new drug within 180 days of application, the firm could market the drug. The only requirement was to demonstrate that, if used as directed, the drug would not harm the patient; there was no requirement to prove to the satisfaction of the FDA that the drug was effective for treating any particular ailment.[12]

In 1962 out of concerns regarding wasteful duplication of research effort, possible collusion in violation of antitrust laws, and, finally, the approval of thalidomide in Europe and Canada,[13] Congress passed the 1962 Kefauver-Harris Amendments, which thoroughly

[10] The R&E tax credit, described above (page 10), can be applied to corporate pharmaceutical R&D with the usual limitations. There is also a more advantageous credit for so-called "Orphan Drugs" described in Section 4.3 (p. 31) below.

[11] This discussion is primarily based on Peltzman (1973) and Grabowski, Vernon, and Thomas (1978).

[12] This is still, more or less, the requirement for nutritional supplements. Companies may market nutritional supplements without proving efficacy as long as they do not claim in their marketing that the supplements actually "treat, cure or prevent any disease." Still, Dranove (1998) has noted that even the requirement to prove safety, if too strictly enforced, can lead to an underinvestment in R&D of preventative medicine, since it increases the liability risk and decreases the return involved in treating healthy individuals.

[13] The role of thalidomide in the passage of the "proof-of-efficacy" requirement is somewhat ironic. As Peltzman (1973) points out, the FDA *did* block introduction of thalidomide into the U.S. under the existing "proof-of-safety" requirement. This would have made the "proof-of-efficacy" requirement irrelevant, even though thalidomide was effective for some of its intended uses. Even more ironically, the story has now

overhauled the 1938 Act and greatly increased the role of the FDA. The time limit for FDA approval was removed, and manufacturers would thenceforth be required not only to prove their new products safe for use, but also to prove that new drugs were effective in providing treatment for the diseases for which they were marketed, according to a testing procedure that itself had to be approved in advance by the FDA.

New drug development is now a thoroughly sequential process, which makes it particularly amenable to study.[14] A pharmaceutical firm will often develop and screen thousands of compounds in search of one with desired biochemical properties, for example, one that inhibits a chemical process critical to some disease. When a particular compound shows promise, it is tested for biochemical efficacy and possible toxicity first *in vitro* and then in animals. Generally a patent is applied for at this stage, so the firm can establish exclusive rights to the compound. Next, the firms files an Investigational New Drug Application (IND) with the FDA. Unless the FDA acts to block the IND within 30 days, the firm may begin human (clinical) testing.

Clinical trials are generally divided into three phases.[15] During Phase I, the drug is usually tested in a small number of healthy individuals (without the target disease) in order to determine safe dosing levels, measure absorption rates, and rule out toxicity and severe side effects. Phase I may last only a few weeks but is critical to rule out toxicity in humans (Wiggins 1981a). The FDA may stop a Phase I trial at any time for reasons of safety (Center

come full circle: The FDA approved thalidomide in July 1998 for treatment of erythema nodosum leprosum (leprosy), and promulgated extremely strict regulations governing its distribution, intended to make sure the drug is not taken by pregnant women.

[14] The drug development process, particularly once the FDA Approval process is started, is well-documented in numerous sources, particularly *The CDER Handbook* published by the FDA Center for Drug Evaluation and Research. The FDA also maintains a web page with information on how to file applications, at `http://www.fda.gov/cder/regulatory/applications/default.htm`. There is also an excellent summary of the process in DiMasi, Hansen, Grabowski, and Lasagna (1991).

[15] Actually, there is also a Phase VI, "post-marketing surveillance." After a drug is approved by the FDA, the manufacturer is required both to track "adverse drug reactions" (ADRs) and to report them to the FDA. Occasionally, the FDA will force a firm to withdraw a drug from the market if ADRs are too frequent and/or too severe. Sometimes, the decision to withdraw a previously approved drug may be influenced by the subsequent approval of a drug that is equally (or more) effective but has fewer or less severe known side effects or reported ADRs.

for Drug Evaluation and Research, (1998), p. 8).

During Phase II, the drug is tested for efficacy and short-term side effects in several hundred patients with the target disease. These tests can run several years and cost millions of dollars (Wiggins 1981a; DiMasi et al. 1991). If Phase II is successful, the drug enters Phase III, in which it is tested in a large number of patients (generally a few thousand) to obtain more detailed efficacy results, to determine the frequency and severity of side effects, and in particular to detect more unusual side effects that would not likely be detected in the smaller samples used for Phases I and II. Concurrent with Phases II and III, the firm generally conducts long-term animal toxicity tests at several times the equivalent human dosage to rule out side effects that might occur as a result of long-term use of the drug. This is obviously particularly important for drugs intended to treat chronic illnesses.

After the completion of Phase III, the company files a New Drug Application (NDA) with the FDA, formally requesting approval to market the drug for a particular use. The FDA then either requests more tests or approves or denies the application. If the FDA decides to approve the application, there is generally an extensive negotiation between the firm and the FDA over the precise content and wording of the packaging, the "label" (i.e., the information sheet inserted into the box that the drug is sold in), and the information that the company will provide to physicians and patients when marketing the drug. Every single piece of information and every health claim made in the course of marketing the drug must be approved in advance by the FDA. Furthermore, if the firm wishes to market the drug for another "indication" (i.e., another use for the drug, e.g., to treat a different disease), it must submit a new NDA. While it is perfectly legal for a physician to prescribe an approved drug for any use, the manufacturer may market the drug only for the FDA-approved use.

4.2 Effects of the 1962 Drug Amendments

Needless to say, the post-1962 drug approval process turned out to be extremely costly both in time and money. DiMasi, Hansen, Grabowski, and Lasagna (1991) surveyed twelve U.S.-owned pharmaceutical firms and estimated that the entire process took an average of 68.6 months from the beginning of Phase I clinical testing to submission of the NDA, and a total 98.9 months until approval of the NDA. That is, a typical drug spends over eight years in the testing-and-approval process, including over two and a half years waiting for FDA approval after testing is complete. In addition, DiMasi et al. estimate that the discounted present value of the expected cost to drug companies of the entire testing-and-approval process is over $17.3 billion (constant 1987 dollars[16]). Note that this is the cost of the clinical testing and regulatory process only, and does not include the costs of R&D to develop the compound in the first place — and it is the average cost per drug approved, not per drug tested, considering an estimate that only 23% of drugs that enter human trials are eventually approved. In fact, Dranove (1991) conjectures that, including both direct costs incurred by drug companies and the costs of basic research performed at universities and funded by the government, the "full cost" of developing a new drug is probably double the estimate of DiMasi et al., which includes only direct costs.

There is no disputing that the costs of bringing a drug to market are high, and increased significantly after the passage of the 1962 Amendments. Based on only the first seven years of post-Amendments data, Baily (1972) estimated that the expected (steady-state) annual development costs had increased by 136%, and the number of new drug introductions had decreased to about a third of its previous level. His figures correspond to an increase of over 500% in the cost per new drug.

In a much more detailed study, Peltzman (1973) found that the increased compliance

[16] Constant dollars according to the GDP implicit price deflator, not the BRDPI used for calculations in this paper.

costs were associated with a significant reduction in the rate of innovation, as measured by new drug introductions. For example, in the twelve years ending in 1962, there were an average of 41.5 new chemical entities (NCEs)[17] introduced per year, and that number was trending slightly upwards. In the eight years after 1963, the average was 16.1 NCEs per year, and trending downwards. This may not necessarily be a bad thing — recall that the purpose of the amendments was to prevent ineffective drugs from reaching the market, so we would expect that the number of drugs reaching the market would drop. The question is whether there is any evidence that the reduction is caused by the elimination of ineffective drugs, rather than by the increased cost of bringing effective drugs to market. Peltzman also demonstrates that there is no significant difference in the demand for drugs based on whether they are introduced before or after 1962, either for individual buyers or for (presumably better-informed) hospital buyers; in fact, hospitals even increase their demand for pre-1962 drugs as those drugs stay on the market longer and more information about their efficacy becomes available. This seems to imply that average efficacy of drugs did not increase after the proof-of-efficacy requirement was imposed. Even with generous assumptions used to calculate the social savings from reducing wasteful spending on ineffective drugs, the foregone benefits due to reduced innovation are several times higher than an upper bound on waste avoided.

Grabowski, Vernon, and Thomas (1978) also try to measure the effect of the 1962 Amendments on the rate of new drug introductions, but instead of comparing the periods before and after 1962, they compare drug introductions in the U.S. in 1960-1974 to those in the U.K. in the same period. The reason for this is to allow for the possibility that perhaps some other factor besides the 1962 regulations was responsible for the decline in U.S. drug introductions, one that might have similarly affected U.K. drug introductions. The authors

[17] "New chemical entities" (NCEs) are chemical compounds being introduced for the first time as drugs. There are other new drug introductions (i.e., NDA approvals), including combinations of existing compounds, and existing compounds approved for treating additional diseases.

mention several possible alternative explanations, including a "depletion of research opportunities" due to rapid drug development in the recent past, the thalidomide episode's possible effect on the public's demand for new drugs and firms' willingness to supply in the face of liability risk, and non-regulatory reasons for higher development costs. The authors do not mention any reason they have to believe that any of these factors suddenly appeared in 1962, though they seem to believe these factors might explain the sudden drop in U.S. drug introductions the following year. Their data, however, show that U.S. drug introductions slowed considerably relative to U.K. introductions, a fact which they conclude can be explained only by a change in the U.S. regulatory regime. This explanation is further supported by the existence of strong complementarities in production of drugs in both countries.

Wiggins (1981b) moves beyond the 1962 Amendments to try to examine the effects of regulation on drug innovation in a more general way. He notes that the FDA has six different divisions, each of which evaluates drugs in different therapeutic categories, and the divisions have different standards for judging efficacy. Thus, it would be reasonable to expect that we could find measures of "regulatory stringency" that would show different effects for different types of drugs. For each therapeutic category, he uses the average NDA approval time as a "regulatory stringency" variable. He then combines this with data from the Pharmaceutical Manufacturers' Association (PMA, since renamed Pharmaceutical Research and Manufacturers of America, i.e., PhRMA) on R&D expenditure by therapeutic category. There is, of course, not a perfect correspondence between the PMA/PhRMA categories (which correspond to five-digit SIC codes) and the FDA drug divisions, but FDA data are available at the level of individual drugs and PMA/PhRMA data are not. Wiggins sorts the drugs into PMA/PhRMA categories and relies on their being roughly correlated with FDA divisions. He then estimates the number of NCEs per category per year as a function of lagged R&D expenditure and lagged regulatory stringency in that category. He finds that a reduction in average delay time (and other stringencies associated with delay time) of six months would

result in the long run in the introduction of about one additional drug per therapeutic class per year. Furthermore, his findings are robust to the specification of the lag structure, and the sixth lag of regulatory stringency and the fifth lag of firm R&D expenditures fully characterize the lag structure. In fact, his final estimates are based only on these particular lagged values.

In a subsequent paper, Wiggins (1983) estimates the impact of regulatory stringency on firm R&D expenditures. He points out that since the 1962 Amendments had an immediate negative effect on drug approvals, one might expect them to have had an immediate negative effect on firms' research expenditures as well. He finds, however, that the effect on R&D expenditures was experienced over several years, and he attributes this to the difficulty firms faced in predicting how the FDA would implement the new legislation. For example, prior to 1962 a firm might have relied on the judgment of a panel of "expert" physicians to determine whether a drug was sufficiently effective to market. When the amendments were passed, there was no way to anticipate that the FDA would not merely examine the testimony of the applicant firm's experts or appoint their own panel of experts to provide independent testimony. The elaborate clinical testing procedure the FDA adopted to determine efficacy was not necessarily foreseeable. Furthermore, it was clearly impossible to tell how strict the FDA would be in evaluating claims of efficacy, regardless of what procedure they used for evaluation. Wiggins estimates a regression equation for research expenditures based on current sales and lagged regulatory stringency. He uses a Chow test to reject the hypothesis that the coefficients for regulatory stringency are the same for both the 1960s and 1970s; then he estimates each set of coefficients separately. He finds that the coefficients for regulatory stringency are both small and insignificant for the 1960s (i.e., the first seven years post-Amendments), but large, significant, and negative for lags two through five in the 1970s. In particular, he finds that a one-month increase in average delay in NDA approval for a therapeutic category induces no reduction in R&D expenditures in the following year but

does induce a reduction of $486,000 in the second year, $733,000 in the third year, and so on, for a total reduction of over $2.6 million by the fifth year (standard error of $0.47 million). It is estimated that eliminating the increase in regulatory stringency from pre-1962 levels would increase total R&D expenditures by 24% from its actual level.

Thomas (1990) finds that almost all the reduction in NCE introductions after 1962 is accounted for by elimination of small firms from the new drug market. This is attributed to the increase in the cost of obtaining NDA approval. Although U.S. firms suffered a severe productivity reduction, elimination of competition from small firms allowed surviving firms to increase prices, and possibly even profits, above what they would have been otherwise able to achieve.

4.3 The Orphan Drug Act of 1983

There have been some significant changes to drug regulations since 1962, though nothing on the scale of the Kefauver-Harris Amendments. One of the problems with the high cost of bringing drugs to market is the often insufficient incentive to invest in research to cure rare diseases, since it would be difficult to recover the cost of such research by selling a drug to only a few people. One attempt to mitigate this problem is the Orphan Drug Act (ODA), which became law in 1983.[18] This act defines as an "orphan drug" any drug intended to treat a disease that afflicts fewer than 200,000 persons in the U.S., or that otherwise afflicts so few people that expected U.S. sales will not cover expected R&D costs. The FDA designates drugs as meeting these requirements upon application from a firm that wishes eventually to introduce the drug.

The ODA provides two major incentives for development of orphan drugs. First, it establishes a seven-year period of exclusive marketing of the designated drug for the "orphan"

[18] This discussion is primarily based on Reaves (1995).

indication, independent of the patent status of the drug. This increases the likelihood that a firm will find it profitable to file an NDA for an additional "indication" (i.e., an additional use) of an already-existing compound even if the compound is in the public domain or there is little time left until the patent expires.[19] The marketing exclusivity pertains to a particular substance for a particular use — that is, if a drug designated an "orphan drug" is later approved for use, the manufacturer will have the exclusive right to market that particular drug for the particular approved indication for seven years, even if that period extends beyond the expiration date of the firm's patent on that drug or if the drug was in the public domain (i.e., not patentable) to start with. Second, the ODA provides firms developing orphan drugs with a 50% tax credit for expenses incurred for clinical trials after a drug receives the orphan drug designation. Since firms generally apply for and receive orphan drug status near the beginning of Phase I, this amounts to the federal government's paying a substantial portion of the cost of clinical trials. Firms may also apply to the FDA for grants from a limited budget to conduct clinical trials for already-designated orphan drugs.

Reaves (1995) reports that in the decade prior to enactment of the ODA, only ten drugs that would have qualified as orphan drugs under ODA were approved for marketing by the FDA. In the first decade after ODA, over 400 substances received the orphan drug designation, and over 100 designated orphan drugs were approved. Reaves also finds that smaller firms were more likely to increase orphan drug efforts than large firms.

[19] If a firm has received an "orphan drug designation" for a substance, it is illegal for other firms to market that substance for that specific use. In other words, if a firm finds that aspirin or table salt cures some rare disease, it can file an NDA. If approved, the firm cannot prevent others from selling aspirin or table salt, but it can prevent them from advertising that their aspirin or table salt cures the rare disease for the seven-year "exclusive marketing" period. In addition, the same or a different firm may apply for orphan drug designation and the exclusive marketing that goes with it for the same substance to treat a different disease, not to mention a different drug to treat the same disease. Originally, the ODA applied only to these non-patentable drugs; in 1985 it was amended to apply to patented drugs as well.

4.4 The 1984 Waxman-Hatch Act

One of the main drawbacks of the 1962 Amendments was the increase in the length of time from development of a new drug to its introduction to the marketplace after FDA approval. This is a drawback from two points of view. On the "demand" side, consumers are deprived of potentially useful drugs for an extended periods, as noted by Peltzman (1973). On the "supply" side, this reduces the incentive for innovation, as producers are deprived of a significant amount of patent protection. Firms apply for patents after the compound is first synthesized but before beginning clinical (or even animal) trials. When patents are valid for a fixed term of 17 years,[20] adding time to the FDA review process reduces the period of exclusive marketing by an equal amount. This in turn reduces the effective length of the patent and thus the value of the innovation to the producer. According to Grabowski and Vernon (1986), the average effective patent term for new drugs in 1984 was about half the statutory term of 17 years. A decade later, Ward and Dranove (1995) reported that the delay between patent to NDA approval in their sample ranges from four to twelve years.

A countervailing problem is that once the patent expires, in principle anyone ought to be able to make and sell the drug. (These post-patent drugs made by different firms are called "generic" drugs.) Indeed, the implied contract of the patent system is the grant of a limited-time monopoly in exchange for full disclosure of the innovation to enable low-cost imitation after the monopoly expires. However, unlike the information contained in patents, evidence of safety and efficacy submitted in support of an NDA is, under the 1962 Amendments, considered a trade secret and may not be legally revealed by the FDA to the public. Furthermore, since approval of an NDA is approval for a specific firm to market a specific drug, the same chemical compound marketed by a different firm is, for purposes

[20] This is the case for all patents granted between 1861 and 1995. In 1995, to meet the requirements of the General Agreement on Tariffs and Trade (GATT), Congress changed the patent term from 17 years from the date of issuance to 20 years from the date of filing (i.e., application). In 1999, Congress provided for adjustments to the expiration date to compensate inventors for delays in the application procedure.

of regulation, a different drug. The result is that, not only would a subsequent producer have to submit a new NDA, but that producer would have to duplicate the testing, possibly including the entire clinical trials process (if the results had not been published) in order to establish the safety and efficacy of drug chemically identical to one already on the market. This replication is clearly socially wasteful, both in time and resources.

The second major change since 1962 was the Drug Price Competition and Patent Term Restoration Act of 1984, also known as the Waxman-Hatch Act, which addressed both these issues. First, the Act increased the effective patent life of approved drugs by an amount equal to the time spent by the FDA in reviewing the application plus half the time spent in clinical trials, up to a maximum of five years beyond the normal patent expiration date and a maximum of 14 years of effective patent life.[21] Second, the Act eliminated the need for duplicate testing by requiring imitators (after patent expiration) to prove only that a "generic" drug was bioequivalent to the previously approved drug. Grabowski and Vernon (1986, 1996) found that most brand-name drugs lost half to two-thirds of their market within two years of patent expiration and estimated that, while the Act substantially increased patent protection and lowered post-patent entry barriers, the net effect on the Net Present Value (NPV) of innovators was about even, with consumers benefiting from lower prices resulting from the introduction of more generic drugs.

4.5 Biomedical Research: Government Grants and Private R&D

Despite the obvious importance of research to the pharmaceutical industry, the significant roles of both the federal government and private firms in conducting this research and the abundant treatment of research issues in general and of the pharmaceutical industry in particular, it is surprising how little work has been done on the interaction between federal

[21] Note that the maximum "guaranteed" effective patent life is *less* than the statutory patent term.

and private research in this field. Fewer of these studies address the main issue in this paper: whether publicly-funded research stimulates (complements) or crowds out (substitutes) private research.[22]

Lichtenberg (1999a) examines federal biomedical research grants at the project level. His is one of the few studies that do not take government funding to be exogenous; on the contrary, the goal of the study is to predict government funding as a function of disease prevalence and severity. He finds that federal expenditures on research related to specific diseases is strongly positively correlated with the total number of life-years lost to those diseases before age 65, and federal expenditures on research related to chronic conditions is strongly positively correlated with the number of people whose activities are limited by those conditions.

Cockburn and Henderson (forthcoming) survey a number of studies of the effects of public research on the pharmaceutical industry. They delineate several plausible routes by which publicly funded basic medical research can help drug companies and increase the productivity of the pharmaceutical industry. They conclude that the overall rate of return from public funding of biomedical research is very high, perhaps as high as 30%. This not out of line with other estimates, though it is lower than estimates derived by Murphy and Topel (1999).

Carreón-Rodríguez (1998) applies distributed-lag regressions to estimate the effect of total expenditures of the NIH on total expenditures of U.S. drug companies as reported by PhRMA. Using no other variables and only aggregate spending figures, he finds that

[22] It is worth noting that pharmaceutical and biotech executives and their trade groups generally view public funding of biomedical research as a good thing, and Pharmaceutical Research and Manufacturers of America (PhRMA) actively lobbies for more of it (Pien 1999; Mullen 2000; PhRMA 2000). This would seem to imply that it is implicitly a subsidy of costs that would otherwise have to be incurred by drug and biotech firms. However, such a subsidy is potentially consistent with either substitution or complementarity. If publicly-funded research reduces the need for the private sector to do its own basic research, then public research will crowd out private research, and we will observe substitution. On the other hand, if public funding of basic research provides new opportunities for applied research, then public research will stimulate private research and we will observe complementarity. To further complicate matters, it is possible for both effects to occur simultaneously.

coefficients are significant at the 5% level up to the 14^{th}-order lag for the raw data, the 12^{th}-order lag for the de-trended series, and the fourth-order lag for the first differences.

