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

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Abstract

We study dynamic effects of government research funding on private-sector R&D in the pharmaceutical industry. Increases in government research grants appear to "crowd out" private expenditures for approximately the first four years, but start to stimulate private research in the fifth year. 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. Anecdotal data on a new class of drugs (COX-2 inhibitors) support this interpretation. Also, empirical results show no clear effect of government funding on output.

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1 Introduction

A major source of economic growth in advanced countries is technological improvement due to organized research effort (Romer 1990). Because of the uncertainty inherent in research and the fact that the output of research activity may be inappropriable, in equilibrium the private sector might provide suboptimal levels of innovation, particularly in areas of "basic" research (Arrow 1962; Nelson 1959). One possible solution, first proposed by Francis Bacon (1561-1626), is for government to provide subsidies for basic research; however, government funding of basic research might "crowd out" private basic research, mitigating its effectiveness. On the other hand, government funding might stimulate private applied research by adding to the stock of knowledge. The goal of this paper is to study the effects of government research funding on private-sector research and development (R&D) expenditures and new product development; in particular, to identify and measure crowd-out and stimulation effects.

I use 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 reasonable interpretation is that the direct effect of government funding is to crowd out private basic research but stimulate private applied research.to

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). In 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 than in other industries. Basic research into disease processes, which is funded by government grants as well as by private companies and nonprofit organizations, produces results which are 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 (as opposed to trade secrets) and are subject to technical regulation by the Food and Drug Administration (FDA),which means that much more data on private R&D are publicly available than for 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 2001 total U.S. private-sector pharmaceutical R&D spending was $23.5 billion, accounting for 18.3% of U.S. pharmaceutical sales (PhRMA 2003). The federal government spent over $17 billion in medical and biological research in 2001, accounting for 23% of federal R&D spending (NSF 2002), not including the implicit subsidies of the research and orphan drug tax credits. 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 Congress appropriated $27.3 billion to NIH for fiscal year 2003.[1]

Finally, biomedical research is important because the social gains are huge: Murphy and Topel (2003) and Nordhaus (2003) 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 (2003) estimates that a large portion of the increased U.S. life expectancy is due to new drugs; in particular, the average new drug introduced between 1970 and 1991 is estimated to have saved 18,800 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 1.3% of total GDP.

Not surprisingly, 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 seems to indicate that it is implicitly a subsidy of costs that would otherwise 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.

[1] While most academic research is government-funded, it is not exclusively so: Blumenthal et al. (1996) estimate that private firms provided about $1.5 billion, or about 11.7%, of the funds supporting academic research in the life sciences in 1994 (the latest year for which figures are available).

The plan of this paper is as follows. Section 2 discusses basic issues important to understanding the economics of innovation and reviews prior work. Section 3 describes the econometric model on which the analysis is based, and Section 4 describes the data used. Section 5 describes the results and their interpretation. Section 6 is a case study, tracing the development of one specific class of drugs from government-funded basic research to privately-funded applied research and product development. Section 7 concludes.

2 Basic Issues in the Economics of Innovation

Technology is a type of information, and is traditionally viewed as a public good: once produced, perhaps at great cost, it can be used by many people and organizations at relatively low marginal cost. Unlike physical goods or money, when technology is transfered 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 it.

While ability to make *use* of technology is unaffected by transmission of information, ability to *profit* from it may be greatly reduced. One may go to great lengths and expend substantial resources on research to produce technology, only to find that the having the technology is no longer profitable 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 is the existence of patent systems, which grant to innovators monopoly rights to their discoveries for substantial (but limited) periods of time. The main problem with patents is that they are *ex post* inefficient, due to these monopoly rights. However, 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 attempts to stimulate innovation without patent protection by giving prizes for successful innovations known in advance to be useful to society (see Sobel (1995) for an intriguing example and Che and Gale (2003) for a theoretical model), or by providing government subsidies, in the form of either tax credits or direct cash subsidies to innovators. Furthermore, for numerous fields in which innovative effort is thought to be under-provided 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, whose results are to some extent publicly available at marginal cost. However, patent rights to derivative innovations