The study that comes closest in intent to the present one is Ward and Dranove (1995). They treat pharmaceutical innovation as a flow of information through three stages: government-funded basic research, publication in medical journals, and industry-funded drug development. Their measure of government funding is the budget of the NIH, broken down into five categories based on the constituent institutes of the NIH. For publication, the measure is the number of articles listed in the MEDLINE database that reference drug therapy and can be categorized by disease. For industry R&D, they use the annual survey of the Pharmaceutical Manufacturers' Association (PMA) (since renamed Pharmaceutical Research and Manufacturers of America, i.e., PhRMA), which reports industry R&D expenditures broken down into seven therapeutic classes corresponding to five-digit SIC codes. This is the same data set used by Wiggins (1981b) and by the present author (though, of course, more recent papers use more recent data). Ward and Dranove find that NIH funding for a disease category is a positive predictor of medical publication in that category with near-unit elasticity: the estimated total effect of a 1% increase in NIH funding is a 0.95% increase in publications in the same category. In turn, industry R&D expenditures respond strongly to the number of journal articles; a 1% increase in articles corresponds to a 0.22-0.36% increase in expenditures in the same category. In addition, and more relevant to our interest here, Ward and Dranove report results of regressions of the logarithms of industry R&D expenditures on the logarithms of NIH expenditures (lagged 0-7 years) for the five PMA/PhRMA categories that can be linked to NIH institutes. A 1% increase in own-category NIH spending corresponds to a cumulative increase in PMA/PhRMA spending of 0.57-0.76% over seven years. Five of the seven lag coefficients are positive, but only the sixth-order lag is significant at the 5% level. When logarithms of NIH expenditures on *other* categories are included (also lagged 0-7 years), nine of the sixteen lag coefficients are

significant at the 10% level or better, and coefficients on four of the coefficients are negative (lags 2 and 3 of NIH own-category expenditures and lags 1 and 6 of NIH other-category expenditures).

5 From Research to Marketplace

Although the empirical results discussed in Section 8 show that there are correlations between private-sector and lagged government biomedical R&D expenditures, it would be useful to have a better picture of the pathway through which government-funded research might lead to private R&D spending and eventually to introduction of new products. In this chapter, we will review some existing qualitative studies linking public research spending to the private R&D process, as well as present as a case study the discovery of the cyclooxygenase-2 ("COX-2") enzyme and the subsequent development of COX-2 inhibitors for the treatment of rheumatoid arthritis and other inflammatory and COX-2-mediated diseases.

5.1 Previous Studies

It is well established that private-sector science-based firms sponsor academic research, including basic research in areas of interest to the firm. Blumenthal et al. (1996) surveyed over 200 firms in the life sciences and found that almost 90% of such firms hire academics on a consulting basis, almost 60% sponsor academic research projects directly, and over a third support students with grants, fellowships, or scholarships. In the case of pharmaceutical firms, some of this support includes clinical trials conducted by researchers in academic hospitals on behalf of those firms, but 98% of such firms in the sample sponsor other research as well. Blumenthal et al. estimate that firms provided about $1.5 billion, or about 11.7% of the funds supporting academic research in the life sciences in 1994.

As noted earlier, there are several studies that link patents to basic science based on the scientific articles cited on patent applications. For example, Narin and Olivastro (1992) found that pharmaceutical patents cited more science articles than patents in any other field, averaging 4.5 articles per patent. In a subsequent study, Narin, Hamilton, and Olivastro (1997) found that a significant and increasing fraction of patents cite government-funded scientific research, including research conducted at both government and academic laboratories. For example, of all scientific papers cited in U.S. patent applications in 1993-1994, 73% were authored at academic or government institutions, and a substantial majority of the academic papers acknowledged a government funding source. More recently, McMillan, Narin, and Deeds (2000) found that the connection between public science and the biotechnology industry was even stronger than for the traditional pharmaceutical industry.[23]

Although "basic science" projects are, by definition, undertaken without a specific commercial product in mind, sponsors of basic research often have as a general goal the development of specific types of knowledge and possibly specific social and economic outcomes. Managers of government agencies often have specific guidelines, mission statements, and goals, not to mention incentives to demonstrate that their programs are worthwhile and should be funded in the future.

This seems to have been the motivation for a study done by the staff of the NIH itself, entitled "NIH Contributions to Pharmaceutical Development: Case study analysis of the top-selling drugs" (National Institutes of Health 2000). This report points out that NIH funding plays a significant role in the training of biomedical scientists who later work in industry (as well as in academia), since research grants are often used by professors to fund the tuition and

[23] The distinction between the biotechnology industry and the pharmaceutical industry is arbitrary and imprecise. Firms regarded as "biotech firms" are typically small, new firms pursuing cutting-edge treatments, often with genetically-engineered drugs. Firms regarded as "traditional" pharmaceutical firms are typically large, older, and pursue treatments based on biochemically-derived drugs. Some people distinguish between the two based on research techniques, but many firms use both techniques. Some prefer to distinguish based on firm size, but there are large biotech firms (Amgen) and small pharmaceutical firms (Purdue Pharma LP). One of the more common practices is to distinguish based on the molecular weight of the firm's product. Of course, some firms produce products with both high and low molecular weights.

stipends of graduate students who are their research assistants. It then goes on to summarize the major events in the development of the "top five" drugs, as measured by worldwide sales in 1994. The five drugs are: Vasotec (for treatment of hypertension), Capoten (for treatment of hypertension), Zovirax (an antiviral agent), Prozac (an antidepressant), and Zantac (an anti-ulcer drug). In each case, early discoveries were made predominantly by academic researchers (who are mostly but not exclusively government-funded) and later discoveries were made predominantly by industry researchers. This pattern is again reflected in the development of COX-2 inhibitors.

5.2 Development of COX-2 Inhibitors

In this section, we will trace the development of an important new class of drugs developed over a decade or so and introduced to the market in 1999, with an emphasis on reviewing the sources of funding for critical pieces of research. These drugs represent a major advance in the treatment of rheumatoid arthritis and other inflammatory ailments, as they reduce pain and fever as well as inflammation, and may also reduce the likelihood of colorectal cancer. Essentially, these drugs have almost all the therapeutic effects of traditional "non-steroidal anti-inflammatory drugs" (NSAIDs) such as aspirin, ibuprofen, naproxen, and indomethacin, but with out the gastrointestinal side effects often experienced by long-term users of traditional NSAIDs.[24]

The term "non-steroidal anti-inflammatory drugs" refers to a long-established class of medications that reduce inflammation, pain, and fever. The term "non-steroidal" distinguishes these drugs from anti-inflammatory corticosteroids, which are much more powerful anti-inflammatory agents but have much more serious side effects. Common NSAIDs include aspirin and related salicylates, ibuprofen (sold, for example under trade names such as Advil

[24] In addition to specific references cited herein, this section is based on Simmons, Wagner, and Westover (2000), Vane and Botting (1998), DeWitt (1999) and conversations with Mr. Sumeet Sud, formerly of Merck & Co. and Mr. Reuben Ehrlich, formerly of G. D. Searle & Co.

and Motrin), naproxen (sold as Naprelan and Aleve), and indomethacin (sold as Indocin). Some common NSAIDs and COX-2 inhibitors are illustrated in Figure 1.

This class of drugs has been well-known for centuries. The first published "clinical trial" of an NSAID was in 1763, when Rev. Edward Stone read a report to the Royal Society on the use of willow bark extract to treat fever (Stone 1763). In the nineteenth century, it was discovered that the active ingredient in willow bark was salicylic acid, which was chemically synthesized in 1860 and subsequently commercialized as a treatment for fever and rheumatism (Vane and Botting 1998). Salicylic acid was effective, but had the side effect of upsetting the stomach and causing ulcers. In 1898, believing that the acidity of the compound was responsible for its ulcerative effect, Felix Hoffman of Bayer synthesized a compound in which the "acid" portion of the molecule was replaced with an acetyl group. This compound, acetylsalicylate, was introduced by Bayer in 1899 as aspirin (Dreser 1899). It turned out to have the same ulcerative side effects as salicylic acid, though to a substantially lesser degree.

By the 1960s, several new drugs with similar therapeutic effects had been discovered, including indomethacin, ibuprofen, and naproxen. However, despite the fact that these kinds of drugs had been in use for over two centuries, and not only had the same therapeutic effects but also the same side effects, the mechanism by which these drugs worked remained unknown until 1971, when the British researchers John R. Vane, J. B. Smith, and A. L. Willis discovered that aspirin and other NSAIDs block prostaglandin synthesis by inhibiting the enzyme Cyclooxygenase (COX), also known as Prostaglandin G/H Synthase (PGHS) (Vane 1971; Smith and Willis 1971), a discovery for which Vane shared the 1982 Nobel Prize in Medicine and was knighted in 1984.[25]

The initial discovery took place when Vane, Smith, and Willis were all in the Depart-

[25] Vane's paper and Smith and Willis' paper appeared back-to-back in the journal *Nature New Biology*. They were, respectively, the fourth and twentieth most-cited 1971 papers in the Institute for Scientific Information's *Science Citation Index* (Garfield 1973).

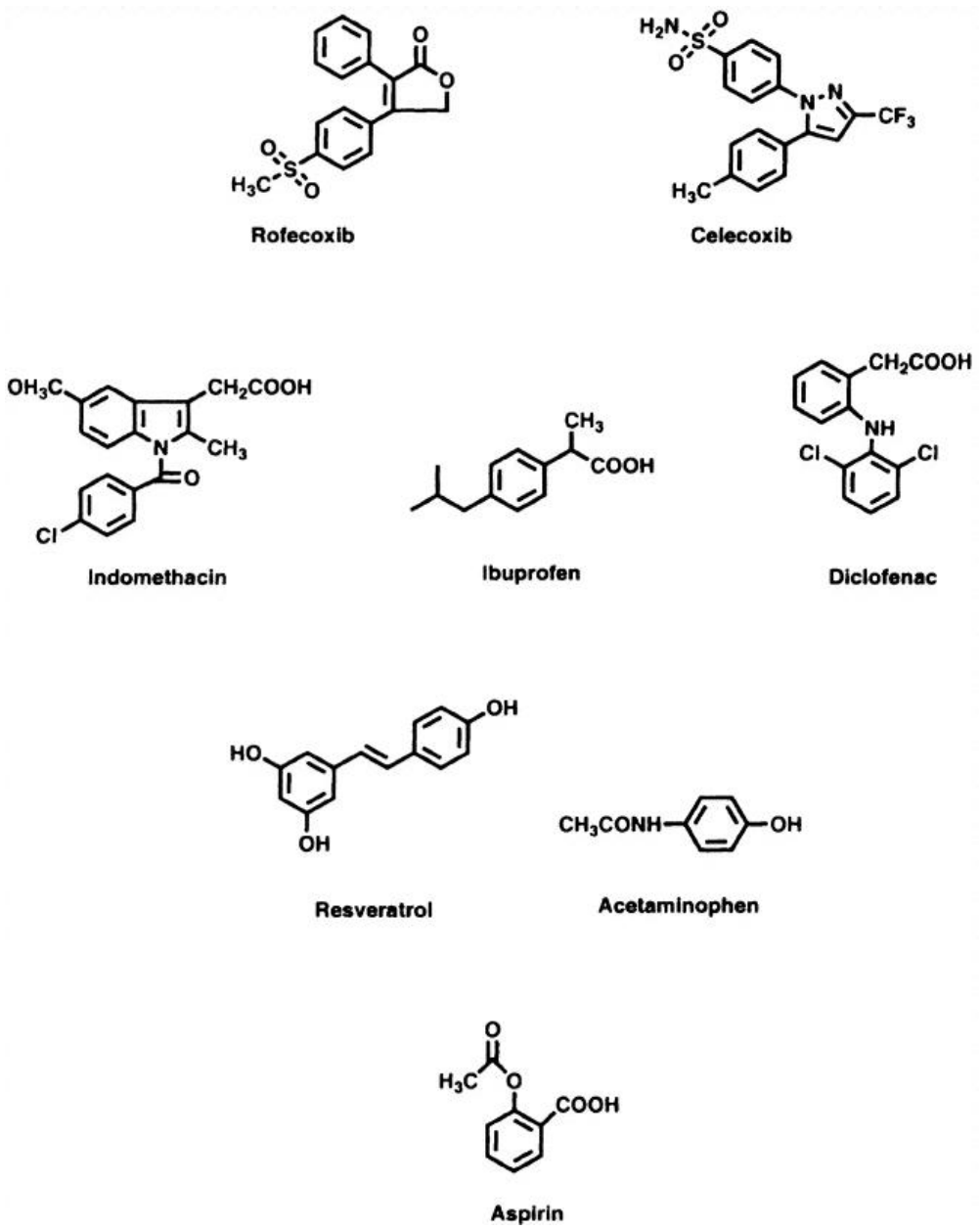

Figure 1: Chemical diagrams of important COX inhibitors and related drugs. Rofecoxib and Celecoxib are selective COX-2 inhibitors developed by Merck and Searle, respectively. Indomethacin, Ibuprofen, and Diclofenac are common non-selective COX inhibitors, known as Non-Steroidal Anti-Inflamatory Drugs (NSAIDs). Acetominophen has minimal anti-inflammatory properties, but is otherwise clinically similar to NSAIDs. Aspirin was the first large-scale commercially-produced NSAID.

ment of Pharmacology at the Royal College of Surgeons of England. Their work was funded by the Medical Research Council, and British Government organization roughly equivalent to the National Institutes of Health in the U.S. Vane also received funding from The Wellcome Trust, a private charitable foundation.[26] In 1973, shortly after making the critical discovery and in the midst of further work to refine the understanding of the relevant mechanisms, Vane left the Royal College of Surgeons and, taking a core group of colleagues with him, became Group Research and Development Director at The Wellcome Foundation,[27] where he continued his work in the private sector. It was at Wellcome, for example, that he and his group discovered prostacyclin, a prostaglandin produced in the walls of blood vessels that acts as a vasodilator and inhibits platelet aggregation. In 1986, Sir John left Wellcome and formed the William Harvey Research Institute, which is part of St Bartholomew's School of Medicine of the University of London. The University is funded by the British government, and the Institute also takes on contract research from clients through its affiliate, William Harvey Research Limited.

Vane's discovery helped explain why the same drugs both reduce inflammation and upset the gastro-intestinal system, since prostaglandin synthesis is involved in both processes. However, it gave no basis for finding a drug that would have the therapeutic effects without the adverse side effects. This research "log-jam" was not broken for almost two decades, until three university labs independently — and approximately simultaneously — discovered that there are actually two forms of cyclooxygenase (DeWitt 1999). The previously-known ("constitutive") form is involved in the workings of the digestive tract, and is now known as

[26] According to the Trust's web page, at `http://www.wellcome.ac.uk/en/1/awt.html`, it is "an independent research-funding charity, established under the will of Sir Henry Wellcome in 1936 ... funded from a private endowment." The Trust appears to have been, at the time of Vane's work, the sole shareholder in The Wellcome Foundation, the successor corporation to the company founded by Henry Wellcome. The Trust diversified its holdings in the 1980s and 1990s, eventually selling the company to Glaxo to form Glaxo Wellcome, which merged with SmithKline Beecham in 2000 to become GlaxoSmithKline. The Wellcome Trust claims to have no continuing special relationship with that or any other pharmaceutical company.

[27] Despite its name, The Wellcome Foundation was a private pharmaceutical company — the corporate successor to Burroughs Wellcome & Co. — not a charitable "foundation." The "foundation" bearing the founder's name was and is known as The Wellcome Trust (see above).

cyclooxygenase-1, or COX-1. The second, ("inducible") form is involved in the inflammatory process, and is known as cyclooxygenase-2, or COX-2.[28]

The three labs that discovered what is now known as COX-2 were all university labs funded by U.S. government grants and private foundations. The first group, led by Daniel L. Simmons of Brigham Young University, discovered a gene that produced COX-2 in murine fibroblasts (Xie et al. 1991). This work was funded by grant from the National Institutes of Health (NIH Grant CA42580) and a grant from the Bireley Foundation. (Simmons actually made the initial breakthrough while a post-doctoral fellow at Harvard, supported first by an NIH fellowship and subsequently by a fellowship from the Leukemia Society of America (Simmons et al. 1989).)

The second group, led by Professor Donald A. Young at the University of Rochester, was funded by two NIH Grants (DK16177 and CA47650) and the team included M. Kerry O'Banion, a recipient of a cancer research fellowship from the J. P. Wilmot Foundation, and Virginia Winn, a medical student at the University of Rochester (O'Banion et al. 1991; O'Banion et al. 1992). The University of Rochester applied for and was granted a patent on this discovery, which has become the basis for a lawsuit against the maker of the COX-2 inhibitor drug Celebrex. The university's patent specifically states that the work was conducted with government support, lists one of the grant numbers, and states that, "The government has certain rights in the invention."[29]

[28] Recently, some researchers has speculated that there may be a third form of cyclooxygenase, which has role in producing fever, and Simmon's group at BYU has isolated a third form. See, for example, Botting (2000), Simmons et al. (1999), and Willoughby et al. (2000) and **?**).

[29] The initial application for this patent was filed in 1992. This initial application and four subsequent applications were abandoned and replaced, with the final application being submitted June 7, 1995. This was prior to the grant dates, but after the filing dates, of the patents Searle and Merck received for Celebrex and Vioxx, respectively (see page 44). The Rochester patent (number 6,048,850) was finally approved on April 11, 2000 — over a year after Celebrex was introduced the the market, and almost a year after Vioxx was introduced. The Celebrex and Vioxx patents claim only the invention of specific drugs; the Rochester patent claims to cover the concept of selectively inhibiting COX-2. Within hours of receiving the patent, the University of Rochester filed a patent infringement suit against both Searle, which developed Celebrex and Pfizer, which was marketing it, claiming that the Celebrex patents were invalid and that Celebrex infringed the University of Rochester's patent on COX-2 inhibition. A federal court invalidated the patent, and as of this writing (Nov. 2003), the appeal is still pending. In an amicus brief in support of Rochester, two other

The third group, led by Professor Harvey R. Herschman at the University of California, Los Angeles, was funded by a Department of Energy research contract (DE FC03 87ER 60615) and three separate NIH grants: a traditional research grant to Professor Herschman (GM24797), an "NIH Health Physician Scientist Award" to Dean A. Kujubu, and an NIH predoctoral "Training Grant" to Brian C. Varnum, who received his Ph.D. in 1989 and went on to use his NIH-funded training in an industry job at Amgen, a biotechnology firm and member of PhRMA (Kujubu et al. 1991).

After these discoveries were made, at least five major pharmaceutical firms — Merck & Co., G. D. Searle & Co., Bristol-Myers Squibb, Novartis, and Johnson & Johnson — began privately-funded efforts to develop drugs that would selectively inhibit COX-2 without affecting the beneficial activity of COX-1. By 1994, both G. D. Searle & Co. and Merck & Co. had started to file for patents to protect compounds that were candidate drugs.

Searle's drug, now known as celecoxib (or by its brand name Celebrex), is protected by U.S. Patents 5,563,165 (issued October 8, 1996), 5,466,823 (issued November 14, 1995), and 5,760,068 (issued June 2, 1998), and was introduced to the research community by (Penning et al. 1997). The drug was approved by the FDA on December 31, 1998, and is currently marketed by Pfizer under an agreement with Pharmacia, which acquired Searle in 2000.

Merck's drug, now known as rofecoxib (or by its brand name Vioxx), was approved less than six months later on May 20, 1999. It is protected by U.S. Patents 5,474,995 (December 12, 1995) and 5,691,374 (November 25, 1997) and was introduced to the research community by (Prasit and Riendeau 1997). The Merck Vioxx team later published an explanation of their research process (Prasit et al. 1999), which described the design of the rofecoxib molecule as a derivative of DuP 697 (see below), with changes aimed at improving oral

universities claimed that "without basic research from the universities, the private sector will be unable to develop pharmaceutical compounds for the public."

absorption while preserving COX-2 selectivity, especially as compared with indomethacin.

Ironically, it turns out that before COX-2 was discovered, two other companies had NSAIDs already in development, which are now known to be selective COX-2 inhibitors (DeWitt 1999). E. I. du Pont de Nemours & Co. had a compound known as DuP 697, which the developers noted was effective against inflammation but produced no intestinal or gastric ulcers in animal studies (Gans et al. 1990). Likewise, Taisho Pharmaceuticals Co. in Japan developed a compound known as NS-398, which they claimed was potent against inflammation, pain, and fever, but produced "minimal stomach lesions" (Futaki et al. 1993). For some reason, development of both these compounds was discontinued, although the structure of DuP 697 became the starting point for the development of celecoxib and rofecoxib, which were eventually brought to market.

The funding of major steps in the development of COX-2 inhibitors, as indicated by landmark publications, is summarized in Table 1.

Despite the many valid criticisms of the so-called "linear model," in which government-funded basic research leads to privately-funded applied research and privately-funded product development, the linear model more or less describes what actually happened in the case of COX-2 inhibitors. COX-2 and its role in inflammation was discovered in academic laboratories funded by government grants and private foundations; as soon as the results became public, private firms funded further research, followed by development of products that took advantage of the publicly-funded research.

It should be noted that the success of the linear model in this case does not carry an unambiguous public-policy message. On the one hand, it might be argued that in this case public funding led to important products that will vastly improve public health, and thus created a net social benefit. However, it would be just as valid to argue that since private firms make substantial profits from these products despite paying only a portion of

Table 1: Major Steps in the Development of COX-2 Inhibitors

Year	Author(s), Affiliation	Source of Funding		Summary & Publication
		Type	Organization(s)	
1971	John R. Vane Royal College of Surgeons	Govt./ Fndn.	Medical Research Council, Wellcome Trust	NSAIDs work by inhibiting COX. *Nature New Biology* **231**:232–235
1971	J. B. Smith & A. L. Willis Royal College of Surgeons	Govt.	Medical Research Council	Aspirin inhibits COX. *Nature New Biology* **231**:235–237
1989	Simmons, et al. Harvard University	Govt./ Fndn.	Natl. Institutes of Health, American Business Cancer Res. Foundation	Discovery of a second COX-producing gene induced in chicken fibroblasts. *Proc. Natl. Acad. Sci. USA* **86**:1178–1182
1990	Gans, et al. DuPont Pharm. R&D Div.	Corp.	E.I. du Pont de Nemours & Co.	Powerful NSAID with no GI lesions (Predecessor to Vioxx and Celebrex) *Journal of Pharmacology and Experimental Therapeutics* **254**:180–187
1991	Kujubu, Herschman, et al. University of California, Los Angeles	Govt.	Natl. Institutes of Health, U.S. Dept. of Energy	Discovery of a second COX-producing gene induced in murine fibroblasts. *J. Biological Chemistry* **266**:12866–12872
1991	Xie, Simmons, et al. Brigham Young University	Govt./ Fndn.	Natl. Institutes of Health, Bireley Foundation	Breakthrough: Two forms of COX exist. *Proc. Natl. Acad. Sci. USA* **88**:2692–2696
1991- 1992	O'Banion, Young, et al. University of Rochester	Govt./ Fndn.	Natl. Institutes of Health, J.P. Wilmot Foundation	Breakthrough: Two forms of COX exist. *J. Biological Chemistry* **266**:23261–23267 *Proc. Natl. Acad. Sci. USA* **89**:4888–4892
1997	Penning, et al. G. D. Searle & Co.	Corp.	G. D. Searle & Co.	Description of celecoxib (Celebrex) *J. Medicinal Chemistry* **40**:1347–1265
1997	Prasit, et al. Merck & Co.	Corp.	Merck & Co.	Description of rofecoxib (Vioxx) *Ann. Rep. Medicinal Chemistry* **32**:211–220
1998	Searle's Celebrex approved by FDA, Dec. 31, 1998			
1999	Merck's Vioxx approved by FDA, May 20, 1999			

the development costs, public funding of the research that led to the discovery of COX-2 represents a significant subsidy to the pharmaceutical industry.

In a high-risk endeavor such as medical research, where hundreds or even thousands of projects must be funded for every one that eventually produces a noticeable impact on public health, it is impossible to evaluate the system of funding and profit incentives simply by examining instances of the relatively few research projects that are known *ex post* to have led to successful products. This is why statistical analyses of the effects of aggregate spending is an essential line of inquiry.

6 Data

6.1 Drug Industry Research

Data on private-sector research are collected by PhRMA, an industry group whose members include virtually all major U.S. firms conducting pharmaceutical research. PhRMA surveys its members annually[30] and publishes data on R&D spending by therapeutic category. These therapeutic categories correspond to the five-digit SIC codes used by the Census Bureau for reporting drug shipments (sales) in the Current Industrial Reports for the pharmaceutical industry. The relevant therapeutic categories, together with private and federal R&D spending and drug sales for the most recent year available, are listed in Table 2.

[30] Except 1984. Available data for 1984 include total budgeted R&D but not total actual R&D or breakdown by therapeutic category. Apparently, PhRMA did not conduct the survey for 1984, and current PhRMA staff (as of early 2000) said they do not know why. In order to avoid losing too many degrees of freedom in distributed-lag regressions, the 1984 values for each category are estimated here by linearly interpolating the share of R&D devoted to that category based on the 1983 and 1985 shares and then multiplying the estimated share by the total budgeted R&D.

Table 2: Therapeutic Categories for reporting Pharmaceutical R&D and Sales

SIC Code	Description	1996 ($mil) Private R&D	Federal Grants	Drug Sales
28341	Affecting neoplasms, endocrine system, and metabolic diseases	2,988.2	1,465.1	4,788.0
28342	Acting on the central nervous system and sense organs	3,071.3	1,669.0	10,123.1
28343	Acting on the cardiovascular system	1,937.7	1,062.0	6,911.9
28344	Acting on the respiratory system	908.4	430.2	4,993.9
28345	Acting on the digestive or genito-urinary system	417.0	859.3	8,494.4
28346	Acting on the skin	203.8	163.5	2,184.8
28348	Acting on infective and parasitic diseases	1,959.9	972.1	7,304.1

Sources: Pharmaceutical Research and Manufacturers of America; U.S. Department of Commerce, Bureau of the Census.

6.2 Government-sponsored Research

Data on publicly-funded biomedical research were obtained from the NIH, which has published on CD-ROM project-level data on virtually every biomedical research project funded by the federal government (through the U.S. Public Health Service) from 1972 to 1996. This database, called CRISP (Computer Retrieval of Information on Scientific Projects), includes both "intramural" projects of government organizations, such as the NIH and the FDA, and "extramural" projects, funded by grants to researchers at outside organizations, primarily universities and teaching hospitals. The bulk of the funding (82% in fiscal 1999) goes to extramural projects.

Each record in the CRISP database corresponds to a single project during a single fiscal year. (Multi-year projects appear in the database separately for each year.) Each record includes the grant number, principal investigator, project title, sometimes an abstract, amount of funding for that fiscal year, various other items, and a list of "thesaurus terms," some of which describe the disease or diseases to which the particular project is related. These "thesaurus terms" come from a controlled vocabulary organized in a hierarchical structure (much like a library's subject index), in which lower-level entries correspond to

more specific diseases. Using this "tree-structure" of diseases,[31] the thesaurus terms can be aggregated into thirty-five "top-level" disease categories, and then those disease categories can be further aggregated into the seven therapeutic categories corresponding to the seven (five-digit) SIC codes used by PhRMA to report private R&D and by the Census Bureau to report drug shipments.

This aggregation process unfortunately cannot perfectly match research grants on diseases to SIC codes of drugs used to treat those diseases. The most obvious problem is that the SIC codes are extremely broad-based, and it is often difficult to determine which of the detailed disease categories match which SIC therapeutic categories. However, the more serious problem is that the SIC codes each correspond, not to a class of diseases, but to a particular organ system or disease process on which the drug acts (see Table 2). In some cases, a drug can act on one organ system to treat a disease that is primarily associated with another organ system. For example, a grant for research on the effects of cholesterol on heart disease might be classified as "cardiovascular" research, since the research concerns diseases of the cardiovascular system. However, development and sales of a cholesterol-reducing drug would be classified in the "digestive" SIC category because the drug itself "acts on the digestive system." PhRMA reports all private-sector data, including both research expenditures and sales, using the SIC "drug acting on organ system" therapeutic categories, and the Census Bureau reports sales on this basis as well.

After assigning each thesaurus term to a therapeutic category, each of the 1,137,498 projects funded between 1972 and 1996 was assigned to one or more therapeutic categories

[31] This "tree-structure" was not publicly available from NIH until recently. While one could look up each project and find the thesaurus terms assigned to it, the list of terms and the hierarchical structure used by NIH to assign them was published only once, in book form in 1989. It was not published again, or in machine-readable form at all, until 1997. In addition, many terms were changed from one year to the next, but a year-by-year historical concordance was never published. NIH did not release the concordance and the updated thesaurus until Prof. Frank Lichtenberg of Columbia University filed a Freedom of Information Act request to obtain the thesaurus tree and the coding system used to link terms which changed from one year to the next. In 1997 and 1998, NIH included a list of thesaurus terms on the CD-ROMs for those years, but not the coding system or the historical concordance — and also did not include the funding levels. I am grateful to Prof. Lichtenberg for providing me with the thesaurus he obtained, complete with the coding system and the year-by-year historical concordance.

based on its thesaurus terms. Following Lichtenberg (1999a), the full funding level of each project is counted in each category for which it has a thesaurus term listed. Although this results in multiple counting of research dollars, this is appropriate when considering research spending at the category level since a project that impacts multiple therapeutic categories will affect private research decisions in all those categories.

6.3 Summary of Data

Figure 2 displays the level of public ("Grants") and private ("PhRMA") funding for each of the seven therapeutic categories for the period 1972-1996. Figure 3 shows log-changes for the same data.

One problem with analyzing spending data covering such a long period of time is that prices change. Fortunately, there is a price index specifically tailored to prices of inputs to medical research. The Biomedical Research and Development Price Index (BRDPI), developed by the Bureau of Economic Analysis (BEA) of the Department of Commerce primarily for NIH budgeting purposes, measures the average price of all inputs (including salaries of scientists) to biomedical research purchased with the NIH budget. These inputs are likely to be similar to those purchased for anyone performing biomedical research, so this price index is used to adjust both public and private expenditure data to constant dollars. The BRDPI, along with grants awarded in current and constant 1972 dollars, is illustrated in Figure 4.

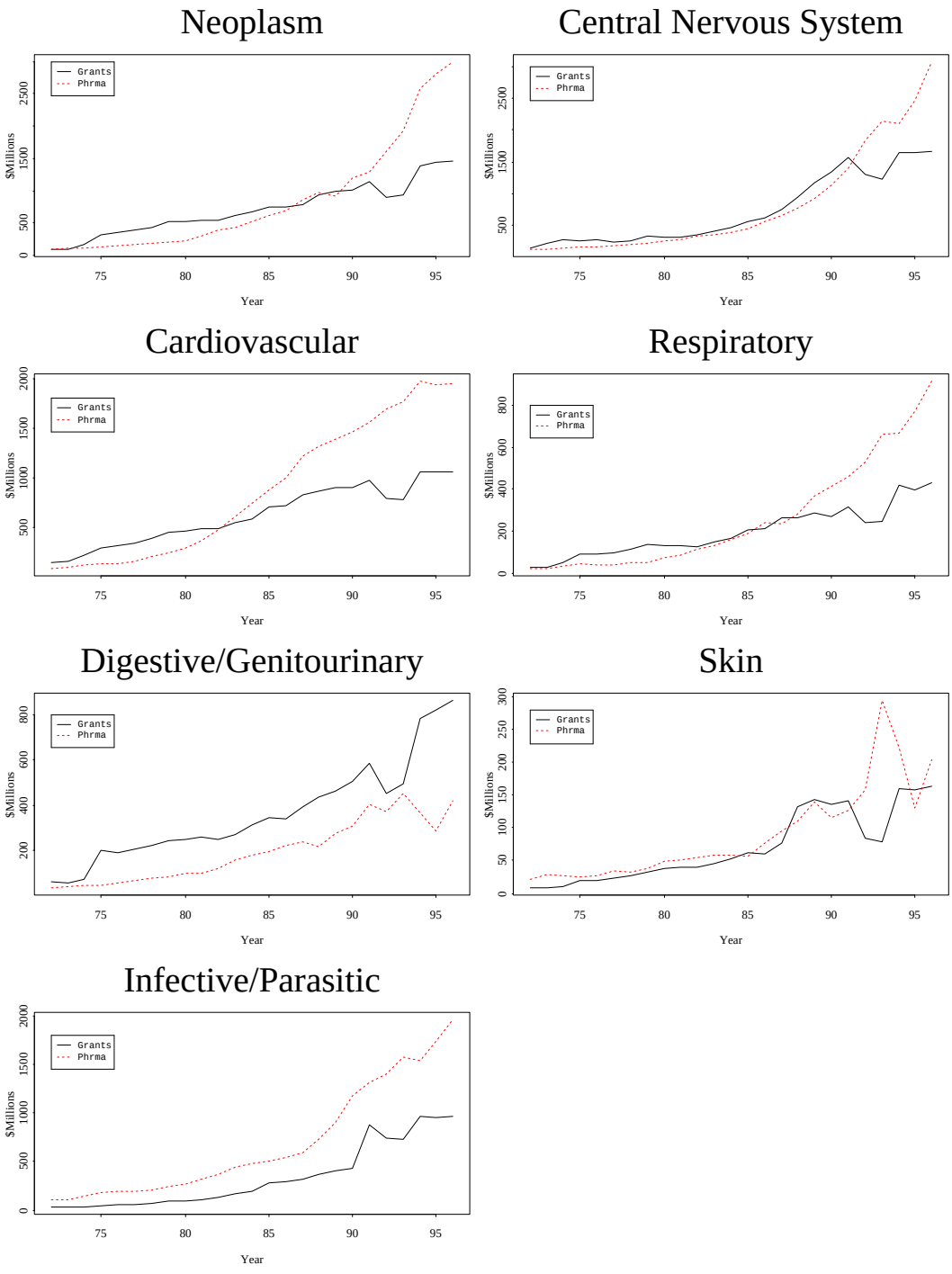

Figure 2: Federal Research Grants ("Grants") and Private R&D of PhRMA members ("PhRMA"), by Therapeutic Category.

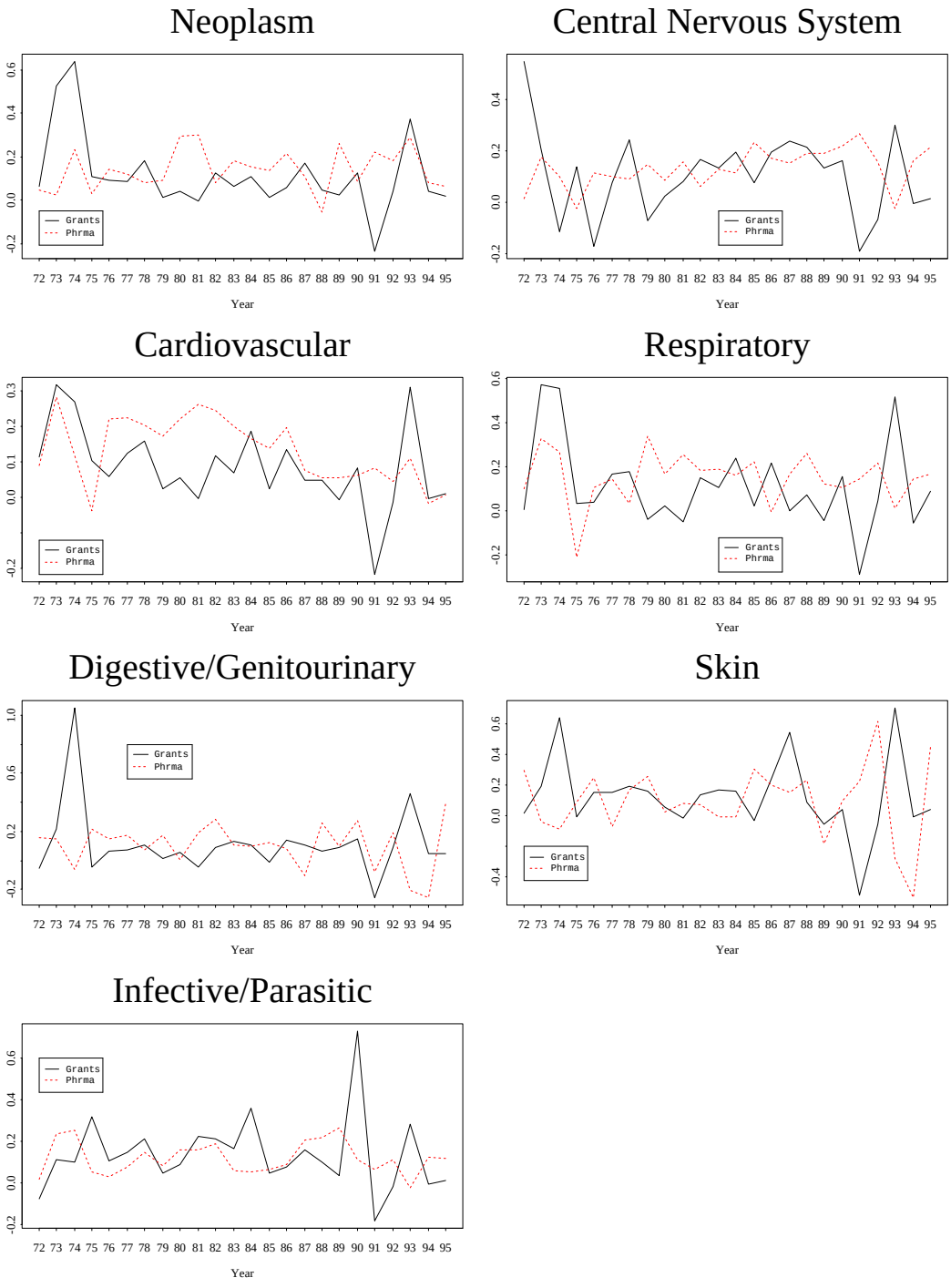

Figure 3: Log of Annual Changes in Federal Grants and Private R&D of PhRMA members, by Therapeutic Category.

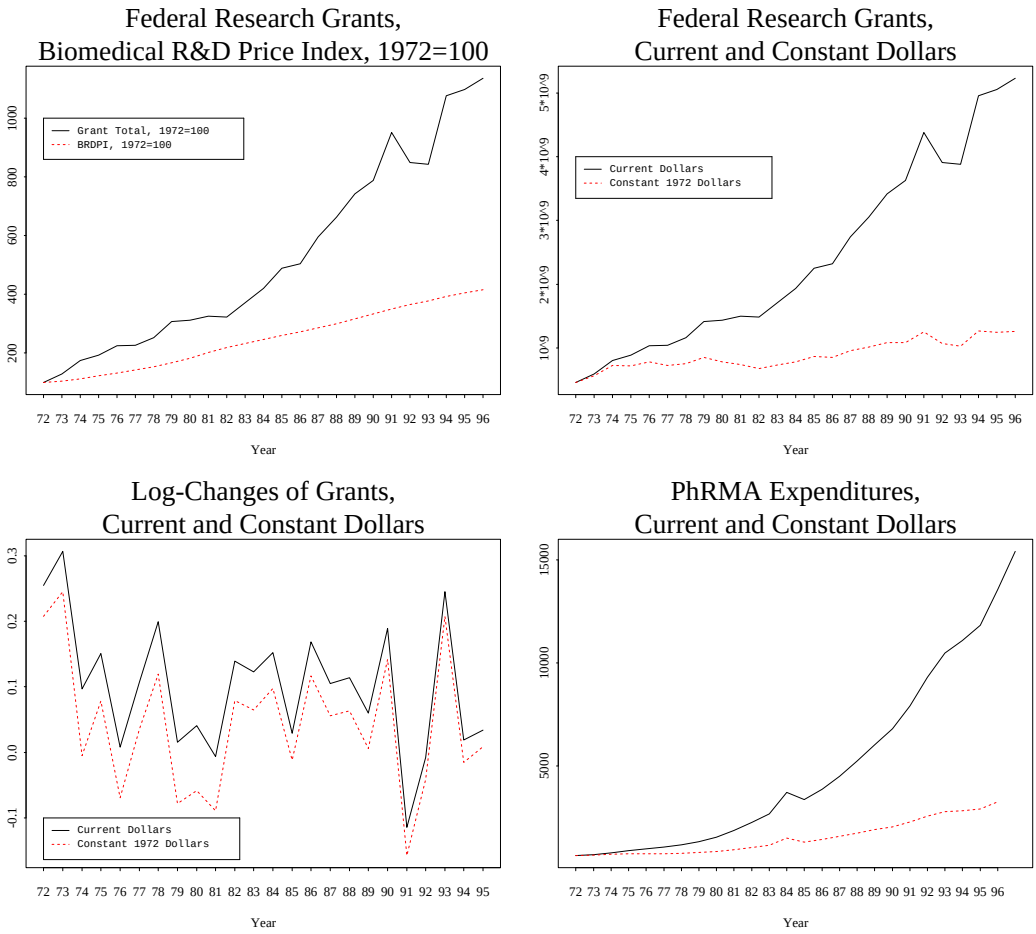

Figure 4: Federal Research Grants in current dollars, and constant 1972 dollars, adjusted according the the Biomedical Research and Development Price Index (BRDPI).

7 Models of Scientific Research

7.1 Models of the Research Process

The simplest — and surely the earliest — "model" of the scientific research process is the so-called "linear model" proposed by Francis Bacon (1561-1626) and still the dominant assumption in science policy discourse today. According this model, technology evolves according to a simple three-step process:

$$\text{Basic Research} \longrightarrow \text{Applied Research} \longrightarrow \text{Development}$$

The first step is "basic research," which is scientific inquiry oriented toward understanding natural processes rather than toward producing marketable products or making profits.[32] Basic research produces "scientific knowledge," which is a non-rival public good. That is, it can be used by anyone without reducing the stock available to others. Scientific knowledge is an input into the second step, "applied research," which is scientific inquiry oriented toward solving specific problems with some practical aim in mind. Applied research produces "technology," which in this context means some new process that might be economically useful. The third step, "development" consists of taking the technology and producing a potentially marketable product or service that makes (potentially) profitable use of the technology. The process is imagined to look something like this:

$$\underset{\text{(Labor)}}{\text{Scientist}} \xrightarrow[\text{Research}]{\text{Basic}} \text{Knowledge} \xrightarrow[\text{Research}]{\text{Applied}} \text{Technology} \xrightarrow{\text{Development}} \text{Product}$$

Like all models, this is somewhat of an oversimplification. Applied research aimed at producing a technology often generates questions that need to be answered, but whose

[32] Some practitioners of basic research are quite explicit about their intent *not* to aim for discoveries with financial value and use the term "pure research" to describe research with scientific but not financial value. Needless to say, many discoveries of pure research are later found to have great financial value. For example, research into abstract algebra and number theory, arguably the purest of "pure mathematics" has produced the main input into cryptography, which is now a multi-billion-dollar industry protecting financial transactions and trade secrets.

answers consist of basic scientific knowledge. Technology is used to develop products (e.g., scientific instruments) that make new types of basic research possible or new lines of inquiry interesting. And, sometimes, basic research results in new technology without any intervening "applied research" step (see footnote 32, for example). Nevertheless, the linear model is a reasonable representation of the pharmaceutical industry, in which basic research into the nature of diseases produces knowledge of their mechanisms or causes. Applied research is aimed at blocking those mechanisms and causes, often by characterizing a hypothetical molecule that could interfere with a biochemical mechanism. Development consists of constructing such a molecule that is effective and non-toxic to humans, developing a form and and determining a level of dosage, and verifying safety and efficacy of the final drug.

7.2 Economic Models of Research

We are concerned primarily with incentives that encourage firms to undertake costly research and development (R&D). Clearly, a firm's decisions must be based on an attempt to equate the firm's (expected) marginal cost of R&D with its (expected) marginal return (appropriately adjusting for risk). The main sources of risk are uncertainty as to whether and when the research will produce a marketable product and what the demand for that product will be. In the case of pharmaceuticals, demand for a product is a fairly predictable function of the prevalence of relevant diseases and availability, cost, and efficacy of other drugs used to treat those diseases. From the standpoint of the pharmaceutical firm, the main source of risk is uncertainty as to the success of the applied research program, which may produce a marketable drug quickly or slowly, at low cost, high cost, or not at all even after incurring large costs.

Basic research is inherently more risky than applied research, since there is additional uncertainty as to whether the knowledge produced will be useful in developing products.

Furthermore, since basic scientific knowledge cannot be protected by patents and is often difficult to keep secret, there is also the risk that the research output will become inappropriable, allowing competing firms to take advantage of the knowledge and produce a competing product without incurring the same costs. The possibility of "free riding" can reduce the *ex ante* expected return to the firm to well below the social return, thus causing the firm to underinvest in basic research relative to the social optimum. This is the fundamental problem with obtaining the optimal level of basic research through ordinary market processes, first explicitly identified by Nelson (1959) and Arrow (1962), and also the basic justification for government subsidies of basic research.

A firm's optimal expenditure on basic research is some function of the following form:

$$BR = f(C, R(A))$$

where

$$\begin{aligned} BR &= \text{Basic Research expenditure} \\ C &= \text{Unit Cost of Research (including wages of researchers)} \\ R &= \text{Firm's (utility) of return, i.e., risk-adjusted expected return} \\ A &= \text{A measure of the degree and likelihood of appropriability of discoveries} \end{aligned}$$

Clearly, $f'(C) < 0$, $f'(R) > 0$, and $R'(A) > 0$. However, the firm's return $R(A)$ may be greater or less than the social return, and $R(A)$ may increase or decrease with an increase in government funding of basic research.

It is possible that a firm's private return may be greater than the social return in a case where the firm's innovation is appropriable and represents an unambiguous improvement over an existing technology. For example, Firm A may have a drug to treat a certain disease, and Firm B might develop a drug that treats the same disease more effectively but at the same or lower cost. Once Firm B's drug is available, there will be very little demand for

Firm A's drug. In this case, the social return is determined by the value of the *improvement* in effectiveness — i.e., the marginal value — of the new drug over the old one. However, Firm B's return is determined by the total value of the benefit of the new drug rather than the marginal value, since consumers' willingness to pay is based on the total benefit received.

More commonly, however, a firm's private return will be less than the social return. Even as a monopolist, the firm generally cannot perfectly price-discriminate, and the utility to some consumers will be very large. Furthermore, the existence of alternative technologies (e.g., drugs) may prevent the firm from charging the full monopoly price, even if at the price actually charged the firm has almost all the market share. More importantly, in many cases the firm will not be able to appropriate fully the value of the underlying innovation. For example, a Firm A might perform basic research and discover how a particular disease works, then develop a drug to block the disease process. In the course of obtaining FDA approval and marketing the drug to potential consumers, Firm A will have to reveal what it discovered about the disease process (its "basic research" results). Unlike the drug itself, this information cannot be protected by patents. Firm B could then use that information to develop a superior ("next-generation") drug, which might eliminate the demand for Firm A's drug.

Public spending on basic research can have two effects on the returns to private research. First, when the government undertakes a research program, the results of which will be publicly available, it is less likely that an individual firm's private research program on the same topic will produce appropriable results, since similar results are likely to be published and thus available to the firm's competitors as a result of the government research program. Furthermore, the firm itself will also be able to access the results of the government research program at a much lower cost than that of conducting its own research, therefore the marginal effect of a private research program on the firm's stock of knowledge will be much lower in the presence of a similar public research program. Both of these factors will

produce a "crowding-out" (substitution) effect, in which each additional dollar of government research reduces the returns to, and thus the level of, private research.

On the other hand, when the government undertakes a research program and makes the results publicly available, the stock of scientific knowledge available to all firms increases, and this results in an increase in the opportunities for applied research. Although the information is available to all firms, the marginal cost to each firm of producing applied results is lower since the firm does not have to incur the cost of basic research. This will produce a "stimulation" (complementarity) effect, in which each additional dollar of government research increases the returns to and thus the level of private research.

In theory, either or both of these effects may be present; if both are present, which effect will dominate is an empirical question.

The goal of this paper is to examine the relationship between public funding of basic biomedical research and private R&D funding and output in the pharmaceutical industry; in particular, to determine whether, on the whole, public research funding "crowds out" (substitutes for) or "stimulates" (complements) private R&D expenditures in this industry.

Since research does not take place instantaneously, it is reasonable to believe that any effect of federal research grants on private R&D will be felt only after some period of time. However, it is not obvious how long the lag will be. If, for example, pharmaceutical research firms regularly monitor grants made by the NIH and take care to complement (or alternatively, take care not to replicate) research funded by the government, then the lag may be quite short, and the effect on private R&D would be positive (alternatively, negative). On the other hand, if not enough information is available at the time the grant is made for firms to use this as as basis for decision-making, then the firms would instead have to base decisions on research results (e.g., publications), and the lag would be longer.[33] Furthermore,

[33] Pharmaceutical firms definitely monitor academic research (Pien 1999; Mullen 2000), which is mostly federally funded (Blumenthal et al. 1996). The question here is not whether firms make use of this information, but at what stage of the process the information becomes useful. It is often the case that as an

if the main interaction between federally funded research and private research is that firms apply knowledge obtained through federally funded research directly to development of new drugs, then we would expect a substantially longer lag and a positive effect.

It is possible, of course, for more than one of these effects to be important. For example, there could be short-run substitution or complementarity due to the effect of federal grant announcements on firms' R&D planning, and long-run complementarity due to the effect of academic research results on firms' applied research and product development. It is difficult, however, to imagine a scenario in which the long-run effect would be substitution. That is, for a unit increase in federal spending at a particular point in time, it would be reasonable to expect either an increase or a decrease in private spending in the short run, but in the long run we should expect an increase in private spending, *ceteris paribus*.

A firm's optimal expenditure on applied research is also a function of the above variables as well as variables that might indicate demand for the type of product that is the ultimate goal of the research program. A reasonable characterization of the research expenditures of the pharmaceutical industry is

$$PhRMA_t = f(X_t, \ldots, X_{t-j}) + g(X_{t-j-1}, \ldots, X_{t-j-k}) + h(\text{other variables}) \qquad (1)$$

where

$PhRMA_t$	is	private research spending by the pharmaceutical industry in year t;
$X_t, \ldots, X_{t-j}$	are	government biomedical research spending in year t and years preceding t (short-run lags);
$X_{t-j-1}, \ldots, X_{t-j-k}$	are	government biomedical research spending in years preceding year $(t-j)$ (long-run lags).

The functions f and g will have negative first derivatives where the "crowd-out" effect dominates, and positive first derivatives where the "stimulant" effect dominates. In particular,

academic research program progresses, it becomes "too applied" to qualify for continued federal funding. At that point, sometimes a private firm will fund further applied research by the academic lab (Pien 1999). Indeed, Blumenthal et al. estimated that more than 11% of academic research in the life sciences is funded by corporations. This counts as private R&D in our data.

if the short-run effect is the opposite of the long-run effect, then j is the lag at which the effect reverses.

8 Empirical Results and Interpretation

Lag structure can be investigated by running distributed lag regressions of the log-changes of private R&D on the log-changes of federal research funding, for each of the seven therapeutic categories for which we have data and for the total funding levels (for all categories put together, netting out the "double-counted" research discussed on page 50). The functional form for these regressions is

$$Y_t = a + \sum_{i=0}^{k} b_i X_{t-i} + h(\text{other variables}) \tag{2}$$

where

$$\begin{aligned} Y_t &= \log\left(\frac{y_t}{y_{t-1}}\right), \quad y_t = \text{Private R\&D in year } t \\ X_t &= \log\left(\frac{x_t}{x_{t-1}}\right), \quad x_t = \text{Federal research grants in year } t \\ k &= \text{the number of lags, ranging from 0 to 7} \end{aligned}$$

For each of the seven therapeutic categories and for the total funding levels, regressions of the above form were run for each possible number of lags $k = 0 \ldots 7$. Regressions using log-changes instead of first differences are reported, since log-changes can be interpreted as relative (percentage) changes and are not sensitive to the scale of the variables, and thus are more useful for comparisons. (In any case, results of regressions using first differences are qualitatively similar.) In addition, regressions were run with data for all categories combined, with dummy variables for each category, as well as year dummy variables and various combinations of other variables. The "other variables" are used as controls, to increase the chance that the effects observed are actually from changes in government funding

rather than from other factors. In particular, we control for autocorrelation (using lagged values of the dependent variable), GDP growth, lagged sales growth (by drug category), current and lagged non-medical federal R&D spending (replacing the independent variables), and category and year dummy variables.

Each regression coefficient b_i may be interpreted as the effect on private R&D in year t of an increase in federal funding in the same therapeutic category in year $t - i$. For any particular regression, the sum of the coefficients $\sum_{i=0}^{k} b_i$ may be interpreted as the cumulative effect on private R&D over k years, of a 1% increase in in federal funding in a single year.

8.1 Basic Results

Table 3 shows the results of the distributed-lag regressions (2), and Table 4 shows the results of the same distributed-lag regressions, but with grants and PhRMA expenditures adjusted to constant (1972) dollars using the BRDPI. Each cell in the table contains the sum of coefficients for the regression with the given number of lags, which represents the cumulative impact on private R&D in the given therapeutic category of a 1% change in federal grants in that category in a single year. Numbers in parenthesis are t-statistics for the hypothesis test that the *sum* of the coefficients is zero for the corresponding regression.[34] Figure 5 displays,

[34] Note that each number in parenthesis in Tables 3 and 4 is the t-statistic of the *sum* of the coefficients $b_i, i = 0 \ldots k$. This is of course different from the standard error of any particular coefficient, and is not calculated as part of the usual regression procedure. To calculate this t-statistic, consider the regression equation (2) above. Add and subtract $\sum_{i=1}^{k} b_i X_t$ to both sides (note that this summation is of the current (non-lagged) value X_t multiplied by the coefficients of the lagged values). Then, collect like terms in X_t as follows:

$$
\begin{aligned}
Y_t &= a + \sum_{i=0}^{k} b_i X_{t-i} + \left(\sum_{i=1}^{k} b_i X_t - \sum_{i=1}^{k} b_i X_t \right) + h(\text{other variables}) \\
Y_t &= a + b_0 X_t + \sum_{i=1}^{k} b_i X_{t-i} + \sum_{i=1}^{k} b_i X_t - \sum_{i=1}^{k} b_i X_t + h(\text{other variables}) \\
Y_t &= a + \left(b_0 X_t + \sum_{i=1}^{k} b_i X_t \right) + \left(\sum_{i=1}^{k} b_i X_{t-i} - \sum_{i=1}^{k} b_i X_t \right) + h(\text{other variables})
\end{aligned}
$$

for each category (and for total research), a plot of the cumulative predicted percentage change in private R&D spending for each subsequent year, corresponding to a +1% change in an initial year, for figures in both current and constant dollars.

Note that although the results are different for each category, there is a discernible pattern: over a small number of lags, the cumulative effect is negative in five of the seven categories, and small but generally increasing in the other two. For longer lags, the cumulative effect is more likely to be positive, and by the seventh lag is positive for all but one category. The final column shows the average, over all therapeutic categories, of the sum of coefficients for a particular number of lags k. Here the same pattern is discernible; the average cumulative effect is negative for lags zero through four, and positive (and increasing) for lags five through seven.

It is apparent from the graphs in Figure 5 that for all categories, the cumulative effect on private R&D spending shows a definite negative response at least at some point within the first two years, and the effect increases at some point thereafter. For all but two categories the cumulative response after seven years is higher than the initial response, and the ultimate response is usually positive. Note also that the responses for constant (i.e., BRDPI-adjusted) dollars are more pronounced and usually more negative than those for current dollars.

In other words, due to the fact that both prices and quantities are increasing over time, the crowd-out (substitution) effect is more pronounced when the expenditures are adjusted for inflation. This may account for the fact that this study finds more crowding-

$$Y_t = a + \left(\sum_{i=0}^{k} b_i\right) X_t + \sum_{i=1}^{k} b_i (X_{t-i} - X_t) + h(\text{other variables})$$

This produces an alternate regression in X_t and the transformed variables $(X_{t-i} - X_t)$, $i = 1 \ldots k$. The coefficients (both true and estimated) of the transformed variables are exactly the same as those of the corresponding original variables X_{t-i}, $i = 1 \ldots k$ in (2), but the coefficient of X_t in the alternate regression is the *sum* of the coefficients of the original variables X_{t-i}, $i = 0 \ldots k$ in the original regression. Thus, I estimate the alternate regression above, and report the t-statistic of the coefficient of X_t in the alternate regression in parenthesis in Tables 3 and 4.

Table 3: Cumulative Effect of a Change in Grants on Private R&D (Current dollars)

Dependent Variable: Y = PhRMA Corporate R&D, by disease category (log changes)
Independent Variable: X = Federal Grants, by disease category (log changes)

Each cell contains the sum of coefficients for the regression with the given number of lags.
(The number in parenthesis is the t-statistic of the *sum* of coefficients.)

Lags of X	Neoplasm	Nervous	Cardio	Respir	Digest	Skin	Infective	Totals[a]	Lag Avg.[b]
0	-0.0159	-0.1915	0.2647	0.0348	-0.1899	-0.2924	-0.0253	-0.0973	-0.0594
	(-0.1394)	(-2.1584)	(1.6423)	(0.2807)	(-1.3985)	(-1.4829)	(-0.2702)	(-0.4049)	
1	-0.1159	0.0382	0.1488	-0.1115	-0.3124	-0.7446	-0.2466	-0.0173	-0.1920
	(-0.8069)	(0.3066)	(0.6739)	(-0.6333)	(-1.5246)	(-2.9890)	(-1.5509)	(-0.0465)	
2	-0.1289	0.1928	0.0226	-0.3971	-0.0492	-0.3022	-0.4336	-0.1377	-0.1565
	(-0.6909)	(1.0392)	(0.0759)	(-1.7191)	(-0.1726)	(-0.8885)	(-1.6425)	(-0.2405)	
3	-0.3401	0.3143	0.3515	-0.8935	0.0441	-0.3380	-0.5872	-0.1047	-0.2070
	(-1.2797)	(1.7301)	(1.0365)	(-3.2771)	(0.0885)	(-0.7440)	(-1.8109)	(-0.1313)	
4	-0.5950	0.4081	0.8797	-0.4774	-0.7930	-0.1845	-0.6576	-0.1628	-0.2028
	(-1.6073)	(2.4012)	(2.5388)	(-1.6264)	(-1.3322)	(-0.3063)	(-1.6259)	(-0.1487)	
5	-0.9408	0.4398	0.9860	-0.2841	0.5596	0.6177	-0.4997	0.6178	0.1255
	(-1.7646)	(2.3932)	(2.2650)	(-0.7496)	(0.7361)	(0.8187)	(-0.5171)	(0.4756)	
6	-0.6430	0.5186	1.2114	-0.2622	0.0949	0.2112	-0.5271	0.5746	0.0863
	(-0.8489)	(2.4830)	(2.3944)	(-0.5393)	(0.0788)	(0.2250)	(-0.3500)	(0.3683)	
7	-1.6358	0.3805	2.0122	0.4550	0.7895	-1.0401	1.8610	-0.3931	0.4032
	(-1.3254)	(1.5449)	(3.3869)	(0.6375)	(0.3621)	(-0.6944)	(1.5839)	(-0.1943)	
Sum	-4.4155	2.1007	5.8769	-1.9358	0.1434	-2.0729	-1.1162	0.2795	-0.2028
Wtd. Avg.[c]	-0.1227	0.0584	0.1633	-0.0538	0.0040	-0.0576	-0.0310		-0.00563
Avg.[d]	-0.5519	0.2626	0.7346	-0.2420	0.0179	-0.2591	-0.1395		

[a]Total Grants includes grants not in any disease category.

[b]The average is taken over category regressions only.

[c]The average cumulative response, weighted by number of coefficients; or equivalently, the average coefficient.

[d]The average cumulative response over the eight regressions; i.e., each regression has equal weight.

Table 4: Cumulative Effect of a Change in Grants on Private R&D (Constant dollars, according to the Biomedical Research and Development Price Index (BRDPI))

Dependent Variable: Y = PhRMA Corporate R&D, by disease category (log changes)
Independent Variable: X = Federal Grants, by disease category (log changes)

Each cell contains the sum of coefficients for the regression with the given number of lags.
(The number in parenthesis is the t-statistic of the *sum* of coefficients.)

Lags of X	Neoplasm	Nervous	Cardio	Respir	Digest	Skin	Infective	Totals[a]	Lag Avg.[b]
0	-0.0535 (-0.4688)	-0.1164 (-1.1386)	0.1861 (1.2181)	0.0211 (0.1691)	-0.2192 (-1.5808)	-0.3045 (-1.4975)	-0.0390 (-0.4285)	-0.0241 (-0.1090)	-0.0751
1	-0.1774 (-1.2542)	0.1400 (0.9796)	-0.0118 (-0.0576)	-0.1382 (-0.7888)	-0.3630 (-1.7596)	-0.7816 (-3.0807)	-0.2536 (-1.6133)	-0.0062 (-0.0185)	-0.2265
2	-0.2187 (-1.1909)	0.3223 (1.5741)	-0.3306 (-1.2568)	-0.4360 (-1.9253)	-0.1227 (-0.4287)	-0.3447 (-0.9883)	-0.3410 (-1.2983)	-0.1627 (-0.3324)	-0.2102
3	-0.4223 (-1.5813)	0.4384 (2.3096)	-0.0796 (-0.2346)	-0.9203 (-3.2325)	0.0282 (0.0581)	-0.4141 (-0.8745)	-0.4837 (-1.4086)	-0.1995 (-0.3039)	-0.2648
4	-0.7133 (-2.0113)	0.5599 (3.0214)	0.3978 (1.0401)	-0.5734 (-2.0989)	-0.7115 (-1.2524)	-0.2896 (-0.4350)	-0.5094 (-1.2213)	-0.2267 (-0.2738)	-0.2628
5	-1.0396 (-2.1779)	0.5952 (3.0319)	0.3309 (0.6625)	-0.4662 (-1.3259)	0.2824 (0.4241)	0.5479 (0.6357)	0.1050 (0.1542)	0.0131 (0.0148)	0.0508
6	-0.8694 (-1.1584)	0.6549 (2.8679)	0.3831 (0.5850)	-0.6437 (-1.2984)	-0.5910 (-0.6612)	-0.0855 (-0.0803)	0.2303 (0.2562)	-0.3217 (-0.3324)	-0.1316
7	-1.2730 (-0.9083)	0.5220 (1.9032)	1.0320 (0.9596)	-0.3441 (-0.4105)	-0.6463 (-0.4665)	-2.3354 (-1.3852)	1.2068 (1.5759)	-0.9100 (-0.8227)	-0.2626
Sum	-4.7672	3.1162	1.9079	-3.5009	-2.3431	-4.0075	-0.0846	-1.8379	-1.3827
Wtd. Avg.[c]	-0.1324	0.0866	0.0530	-0.0973	-0.0651	-0.1113	-0.0024		-0.0384
Avg.[d]	-0.5959	0.3895	0.2385	-0.4376	-0.2929	-0.5009	-0.0106		

[a] Total Grants includes grants not in any disease category.

[b] The average is taken over category regressions only.

[c] The average cumulative response, weighted by number of coefficients; or equivalently, the average coefficient.

[d] The average cumulative response over the eight regressions; i.e., each regression has equal weight.

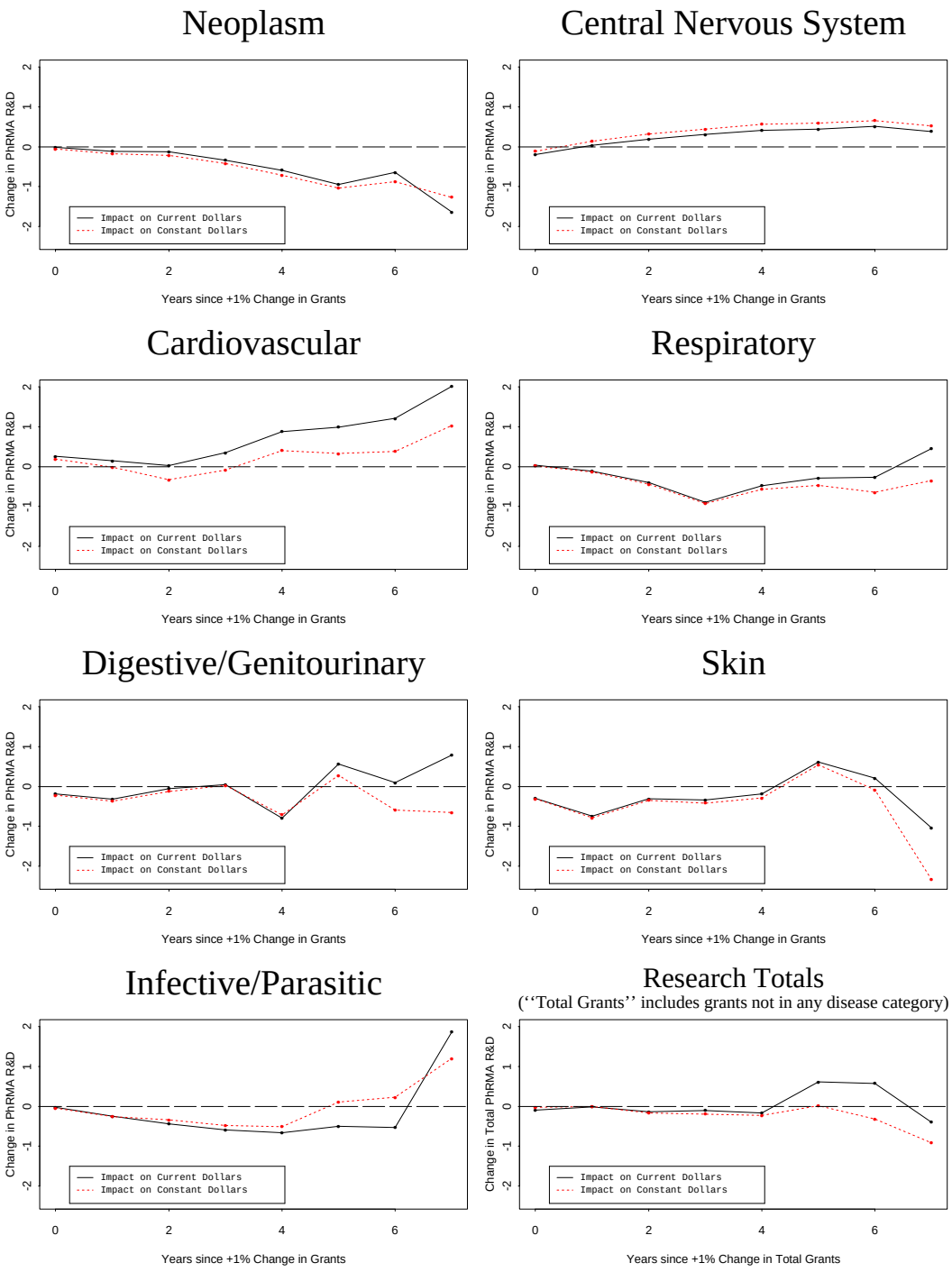

Figure 5: Cumulative predicted percent change in Private (PhRMA) R&D corresponding to a one-time +1% change in Federal Research Grants, by Therapeutic Category. In each plot, the solid line represents the response in current dollars; and the dashed line in constant dollars according to the Biomedical Research and Development Price Index (BRDPI).

out than do previous studies, since previous studies either used only current-dollar data or adjusted prices using the more general GDP implicit price deflator rather than the BRDPI, a price index that is specific to biomedical R&D inputs.

8.2 Interpretation

To interpret these results, first note that for regressions with "Grants" as the independent variable and "PhRMA spending" as the dependent variable, the sums of coefficients are generally negative when zero through four lags are in the regression (5 negative, 2 positive), split (3 negative, 4 positive) when 5 or 6 lags are included, and generally positive (6 positive, 1 negative) with 7 lags. (The results are similar for a "pooled" regression, i.e., a single regression that includes observations for all categories.)

There is one very obvious story that would explain the existence of positive sums only in the higher lags — specifically, that government grants stimulate private research, but only 5 or more years into the future — but the combination of negative and positive results requires a more complicated explanation. One possibility is the following scenario: government grants are primarily intended for so-called basic research. These grants crowd out private basic research, because private firms are not willing to spend their resources doing basic research in a particular field if the government is doing it anyway and will publish the results for all to see. On the other hand, when basic research *results* become known to a private firm (either through reading results of public research, as in this story, or by doing their own research, as in the counterfactual case of no government funding), this increased knowledge leads to an increase in *applied* research by firms in the future. So, what we observe in these data is the effect of government (basic) research crowding out private basic research but stimulating private applied research. Since the lag for stimulating applied research is longer (firms can respond only after the research is completed and the results

become known), this shows up in the data as crowding-out in the short run but stimulation in the long run.

This story has the advantage that it is consistent with the prediction of any reasonable theoretical model that distinguishes between basic and applied research (a distinction that is somewhat problematic, but less so in biomedical research than in other fields) and allows that the government specializes in basic research. It also implies that in this case, we can rule out the extreme crowd-out effect described on page 12.

8.3 Robustness Checks

Numerous robustness checks were performed to verify that the results obtained above were not spurious, or the result of other factors. For example, vector autoregressions (VAR) of the form

$$Y_t = a + \sum_{i=0}^{k} b_i X_{t-i} + \sum_{i=1}^{k-1} a_i Y_{t-i} + b \log\left(\frac{y_{t-1}}{x_{t-1}}\right) \tag{3}$$

can be used to determine whether the observed lag effects are due to actual lagged correlation between federal and private research, as opposed to mere autocorrelation in private research combined with the fact that both types of spending are generally increasing. An an F-test can then be applied to test this form against the corresponding regression without the autocorrelation terms.

Table 5 lists the results of running regressions (3) and using the F-test to decide whether the additional coefficients included in (3) but not (2) are significantly different from zero. For six of the seven therapeutic categories, the hypothesis that autoregressive terms should be excluded cannot be rejected at significance level $\alpha = .05$. Thus, we might reasonably conclude that changes in the level of grants are better predictors of changes in private R&D than previous ("momentum") changes in private R&D. However, this result is rather weak, since for four of the seven categories, the complementary hypothesis (that

all but the autoregressive terms should be excluded) also cannot be rejected at significance level $\alpha = .05$.

In addition to the F-tests, the coefficients of the vector autoregressions (VAR) can be used to calculate the cumulative average effect of a single unit change in federal research spending on private spending in subsequent years, considering direct as well as autoregressive effects. Results of these calculations appear in Table 6 and are plotted in Figure 6. Note that there is no consistent pattern of cumulative effects when autoregressive terms are included; in particular, the "$\cup$-shaped" pattern of short-run substitution and long-run complementarity observed for grants is not observed for lagged private R&D. Therefore, it is reasonable to conclude that this effect is not due to spurious autocorrelation in private R&D.

Having ruled out autoregressive effects, it is necessary to control for other factors that might affect private R&D spending. Clearly, private pharmaceutical R&D spending is driven by demand for pharmaceuticals. Firms may allocate funds to different disease categories based on estimates of demand for drugs used to treat those diseases. To control for this effect, we use lagged drug sales (dollar volume) in each category to represent demand in that category. Firms may also respond to a general increase in demand caused by an increase in overall income. To control for this effect, we use GDP as the measure of income. In addition, we can increase the effective sample size by including data for all categories in the sample, in some cases with dummy variables to examine category fixed effects. The functional form is

$$Y_{jt} = a + \sum_{i=0}^{k} b_i X_{j,t-i} + h(\text{other variables}) \tag{4}$$

where

$$\begin{aligned} Y_{jt} &= \log\left(\frac{y_{jt}}{y_{j,t-1}}\right), \quad y_{jt} = \text{Private R\&D for category } j \text{ in year } t \\ X_{jt} &= \log\left(\frac{x_{jt}}{x_{j,t-1}}\right), \quad x_{jt} = \text{Federal grants for category } j \text{ in year } t \end{aligned}$$

Tables 7 and 8 shows the results of the distributed-lag regression (4) with various

Table 5: Hypothesis Test of Vector Autoregression vs. Distributed Lag Regression

$$\text{VAR Regression: } Y_t = a + \sum_{i=0}^{k} b_i X_{t-i} + \sum_{i=1}^{k-1} a_i Y_{t-i} + b \log\left(\frac{y_{t-1}}{x_{t-1}}\right)$$

$$\text{Hypothesis Test:} \quad H_0: \quad a_i = 0 \text{ for all } i = 1 \ldots k = 1 \text{ and } b = 0$$
$$H_A: \quad a_i \neq 0 \text{ for at least one } i$$

At Significance Level $\alpha = .05$, Reject H_0 if $F > F_{.05}$

(In the table below, "Accept" is shorthand for "Fail to Reject.")

Lags of X	Lags of Y	Test Statistic F	Critical Value $F_{.05}$	Decision
Neoplasm				
2	1	0.9648	3.6337	Accept
3	2	0.2675	3.4105	Accept
4	3	0.3828	3.4781	Accept
5	4	0.4933	3.9715	Accept
6	5	0.1839	6.1631	Accept
7	6	0.1835	236.77	Accept
Nervous				
2	1	2.7405	3.6337	Accept
3	2	2.1960	3.4105	Accept
4	3	1.4429	3.4781	Accept
5	4	1.8754	3.9715	Accept
6	5	1.8284	6.1631	Accept
7	6	4.2841	236.77	Accept
Cardio				
2	1	12.834	3.6337	Reject
3	2	4.9248	3.4105	Reject
4	3	7.4959	3.4781	Reject
5	4	7.5147	3.9715	Reject
6	5	8.6870	6.1631	Reject
7	6	1.5835	236.77	Accept
Respir				
2	1	0.4672	3.6337	Accept
3	2	2.0460	3.4105	Accept
4	3	1.9413	3.4781	Accept
5	4	1.8909	3.9715	Accept
6	5	0.7872	6.1631	Accept
7	6	12.122	236.77	Accept

Lags of X	Lags of Y	Test Statistic F	Critical Value $F_{.05}$	Decision
Digest				
2	1	2.2875	3.6337	Accept
3	2	1.0788	3.4105	Accept
4	3	1.4012	3.4781	Accept
5	4	1.0504	3.9715	Accept
6	5	1.9518	6.1631	Accept
7	6	5.0164	236.77	Accept
Skin				
2	1	0.8903	3.6337	Accept
3	2	2.3541	3.4105	Accept
4	3	2.0954	3.4781	Accept
5	4	1.8744	3.9715	Accept
6	5	1.2102	6.1631	Accept
7	6	14.430	236.77	Accept
Infective				
2	1	1.7332	3.6337	Accept
3	2	0.6028	3.4105	Accept
4	3	1.1164	3.4781	Accept
5	4	0.6563	3.9715	Accept
6	5	1.0409	6.1631	Accept
7	6	2.0116	236.77	Accept

Table 6: Cumulative Direct and VAR Effects of Log of Annual Changes in Federal Grants on Private R&D.

(Each cell contains the change in Y_t, t periods after a unit log-change in X, implied by the regression with k lags of X and $k-1$ lags of Y.)

		t								
	k	0	1	2	3	4	5	6	7	8
Neoplasm	2	0.0820	-0.1264	-0.0952	0.0535					
	3	-0.0686	-0.1488	-0.0840	0.0688	0.0145				
	4	-0.0731	-0.1680	-0.1643	0.1951	-0.1568	0.1005			
	5	-0.0325	-0.1661	-0.2430	0.1458	-0.0378	-0.0732	0.1588		
	6	-0.0842	-0.0277	-0.2945	-0.1024	0.0632	0.1464	0.0432	0.1687	
	7	-0.1449	-0.4939	-0.6464	-0.3053	-0.0949	0.1539	-0.4056	0.2742	-0.4388
Nervous	2	0.1993	0.1249	0.0066	-0.0508					
	3	0.2451	0.1633	0.1604	0.0620	-0.0647				
	4	-0.2162	-0.0153	0.1742	0.1486	0.0201	-0.2657			
	5	-0.2848	0.0371	0.2170	0.2871	-0.0045	-0.2708	-0.2845		
	6	-0.2817	-0.0141	0.3821	0.2406	0.0340	-0.3343	-0.1236	-0.0683	
	7	-0.4545	-0.3835	-0.3726	-0.5444	-0.8403	-1.5810	-2.0704	-2.9100	-3.9472
Cardio	2	-0.0100	-0.1734	-0.1376	0.1248					
	3	-0.0002	-0.1656	-0.1691	0.2175	0.1361				
	4	0.0798	-0.0173	-0.0460	0.1776	0.0694	0.1041			
	5	0.0019	0.0507	-0.1204	0.1929	-0.0075	-0.0414	0.1165		
	6	0.0669	0.0790	-0.1726	0.1489	-0.0189	-0.0855	0.1239	0.1228	
	7	0.0478	0.2919	-0.5498	0.6146	-0.5902	0.3795	-0.2737	0.5444	-0.2306
Respir	2	-0.0755	-0.0463	-0.1646	0.0753					
	3	-0.2908	-0.0999	-0.0267	-0.1356	0.1684				
	4	-0.2154	0.0979	-0.0734	-0.1606	0.0049	0.1991			
	5	-0.1814	0.1621	-0.1135	-0.0247	-0.1007	0.1233	0.1254		
	6	-0.3011	0.2987	-0.1910	-0.0469	-0.0848	0.0193	0.3140	-0.0500	
	7	0.5446	-1.2545	2.3197	-4.8543	8.8840	-12.7975	21.9974	-39.332	71.547
Digest	2	-0.0551	0.2117	0.1161	0.1137					
	3	-0.1091	0.2205	0.1150	0.1616	0.0551				
	4	-0.1716	-0.3202	0.3934	0.0934	0.1370	0.0341			
	5	0.2144	-0.4541	0.8081	-0.2726	0.2440	-0.0605	-0.1054		
	6	0.5413	-0.1750	0.7790	-0.3744	-0.2197	-0.5083	0.1391	0.0136	
	7	0.9519	-0.2507	1.0648	-0.7386	0.6054	-2.7973	3.2996	-5.0791	8.5674
Skin	2	0.0471	-0.0571	0.4519	0.0206					
	3	0.1728	0.1168	0.1228	-0.1468	0.2507				
	4	0.3328	0.0503	0.1193	-0.3386	0.6572	-0.0976			
	5	0.1936	0.2742	0.0687	-0.2924	0.3033	0.3883	-0.2598		
	6	0.3286	0.2666	-0.2056	0.1589	-0.0599	0.6005	-0.4069	0.6669	
	7	12.637	-305.45	-7145.1	-1.67E5	-3.91E6	-9.15E7	-2.14E9	-5.0E10	-1.2E12
Infective	2	-0.1897	-0.1879	-0.1333	-0.0258					
	3	-0.0914	-0.0571	-0.0503	-0.0812	0.0577				
	4	-0.0827	-0.1746	-0.1014	-0.1737	0.0152	0.0112			
	5	-0.1759	-0.0614	-0.0607	-0.1163	-0.1939	-0.2660	0.2560		
	6	-0.2465	0.2277	-0.0791	-0.0229	-0.6192	-0.6317	0.3781	1.6364	
	7	-0.2106	0.2351	-0.0991	0.1660	-0.5445	-0.4615	0.3083	0.9368	0.9755

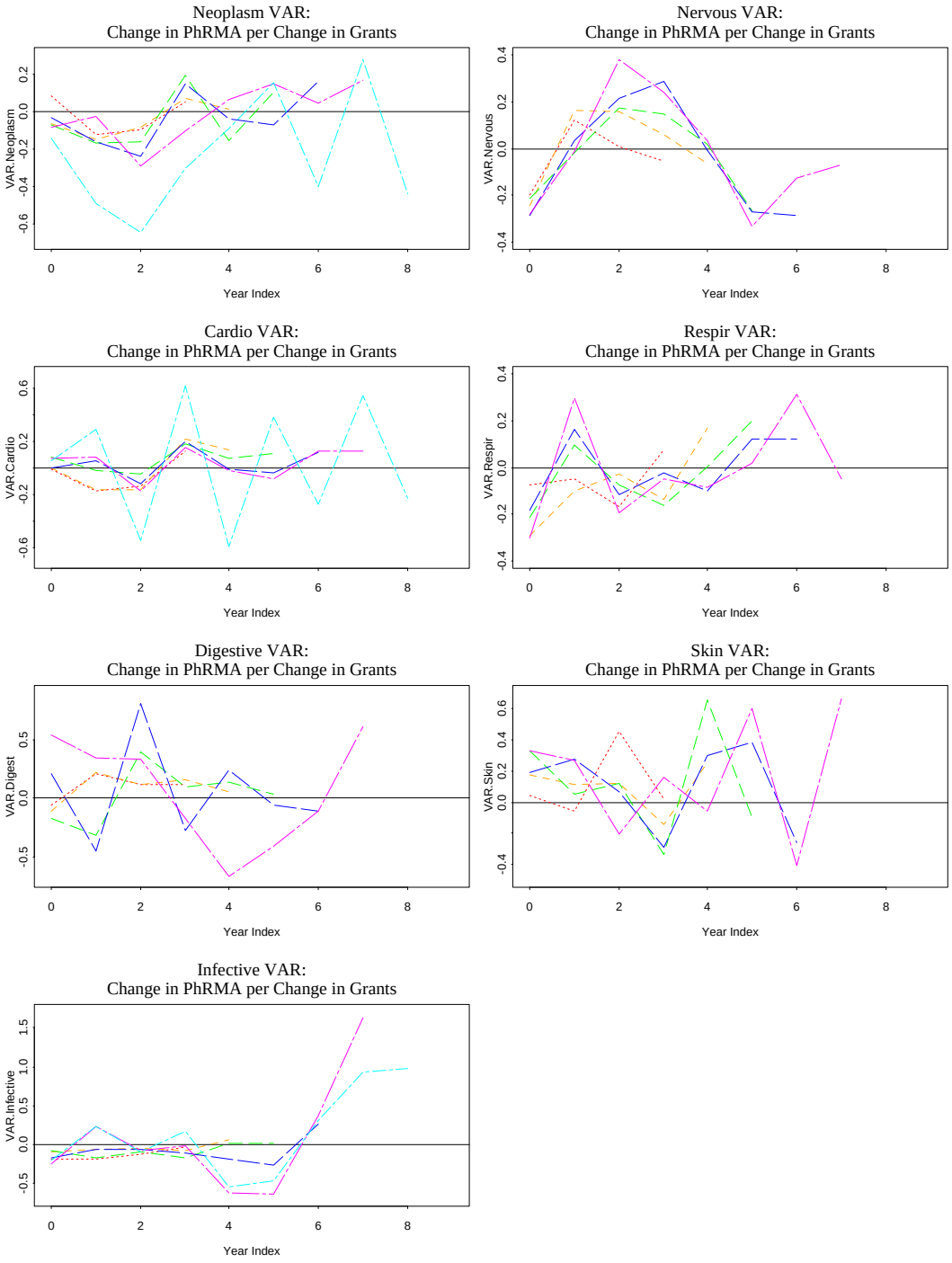

Figure 6: Cumulative Direct and Autoregressive Effects of Log of Annual Changes in Federal Grants, on Private R&D of PhRMA members, by Therapeutic Category. (Each line shows the cumulative change at each stage in a regression with a given number of lags; the number of lags is shown by the extent of the line. Thus, each chart has a line with three lags, a line with four lags, and so on.)

combinations of other variables, including GDP, drug sales (by category), and category and year dummy variables to control for fixed effects. These results show the same pattern in the coefficients as those without the control variables, indicating that the profile of negative short-run effects and positive long-run effects is not driven by these other variables. In fact, estimates of the regression coefficients are only slightly affected by including these other variables. This may be seen clearly in the plots shown in Figure 7.

In order to quantify the significance of the '$\cup$-shaped" pattern of coefficients, Table 9 shows the t-statistics for test of the null hypothesis that the cumulative effect of a change in PhRMA spending is linear over time, against the alternative that the cumulative effect is lower in the short run than the long-run linear trend. The idea here is that in the absence of crowding-out in the short run, the sum of the first k lag coefficients in a regression with n lags, will be about k/n of the sum of all n lag coefficients. Relative crowding-out in the shorter lags is indicated by negative t-statistics for the corresponding coefficient sums.

The pattern of effects of grants on private spending is not present in the pattern of effects of drug sales on private spending, as one can see immediately from the results in Table 10 and Figure 8. Indeed, in the early years (short lags), the effect of sales on private research is the opposite of the effect of grants. The effect of sales is positive in the first three years and negative in the fourth year. This pattern holds whether or not we control for grants, GDP, and category and year fixed effects. From this, we may conclude that the '$\cup$-shaped" pattern of short-run substitution and long-run complementarity is driven by federal grants and not drug sales.

Next, we wish to rule out the possibility that the "$\cup$-shaped" pattern of coefficients is the result of some omitted variable driving all sorts of federal support for research (rather than just in-category medical research) and perhaps private research as well. To do this, non-medical federal R&D spending was obtained by subtracting total federal spending on medical research from total federal R&D spending, as reported by the National Science

Table 7: Regression Results: Determinants of PhRMA R&D Spending

Dependent Variable: $PhRMA_{it}$ = PhRMA R&D in disease category j in year t (log changes)

Independent Variable	Coef.	(t-stat.)	Coef.	(t-stat.)	Coef.	(t-stat.)
Intercept	0.1875	(2.41E-7)	0.0946	(1.6002)	0.0727	(1.4207)
$\log \frac{GDP_t}{GDP_{t-1}}$	-0.3226	(-3.04E-8)	0.1676	(0.5104)	0.2100	(0.6435)
$GRANTS_t$	-0.0155	(-0.1001)	-0.1030	(-1.1195)	-0.1359	(-1.6777)
$GRANTS_{t-1}$	-0.2698	(-1.7907)	-0.2380	(-2.8934)	-0.2617	(-3.4070)
$GRANTS_{t-2}$	0.1569	(1.0240)	0.1999	(2.1082)	0.1639	(2.0469)
$GRANTS_{t-3}$	0.0321	(0.2019)	0.0862	(0.8925)	0.0624	(0.7021)
$GRANTS_{t-4}$	0.1569	(0.9551)	0.1242	(1.1568)	0.0923	(1.0083)
$GRANTS_{t-5}$	0.1334	(1.2367)	0.1208	(1.4286)	0.0818	(1.0409)
$GRANTS_{t-6}$	0.0159	(0.1486)	-0.0748	(-0.9271)	-0.0836	(-1.0442)
$GRANTS_{t-7}$	-0.0119	(-0.1166)	-0.0338	(-0.4104)	-0.0559	(-0.7057)
$SALES_t$	-0.1501	(-0.7219)	-0.0609	(-0.3444)	-0.1069	(-0.6149)
$SALES_{t-1}$	0.1173	(0.5572)	0.0034	(0.0181)	-0.0055	(-0.0299)
$SALES_{t-2}$	0.2340	(1.1226)	0.2866	(1.5895)	0.2694	(1.5073)
$SALES_{t-3}$	0.2120	(1.0193)	0.2693	(1.5005)	0.2593	(1.4658)
$SALES_{t-4}$	-0.2108	(-0.9876)	-0.2094	(-1.1321)	-0.1945	(-1.0670)
$SALES_{t-5}$	0.0059	(0.0275)	0.0464	(0.2399)	0.0611	(0.3310)
$SALES_{t-6}$	-0.4706	(-2.1543)	-0.4779	(-2.4466)	-0.4804	(-2.5706)
$SALES_{t-7}$	-0.0197	(-0.0896)	0.0622	(0.3219)	0.0830	(0.4617)
Category Dummy Variables:						
Nervous	-0.0016	(-0.0336)	-0.0055	(-0.1241)		
Cardio	-0.0068	(-0.1270)	-0.0215	(-0.4321)		
Respir	0.0137	(0.2931)	0.0076	(0.1719)		
Digest	-0.0588	(-1.2396)	-0.0654	(-1.4538)		
Skin	-0.0630	(-1.3174)	-0.0603	(-1.3487)		
Infective	-0.0540	(-0.9137)	-0.0565	(-1.0916)		
Year Dummy Variables:						
1979	-0.0188	(-1.44E-8)				
1980	-0.0576	(-5.66E-8)				
1981	0.0448	(3.20E-8)				
1982	-0.0259	(-5.18E-8)				
1983	-0.0427	(-1.19E-7)				
1984	-0.0447	(-5.65E-8)				
1985	0.0605	(1.75E-7)				
1986	-0.0568	(-5.16E-7)				
1987	-0.0125	(-1.26E-7)				
1988	0.0280	(7.90E-8)				
1989	-0.0318	(-7.58E-8)				
1990	-0.0568	(-2.27E-7)				
1991	-0.0170	(-3.54E-7)				
1992	-0.0538	(-2.45E-6)				
1993	-0.1353	(-2.66E-6)				
1994	-0.0888	(-1.22E-6)				

Table 8: Cumulative Effect of a Change in Federal Grants on Private R&D, (Controlling for drug sales, GDP, and category and year fixed effects)

Dependent Variable: $PhRMA_{it}$ = PhRMA R&D in disease category j in year t (log changes)

Independent Variables				Cumulative effect of *GRANTS* (Each cell contains the log-change in $PhRMA_{jt}$, k periods after a unit log-change in $GRANTS_{j,t-k}$, implied by a regression with the checked independent variables, calculated by summing the regression coefficients of $GRANTS_{jt}, \ldots, GRANTS_{j,t-k}$.)							
$SALES^a$	GDP^b	Category^c	Year^d	0	1	2	3	4	5	6	7
√	√	√	√	-0.0155	-0.2853	-0.1283	-0.0963	0.0607	0.1941	0.2100	0.1981
√	√	√		-0.1030	-0.3410	-0.1411	-0.0549	0.0694	0.1901	0.1153	0.0815
√	√			-0.1359	-0.3975	-0.2337	-0.1713	-0.0791	0.0028	-0.0808	-0.1367
√		√		-0.1074	-0.3444	-0.1430	-0.0525	0.0698	0.1949	0.1333	0.1117
√				-0.1428	-0.4042	-0.2400	-0.1734	-0.0850	0.0010	-0.0662	-0.1075
	√	√		-0.1069	-0.3541	-0.1934	-0.1395	-0.0949	0.0165	-0.0803	-0.1325
		√		-0.1120	-0.3602	-0.2015	-0.1448	-0.1030	0.0107	-0.0734	-0.1141
	√			-0.1189	-0.3741	-0.2233	-0.1757	-0.1405	-0.0468	-0.1481	-0.2075

[a]Each regression checked includes log changes of current and 7 lagged values of drug sales for each category.

[b]Each regression checked includes log changes of GDP.

[c]Each regression checked includes category dummy variables.

[d]Each regression checked includes year dummy variables.

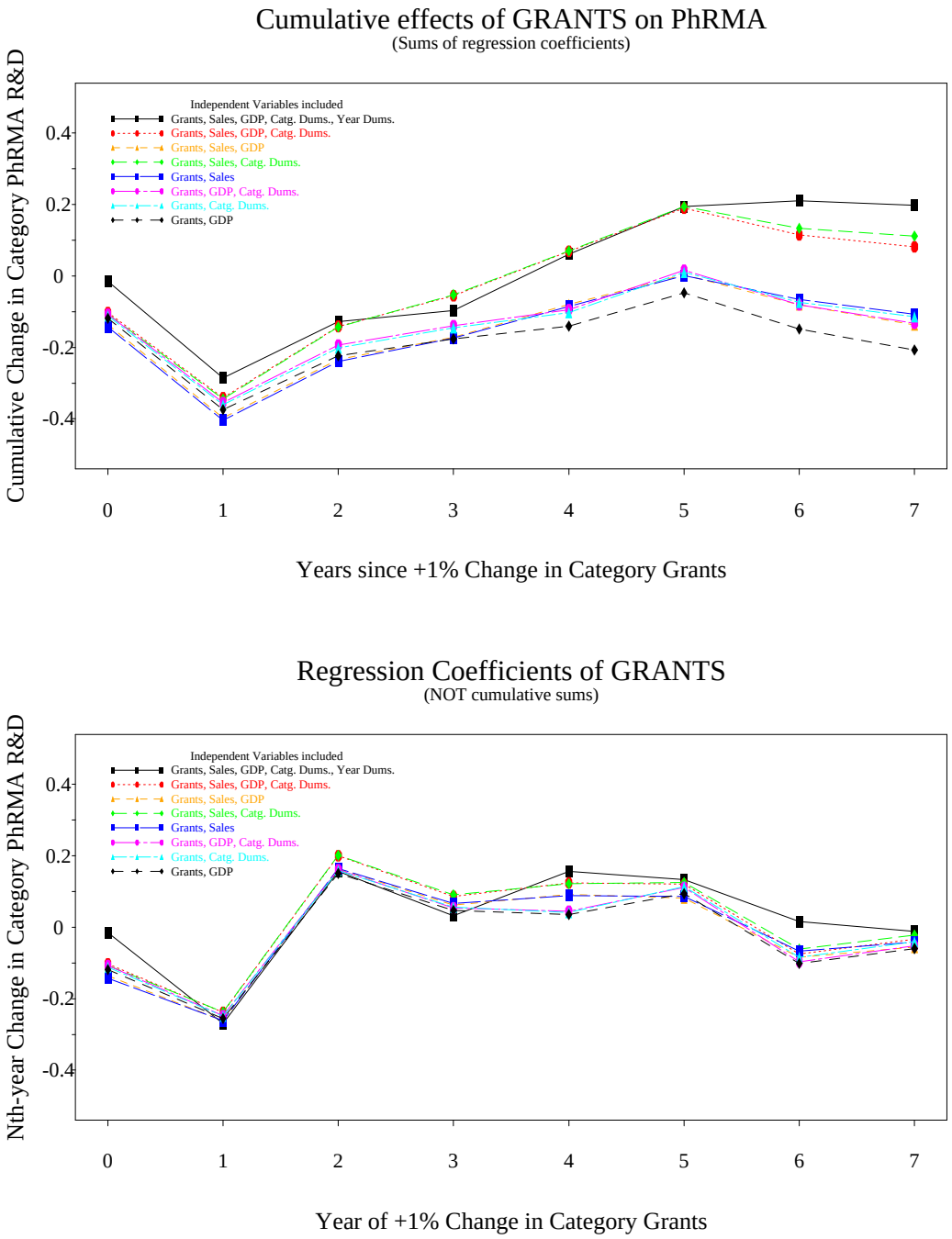

Figure 7: *Upper plot:* Cumulative predicted percent change in Private (PhRMA) R&D in a category, corresponding to a one-time +1% change in Federal Research Grants in that same category, controlling for the variables indicated.
Lower plot: Regression coefficients of Federal Research Grants used to generate cumulative predicted percent change in the upper plot. See Equation 4 on page 68 for the functional form of the regressions.

Table 9: Hypothesis Tests of Cumulative Effects of Changes in Federal Grants

$$Y_{jt} = a + \sum_{i=0}^{k} b_i X_{j,t-i} + h(\text{other variables})$$

"Other variables" include category drug sales (lagged 0 through 7 periods), category dummy variables, and year dummy variables where noted.

This is a test of the null hypothesis that effect of federal grants propogates linearly, against the alternative that the cumulative effect after k years is less than $^{k}/_{8}$ of the effect over 8 years.

$$H_0: \sum_{i=0}^{k} b_i X_{j,t-i} = \frac{1}{k} \sum_{i=0}^{7} b_i X_{j,t-i}$$

$$H_A: \sum_{i=0}^{k} b_i X_{j,t-i} < \frac{1}{k} \sum_{i=0}^{7} b_i X_{j,t-i}$$

Regressions *Including* Year dummy variables:

k	Sum of k Coef's.	Standard Error	Avg. Growth of Coef. Sum	t-stat
0	-0.0155	0.1547	0.0248	-0.2602
1	-0.2853	0.2110	0.0495	-1.5865
2	-0.1283	0.2737	0.0743	-0.7403
3	-0.0963	0.3286	0.0991	-0.5944
4	0.0607	0.4131	0.1238	-0.1529
5	0.1941	0.4527	0.1486	0.1005
6	0.2100	0.4573	0.1734	0.0802

Regressions *Without* Year dummy variables:

k	Sum of k Coef's.	Standard Error	Avg. Growth of Coef. Sum	t-stat
0	-0.1030	0.0920	0.0102	-1.2302
1	-0.3410	0.1336	0.0204	-2.7044
2	-0.1411	0.1973	0.0306	-0.8698
3	-0.0549	0.2437	0.0408	-0.3924
4	0.0694	0.3061	0.0509	0.0602
5	0.1901	0.3437	0.0611	0.3753
6	0.1153	0.3466	0.0713	0.1270

Table 10: Cumulative Effect of a Change in Drug Sales on Private R&D, (Controlling for Grants, GDP, and category and year fixed effects)

Dependent Variable: $PhRMA_{it}$ = PhRMA R&D in disease category i in year t (log changes)

Independent Variables				Cumulative effect of $SALES$ (Each cell contains the log-change in $PhRMA_{it}$, k periods after a unit log-change in $SALES_{i,t-k}$, implied by a regression with the checked independent variables, calculated by summing the regression coefficients of $SALES_t, \ldots, SALES_{t-k}$.)							
$SALES^a$	GDP^b	Category^c	Year^d	0	1	2	3	4	5	6	7
√	√	√	√	-0.1501	-0.0327	0.2013	0.4133	0.2025	0.2084	-0.2622	-0.2820
√	√	√		-0.0609	-0.0575	0.2291	0.4984	0.2890	0.3353	-0.1426	-0.0803
√	√			-0.1069	-0.1123	0.1571	0.4163	0.2218	0.2829	-0.1975	-0.1144
√		√		-0.0433	-0.0293	0.2523	0.5204	0.3034	0.3524	-0.1260	-0.0751
√				-0.0848	-0.0765	0.1864	0.4444	0.2414	0.3078	-0.1716	-0.1002

[a]Each regression includes log changes of current and 7 lagged values of drug sales for each category.

[b]Each regression checked includes log changes of GDP.

[c]Each regression checked includes category dummy variables.

[d]Each regression checked includes year dummy variables.

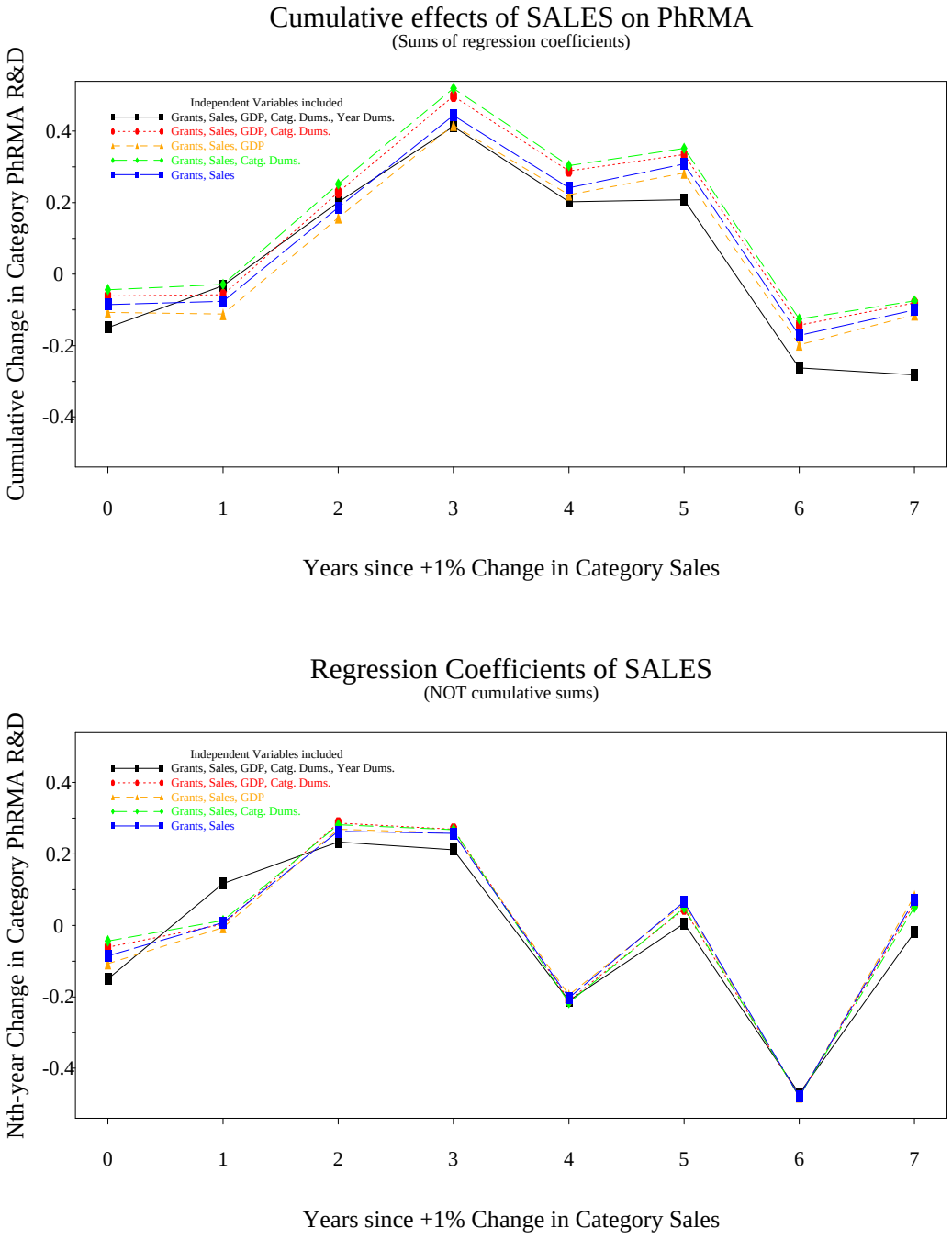

Figure 8: *Upper plot:* Cumulative predicted percent change in Private (PhRMA) R&D in a category, corresponding to a one-time +1% change in Pharmaceutical Sales in that same category, controlling for the variables indicated.
Lower plot: Regression coefficients of Pharmaceutical Sales used to generate cumulative predicted percent change in the upper plot. See Equation 4 on page 68 for the functional form of the regressions.

Table 11: Cumulative Effect of a Change in Federal Grants on Private R&D, (Controlling for drug sales, GDP, and category and year fixed effects)

Dependent Variable: $PhRMA_{it}$ = PhRMA R&D in disease category i in year t (log changes)

Independent Variables			Cumulative effect of *NonMed* (Each cell contains the log-change in $PhRMA_{it}$, k periods after a unit log-change in $NonMed_{t-k}$, implied by a regression with the checked independent variables, calculated by summing the regression coefficients of $NonMed_t, \ldots, NonMed_{t-k}$.)							
NonMed[a]	*SALES*[b]	Category[c]	0	1	2	3	4	5	6	7
√	√	√	-0.8607	-0.0321	1.6718	0.8551	-0.1601	0.0732	0.4733	0.5999
√			-1.0576	-0.0990	1.7048	0.6208	-0.3377	-0.0331	0.3779	0.6885

[a]Each regression includes log changes of current and 7 lagged values of federal non-medical R&D spending.

[b]Each regression checked includes log changes of current and 7 lagged values of drug sales for each category.

[c]Each regression checked includes category dummies. Even though there are no categories for *NonMed*, there are categories for *SALES* and for the dependent variable *PhRMA*.

Foundation (NSF, 2000). Then, total *non-medical* federal research expenditures replaced the federal grants for medical research as the independent variable in regression (4).

The results are shown in Table 11 and Figure 9. The obvious absence of the same "∪-shaped" pattern of coefficients of non-medical federal research spending indicates that the pattern is not the result of some other factor driving all research spending.

Attempting to use instrumental variables to check for serial correlation in the residuals was impractical due to the lack of suitable instruments. All reasonable candidates proved to be uncorrelated with the independent variables.

8.4 Medical Research and Drug Sales

Of course, research expenditure, whether by a private or public entity, benefits consumers only when it results in production of useful new goods or services. While the connection

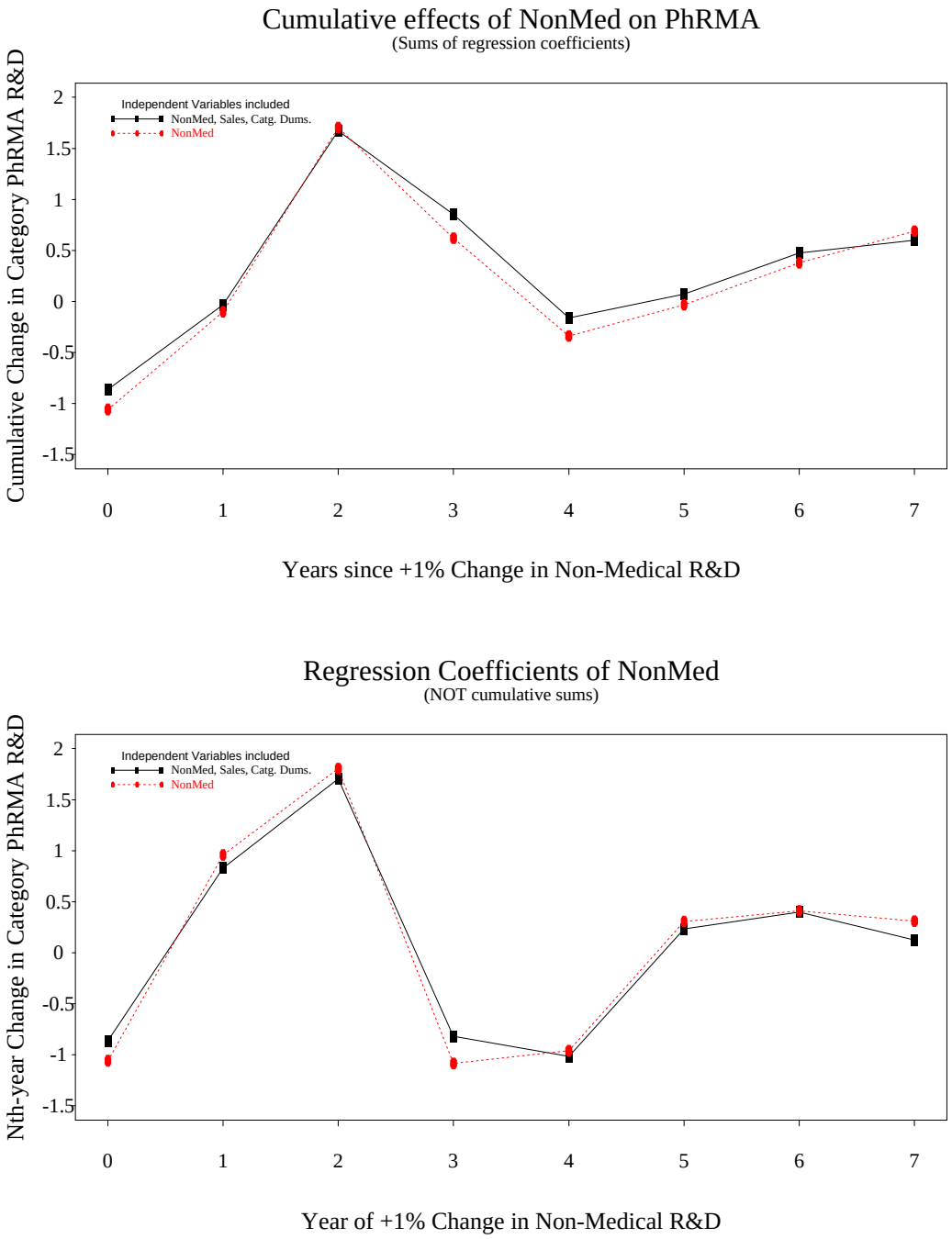

Figure 9: *Upper plot:* Cumulative predicted percent change in Private (PhRMA) R&D in a category, corresponding to a one-time +1% change in Non-Medical Federal R&D, controlling for the variables indicated.
Lower plot: Regression coefficients of Federal Non-Medical R&D used to generate cumulative predicted percent change in the upper plot. See Equation 4 on page 68 for the functional form of the regressions.

between specific research projects and specific new products is often difficult to discern (especially for basic research), it should be the case that increases in overall research effort should eventually lead to increased consumption of related goods. Research by pharmaceutical companies should lead to new drugs, an outcome that may well be observable as increases in total drug sales in a particular therapeutic category.[35] In addition, if government-sponsored research is of ultimate economic benefit, increases in government research funding in a particular category may eventually show up as an increase in drug sales in that category.[36]

Running distributed-lag and VAR regressions with the dollar value of drug sales as the dependent variable and federal and private research spending (separately) as the independent variables allows examination of this effect. The forms of these regressions are the same as in (2) and (3), but with y_t as the dollar value of drug sales in year t, and x_t as the amount of public grants or private R&D expenditures, respectively.

Figure 10 shows log-changes of drug sales and federal research spending for each therapeutic category, and Figure 11 shows log-changes of drug sales and private R&D spending for each therapeutic category. Table 12 shows results of the distributed lag regressions with y_t as the dollar value of drug sales in year t and x_t as federal research spending, and Table 13 shows comparable results with x_t as PhRMA research spending. Figure 12 illustrates the cumulative response of drug sales in each category to a unit change in federal grants and (separately) a unit change in PhRMA spending in that category. Note that, as we would expect, the magnitude of the apparent effect for both types of R&D spending is small in the short run, and large in the long run. However, for some categories the long-run effects are large and negative rather than large and positive. This is the case for both grants and PhRMA spending in two categories and for PhRMA spending in a third category as well.

[35] But not necessarily, since new drugs may simply replace older drugs they render obsolete.

[36] Unfortunately, for reasons described on p. 49, there is not perfect correlation between the disease category in which research is classified and the therapeutic category in which sales of the resulting drug is classified.

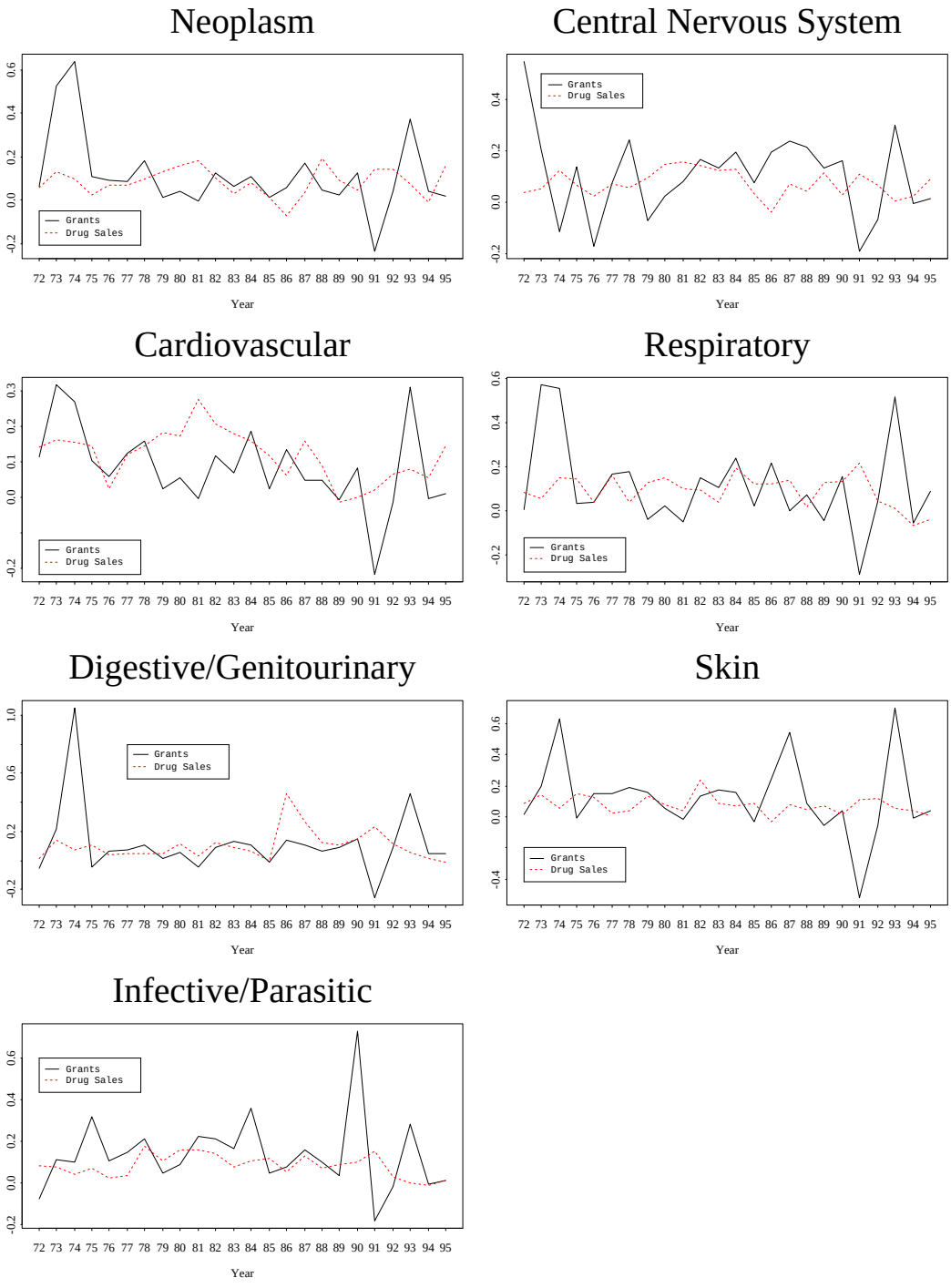

Figure 10: Log of Annual Changes in Federal Grants, and Pharmaceutical Sales, by Therapeutic Category.

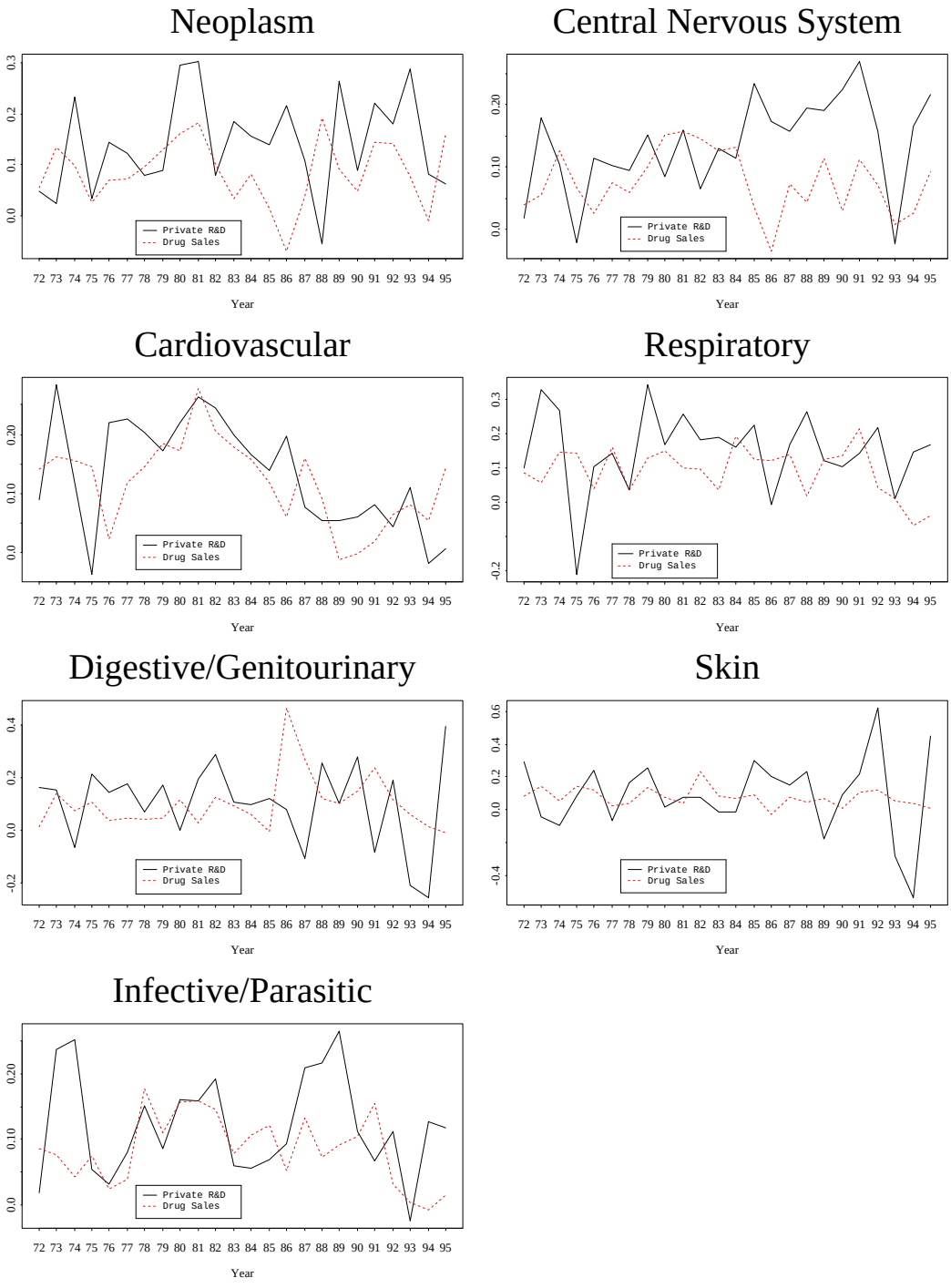

Figure 11: Log of Annual Changes in Private R&D of PhRMA members, and Pharmaceutical Sales, by Therapeutic Category.

Table 12: Distributed Lag Regressions of Sales on Grants, Sum of Coefficients

Dependent Variable: Y = Shipments of Pharmaceuticals (log changes)
Independent Variable: X = Federal Grants, by disease category (log changes)
(Each cell contains the sum of coefficients for the regression with the given number of lags.)

Lags of X	Neoplasm	Nervous	Cardio	Respir	Digest	Skin	Infective	Lag Avg.
0	-0.0151	-0.0876	0.1586	-0.0467	-0.0133	-0.0335	0.0347	-0.0004
1	-0.0826	-0.1103	0.2283	-0.0148	-0.0775	-0.0480	0.1982	0.0133
2	-0.0921	-0.0220	0.2686	-0.0745	-0.1885	-0.0768	0.2983	0.0161
3	-0.2806	-0.0695	0.3000	-0.0618	-0.2594	-0.1030	0.4147	-0.0085
4	-0.3314	-0.2872	0.3025	-0.2752	-0.5096	-0.0994	0.4367	-0.1091
5	-0.2005	-0.3959	0.7243	-0.1225	-0.8496	0.0578	0.6751	-0.0159
6	-0.1168	-0.5538	0.8984	0.2123	-0.0419	0.1558	0.0594	0.0876
7	-0.7604	-0.6579	1.5935	0.2462	2.4307	-0.0366	1.2542	0.5814
Sum	-1.8796	-2.1841	4.4743	-0.1369	0.4909	-0.1837	3.3713	0.5646
Wt. Avg.[a]	-0.0522	-0.0607	0.1243	-0.0038	0.0136	-0.0051	0.0936	0.0157
Avg.[b]	-0.2349	-0.2730	0.5593	-0.0171	0.0614	-0.0230	0.4214	

[a]The average cumulative response, weighted by number of coefficients; or equivalently, the average coefficient.

[b]The average cumulative response over the eight regressions; i.e., each regression has equal weight.

Table 13: Distributed Lag Regressions of Sales on Private R&D, Sum of Coefficients

Dependent Variable: Y = Shipments of Pharmaceuticals (log changes)
Independent Variable: X = PhRMA Corporate R&D, by disease category (log changes)
(Each cell contains the sum of coefficients for the regression with the given number of lags.)

Lags of X	Neoplasm	Nervous	Cardio	Respir	Digest	Skin	Infective	Lag Avg.
0	0.0141	0.0055	0.3598	-0.0250	-0.0980	0.0288	0.1693	0.06493
1	-0.1550	0.0100	0.6439	0.1648	0.1049	0.0804	0.2537	0.15752
2	-0.0612	-0.1942	0.8156	0.2128	0.1756	-0.0584	0.4354	0.18937
3	-0.2125	-0.2371	0.7815	0.3658	0.0795	-0.0347	0.4427	0.16933
4	-0.4701	-0.2705	0.7529	0.3567	0.2290	0.3125	0.6641	0.22494
5	-1.1708	-0.4663	0.6550	0.3161	1.2158	-0.0416	0.2515	0.10852
6	-1.6135	-0.6936	0.4646	0.9625	1.1020	0.5136	-2.1847	-0.20703
7	-2.4096	-0.8243	0.4366	2.2342	2.0070	0.2051	-2.5360	-0.12671
Sum	-6.0786	-2.6706	4.9099	4.5879	4.8159	1.0055	-2.5040	0.58086
Wt. Avg.[a]	-0.1689	-0.0742	0.1364	0.1274	0.1338	0.0279	-0.0696	0.01614
Avg.[b]	-0.7598	-0.3338	0.6137	0.5735	0.6020	0.1257	-0.3130	

[a]The average cumulative response, weighted by number of coefficients; or equivalently, the average coefficient.

[b]The average cumulative response over the eight regressions; i.e., each regression has equal weight.

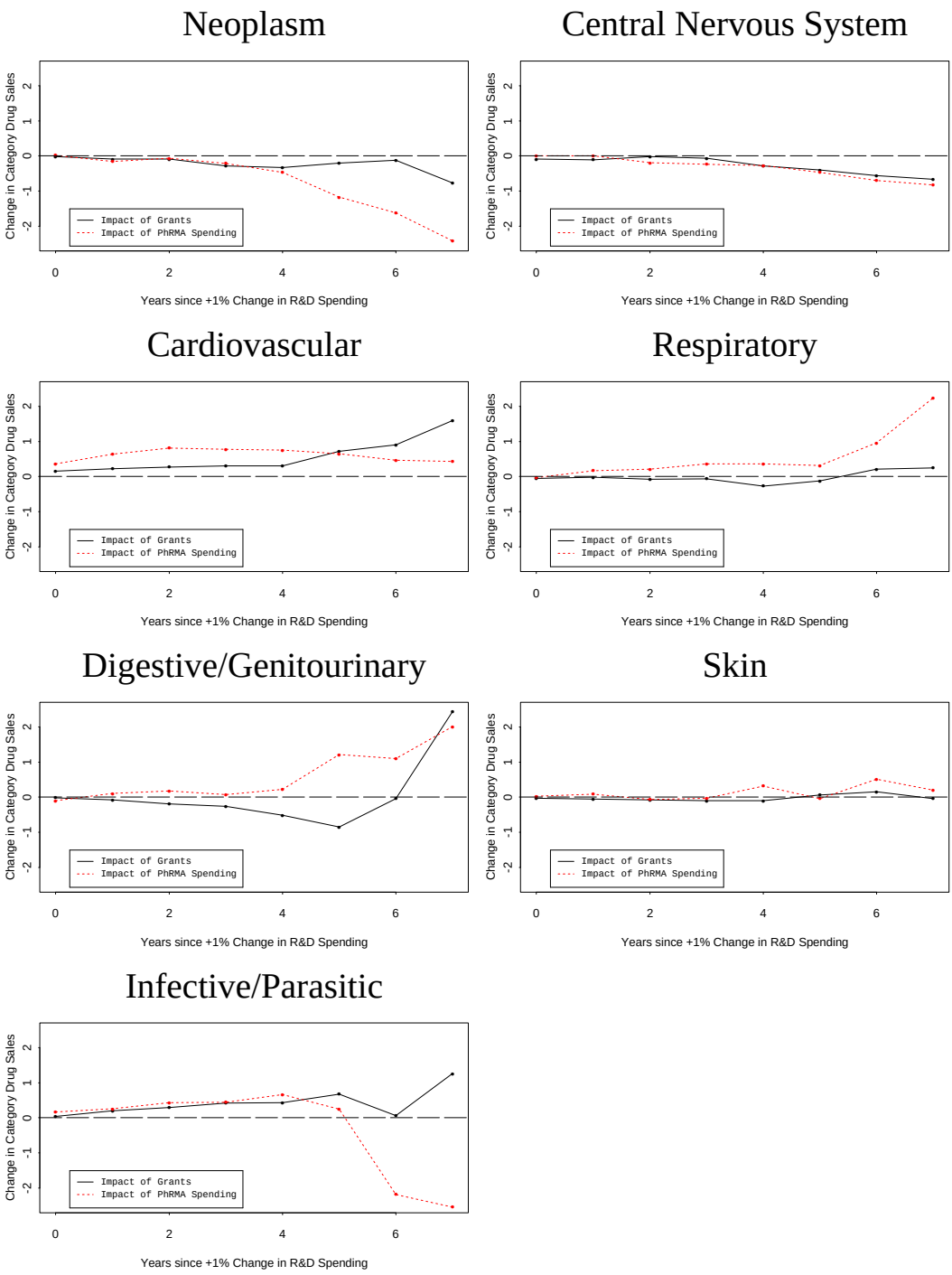

Figure 12: Cumulative predicted percent change in drug sales corresponding to a one-time +1% change in R&D, by therapeutic category. In each plot, the solid line represents the response to a change in federal research grants, and the dashed line the response to a change in private (PhRMA) R&D.

The presence of negative effects of R&D spending on sales bears further investigation. It is quite likely, given the length of time it takes to do research and the lengthy regulatory process required to bring a drug to market, that the true effect of R&D spending on drug sales is not seen in the first seven years after the research dollars are spent. Unfortunately, with only 25 years' worth of data, it is not possible to study such long-term effects adequately. It is possible to drop early lag terms from the regression, but extending the lag structure back much farther would result in the loss of too many degrees of freedom.

Table 14 shows the results of VAR simulations and F-tests for the same data, and Figure 13 displays plots of the direct and VAR effects of an increase in federal research spending in one year on drug sales in subsequent years. Likewise, Table 15 lists the results of VAR simulations and F-tests for the same data, and Figure 14 contains plots of the average effect of an increase in private R&D spending in one year on drug sales in subsequent years.

Compared with regressions in which private R&D is the dependent variable, regressions with pharmaceutical sales as the dependent variable are less conclusive, but still somewhat interesting. The distributed lag regressions show a negative effect of grants on sales for five of the seven categories for zero through four lags, but three of these five turn positive by the seven-lag regressions. The other two are positive for all (zero through seven) lags. With private rather than government research as the independent variable, more coefficients are positive, but there is no clear pattern. (The proportion of negatives and positives is roughly the reverse of that with government research as the independent variable.) As noted above, one possible reason for this is that the effect of research on sales probably has much longer lags.

Table 14: Simulation of Direct and VAR Effects of Log of Annual Changes in Federal Grants on Pharmaceutical Sales.

(Each cell contains the change in Y_t, t periods after a unit log-change in X, implied by the regression with k lags of X and $k-1$ lags of Y.)

		t								
	k	0	1	2	3	4	5	6	7	8
Neoplasm	2	0.0340	0.1250	0.1298	0.1053					
	3	-0.0604	0.1189	0.2083	0.0669	0.0644				
	4	0.1953	0.4510	0.1254	-0.0492	0.2123	0.2163			
	5	0.2516	0.2526	0.0924	0.1385	0.0873	-0.0208	0.0442		
	6	0.3893	0.4197	0.1465	0.3568	0.3965	-0.1860	-0.5788	-0.1161	
	7	0.9249	0.6957	0.7526	1.0263	1.8112	0.5771	-1.0959	0.0865	0.7371
Nervous	2	-0.1099	-0.1151	-0.0140	-0.0629					
	3	-0.1017	-0.1183	-0.0178	-0.1029	-0.0970				
	4	-0.1511	-0.1735	-0.0892	-0.1040	-0.2153	-0.1566			
	5	-0.2053	-0.2589	-0.2097	-0.1553	-0.2327	-0.1448	-0.1970		
	6	-0.1454	-0.2970	-0.1805	-0.2413	-0.2562	-0.1590	-0.1386	-0.1991	
	7	0.2918	-0.2602	-0.0251	0.0046	-0.5939	-0.2023	-0.5246	0.6894	-0.1323
Cardio	2	-0.0038	0.0521	-0.0182	0.0578					
	3	-0.0038	0.0511	-0.0172	-0.0938	0.0907				
	4	0.0090	0.1287	-0.0997	-0.0927	-0.0983	0.1733			
	5	0.0365	0.2961	0.0736	0.0980	-0.2123	-0.1729	0.1790		
	6	0.2006	0.2212	0.1317	0.1131	-0.0565	-0.2127	-0.1327	0.1319	
	7	0.0335	0.1257	0.1047	-0.4162	-0.0014	0.5199	-0.5513	0.1740	1.2105
Respir	2	0.0153	0.2746	0.0138	0.1056					
	3	-0.0769	0.2382	0.0248	0.1836	0.1114				
	4	-0.0848	0.1864	-0.1085	0.2478	0.0227	0.1599			
	5	-0.0466	0.2873	-0.1536	0.2122	-0.0975	-0.0337	0.1162		
	6	0.0143	0.2366	-0.1182	0.2261	-0.0085	0.0197	0.1854	-0.0153	
	7	-0.3165	0.1710	-0.0624	2.2143	-2.6741	-5.6777	10.867	11.9494	-35.532
Digest	2	-0.0342	0.0161	-0.0346	0.0310					
	3	-0.0417	0.00043	-0.0426	0.0022	0.0383				
	4	-0.0597	-0.1776	-0.1048	-0.0058	0.0281	0.0503			
	5	-0.0363	-0.0634	-0.0600	0.0183	0.0799	0.0111	0.1166		
	6	0.4548	0.2948	0.1151	0.1673	0.2209	0.3419	0.1271	0.0710	
	7	0.7910	0.2417	0.8631	0.7027	0.9661	-0.3133	-0.6185	0.4951	-0.1931
Skin	2	-0.0988	-0.1596	-0.0991	-0.0973					
	3	-0.1060	-0.2322	-0.1104	-0.0955	-0.1396				
	4	-0.1028	-0.2337	-0.1040	-0.0741	-0.1339	-0.1380			
	5	-0.0916	-0.1899	-0.1337	-0.0571	-0.1109	0.0500	-0.1088		
	6	-0.0731	-0.2186	-0.1256	-0.0636	-0.1369	0.0588	-0.0167	-0.1746	
	7	-0.0852	-0.5632	-0.2924	-0.2770	-0.0766	0.1352	0.0648	-0.4410	-0.6472
Infective	2	0.0767	0.1256	0.0412	0.0072					
	3	0.0412	0.0813	0.0138	0.0444	-0.0084				
	4	0.0720	0.1133	0.0311	0.0384	-0.0195	-0.0299			
	5	0.1321	0.2531	0.1629	0.1652	0.0451	0.1149	-0.0636		
	6	0.0840	0.1431	0.1638	0.0508	-0.0456	-1.6E-4	-0.0639	-0.1600	
	7	0.1455	0.4090	0.5087	0.3058	0.1463	0.2340	0.3967	-0.6934	-0.4365

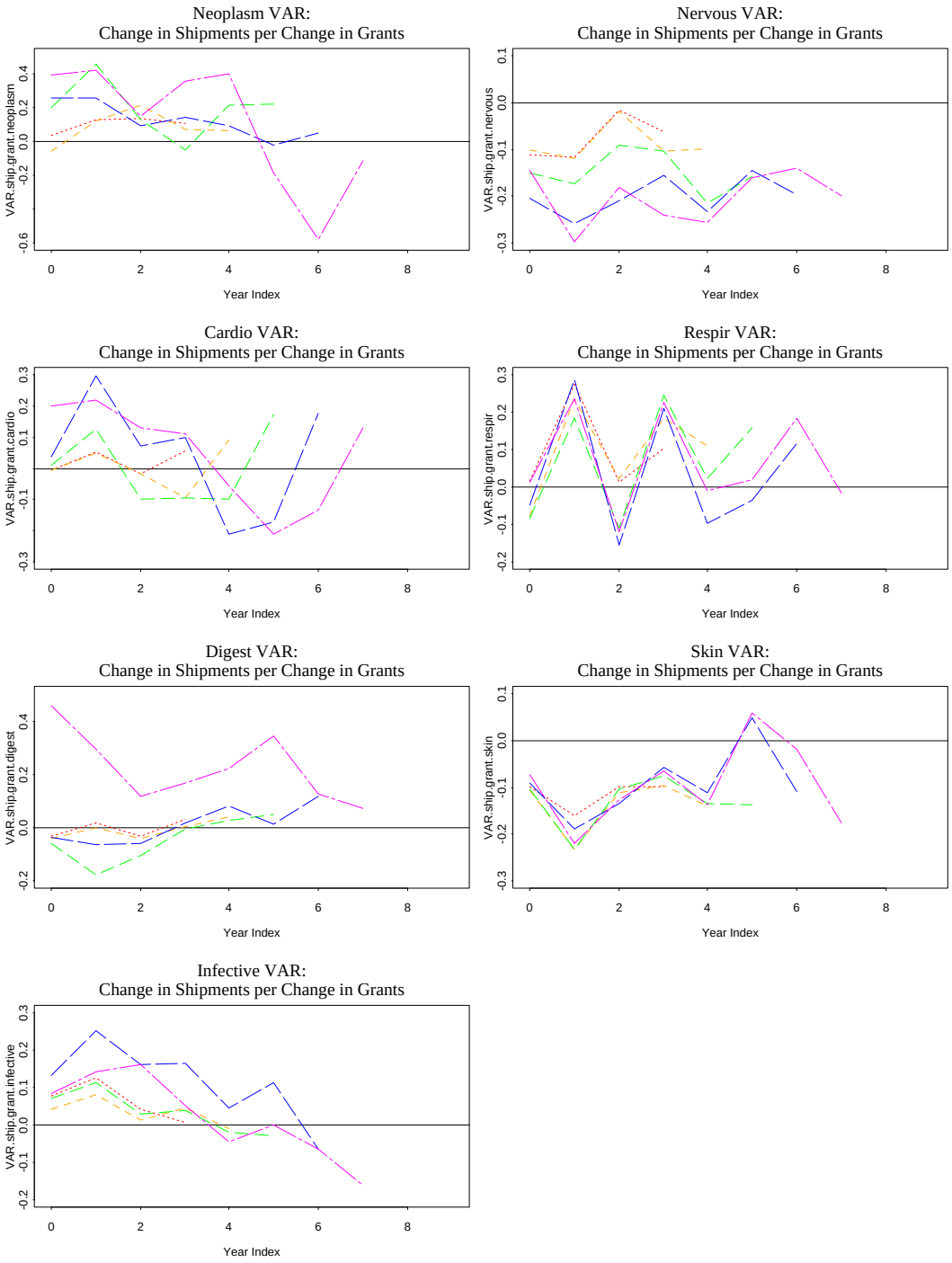

Figure 13: Simulation of Direct and VAR Effects of Log of Annual Changes in Federal Grants, on Drug Sales, by Therapeutic Category.
(Each line shows the cumulative change at each stage in a regression with a given number of lags; the number of lags is shown by the extent of the line. Thus, each chart has a line with three lags, a line with four lags, and so on.)

Table 15: Simulation of Direct and VAR Effects of Log of Annual Changes in Private R&D on Pharmaceutical Sales.

(Each cell contains the change in Y_t, t periods after a unit log-change in X, implied by the regression with k lags of X and $k-1$ lags of Y.)

		t								
	k	0	1	2	3	4	5	6	7	8
Neoplasm	2	-0.0914	-0.1560	0.0019	0.0177					
	3	-0.0105	-0.0103	0.0736	-0.1014	-0.0645				
	4	-0.1262	-0.2123	-0.2198	-0.3070	-0.1406	-0.0009			
	5	-0.1285	-0.1955	-0.1058	-0.1990	-0.1634	-0.2805	-0.1433		
	6	0.0019	-0.0327	-0.0395	-0.0844	-0.0340	-0.3474	-0.2431	0.1092	
	7	0.2744	-0.0064	0.2404	-0.7645	0.9587	-2.2381	2.6067	-5.1732	9.7175
Nervous	2	0.0175	0.0812	-0.1975	-0.0767					
	3	0.0391	0.0728	-0.1621	-0.0981	-0.0378				
	4	0.0062	0.0057	-0.1923	-0.1522	0.0696	0.0331			
	5	0.1282	0.0840	-0.0902	-0.1433	-0.1708	-0.5156	-0.0730		
	6	-0.0557	-0.2495	-0.4054	0.1123	0.1853	-0.4582	0.0907	0.1227	
	7	-0.5103	-0.6220	-0.1842	-0.0343	0.6602	-0.1409	0.0514	0.0444	-0.6569
Cardio	2	0.0934	0.4794	0.3042	0.0274					
	3	0.1563	0.4458	0.3395	-0.0928	0.0388				
	4	0.3141	0.4522	0.3919	-0.1634	0.0110	-0.1440			
	5	0.2765	0.6192	0.4091	-0.2089	0.0550	-0.3582	0.0718		
	6	0.2399	0.5946	1.0801	-1.1658	0.8753	-1.4580	1.2736	-1.7544	
	7	1.0276	-2.4204	11.8703	-43.486	164.20	-624.02	2366.1	-8972.5	3.40E4
Respir	2	0.0122	0.0753	-0.0297	-0.0631					
	3	-0.0132	0.0984	-9.0968	0.1335	-0.0209				
	4	-0.0391	0.0960	-0.0222	0.1139	-0.0744	-0.0710			
	5	-0.1769	-0.2387	-0.0267	0.2287	0.2034	0.0607	-0.2660		
	6	-0.2898	-0.3827	-0.2066	-0.1134	-0.3095	-0.8534	-1.2032	-1.4934	
	7	-13.818	-210.41	-3005.6	-4.30E4	-6.16E5	-8.81E6	-1.26E8	-1.81E9	-2.6E10
Digest	2	-0.0434	0.3184	0.0450	0.1375					
	3	-0.0578	0.3767	-0.0654	-0.0530	0.1853				
	4	-0.1101	0.4826	-0.1827	-0.1341	0.1212	0.2396			
	5	-0.1315	0.6564	-0.4576	0.1157	0.1679	0.7307	-0.3429		
	6	0.1327	0.5955	-0.3748	-0.1707	0.6426	0.7012	0.0205	-0.4967	
	7	0.2777	0.5359	1.0629	1.3391	3.4229	4.9002	5.6947	8.3283	11.331
Skin	2	-0.0148	0.0226	-0.1018	-0.0018					
	3	-0.0509	0.0031	-0.1281	-0.0349	0.0041				
	4	0.1381	0.3593	0.3100	0.6857	0.9744	0.7715			
	5	-0.0435	0.0058	-0.3637	-0.2427	-0.1014	-0.4277	0.2192		
	6	-0.0418	0.0770	-0.3073	-0.1141	0.0446	-0.3929	0.2330	-0.0028	
	7	0.0213	-0.4530	-1.0431	-1.0053	-1.5809	-1.7191	-0.0341	2.7344	6.9342
Infective	2	0.1988	-0.0469	0.0900	-0.0028					
	3	0.2399	-0.0186	0.0281	-0.0819	-0.0928				
	4	0.2447	0.0216	0.1012	-0.1646	0.0800	-0.0622			
	5	0.0698	-0.2208	0.1008	-0.2327	-0.1811	-0.2700	-0.3432		
	6	-0.2370	-0.8207	-0.3540	-0.0761	-0.7344	-0.5896	-0.9846	-0.9006	
	7	-0.1579	-0.9906	-0.2746	-0.0596	-0.6801	-0.5073	-0.6778	-1.0273	-0.9447

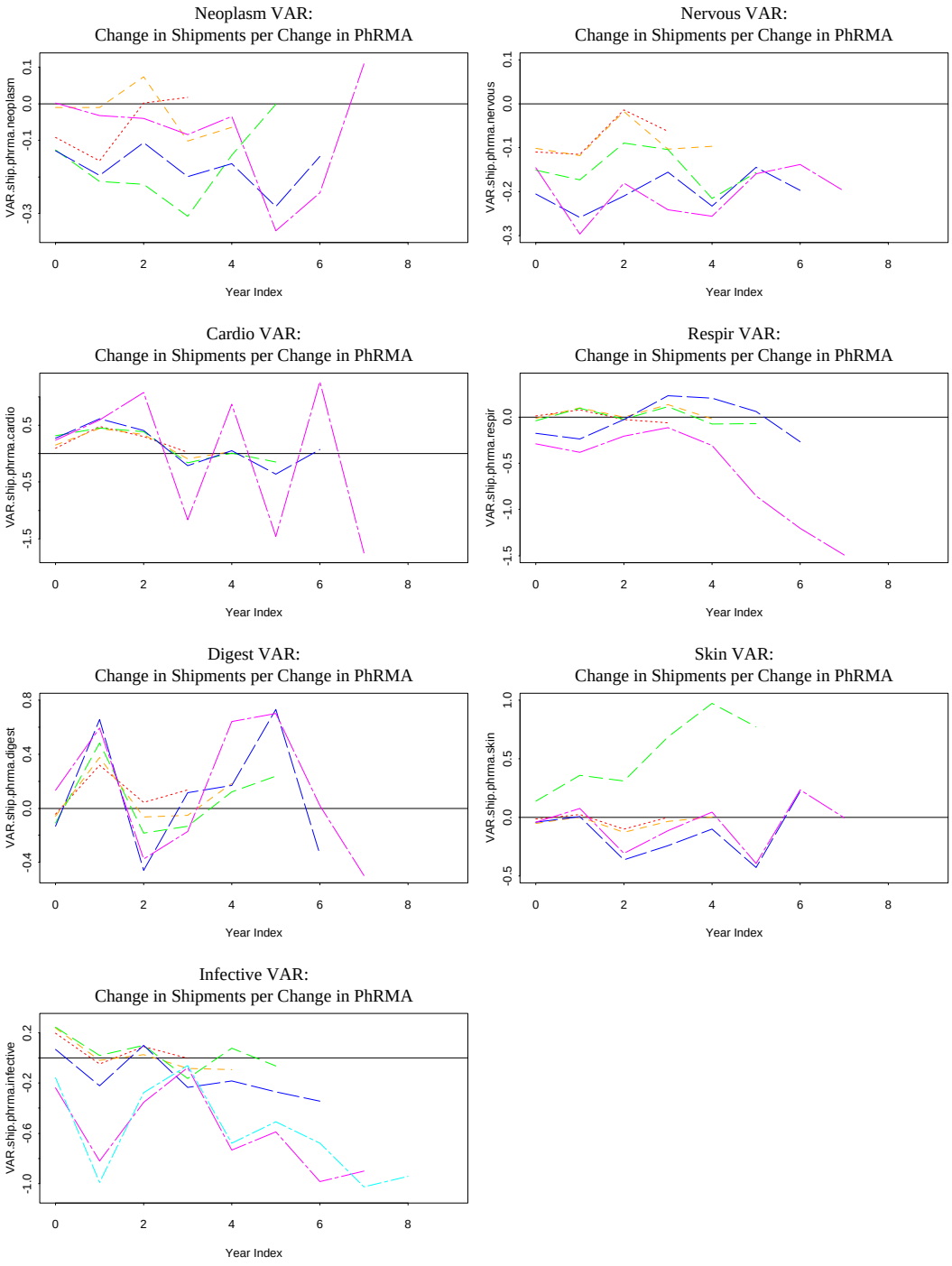

Figure 14: Simulation of Direct and VAR Effects of Log of Annual Changes in Private R&D, on Drug Sales, by Therapeutic Category.
(Each line shows the cumulative change at each stage in a regression with a given number of lags; the number of lags is shown by the extent of the line. Thus, each chart has a line with three lags, a line with four lags, and so on.)

9 Conclusion

Due to the uncertainty inherent in research activity and the fact that the research output may be imperfectly appropriable, the private sector might in equilibrium provide suboptimal levels of innovative effort, particularly in areas of basic research. One possible solution to this problem is for government to provide subsidies for basic research, in the hope that the increased stock of basic scientific knowledge that results will stimulate the private sector to increase its investment in more-appropriable applied research, and thus ultimately stimulate private-sector innovation. However, since basic research is at least partly appropriable and because research inputs are inelastically supplied, government funding of basic research may in fact crowd out private research.

Based on an analysis of data on public funding of biomedical research and private-sector funding of R&D in the pharmaceutical industry, one finds that increases in government research funding appear to crowd out private R&D in the short run, but stimulate private R&D in the long run. Because there is a time lag between funding of basic research and utilizing the results, this finding is consistent with a theory that government funding crowds out private basic research but stimulates private applied research.

The crowd-out effect is more pronounced when expenditures are deflated to constant dollars using the Biomedical Research and Development Price Index (BRDPI), relative to the effect observed when using current dollars, or constant dollars according to the GDP deflator. This is consistent with the observation that R&D inputs, particularly the services of scientific personnel, are inelastically supplied; therefore, research subsidies increase the price of research for private firms and thus directly crowd out private R&D.

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Acronyms

ADR Adverse Drug Reaction.

ATP Advanced Technology Program. Operated by NIST, this program provides federal grants for development of certain technologies by private for-profit firms.

BRDPI Biomedical Research and Development Price Index. A price index for inputs into biomedical research, including personnel, laboratory equipment, and other inputs, developed by the Bureau of Economic Analysis of the Department of Commerce in cooperation with the NIH and used by the NIH for budgeting purposes.

CDER Center for Drug Evaluation and Research. The unit of the FDA that evaluates applications for drug approval (INDs and NDAs).

CRADA Cooperative Research and Development Agreement. A formal agreement between a national laboratory and a private firm, one purpose of which is commercialization by the firm of discoveries made by the lab.

CRISP Computer Retrieval of Information on Scientific Projects, a database containing information on all biomedical research projects funded by the U.S. Public Health Service, which includes the NIH and other federal agencies which sponsor or conduct biomedical research.

COO Chief Operating Officer.

COX Cyclooxygenase, an enzyme, also called Prostaglandin G/H Synthase (PGHS). At least two forms of COX are known to exist: the "constitutive" form, COX-1, which has an important role in the digestive system, and the "inducible" for, COX-2, which has a critical role in the inflammatory process. Some researchers think there may be a third form (COX-3) that has some role in producing fever.

FDA Food and Drug Administration.

GATT General Agreement on Tariffs and Trade.

GI Gastro-intestinal.

GDP Gross Domestic Product.

IND Investigational New Drug Application, submitted to the FDA before clinical (i.e., human) testing of the drug. If the FDA does not object within 30 days, the applicant may begin clinical testing.

NASA National Aeronautics and Space Administration.

NBER National Bureau Of Economic Research.

NCE New Chemical Entity. A new drug that is not merely a reformulation or combination of existing drugs, but one based on entirely new molecule. Most pharmaceutical R&D is directed at discovering and developing NCEs.

NDA New Drug Application, submitted after clinical testing is completed. If the FDA believes the information contained in the NDA (including the results of clinical and animal testing) shows that the drug is both safe and effective for a particular use, the FDA approves the drug for marketing for that use.

NIH National Institutes of Health.

NIST National Institute of Standards and Technology.

NPV Net Present Value.

NSAID Non-Steroidal Anti-Inflammatory Drug. Historically, the term is used to refer to non-selective COX inhibitors developed after aspirin, but technically aspirin and the new COX-2 inhibitors are also NSAIDs.

PGHS Prostaglandin G/H Synthase, an enzyme, also known as Cyclooxygenase (COX, q.v.).

NSF National Science Foundation.

PhRMA Pharmaceutical Research and Manufacturers of America, previously known as Pharmaceutical Manufacturers' Association (PMA).

PMA Pharmaceutical Manufacturers' Association, later renamed Pharmaceutical Research and Manufacturers of America (PhRMA).

R&D Research and Development. Includes basic research, applied research and product development.

SBIR Small Business Innovation Research Program. Operated by the Small Business Administration, this program sets aside a certain percentage of R&D contracts in each federal government department for qualified small businesses.

SIC Standard Industrial Classification. The Census Bureau assigns SIC codes to each of thousands of industries for reporting sales and other data on a per-industry basis. SIC codes are hierarchical; that is, "two-digit industries" are aggregations of "four-digit" industries, and so on. For example, SIC code 28 refers to "Chemicals and Allied Products," 283 refers to "Drugs," 2834 to "Pharmaceutical Preparations," and 28341-28348 refer to drugs in different therapeutic classes, as shown in Table 2.

VAR Vector Autoregression. A regression model containing, as "independent" variables, lagged values of the dependent variable.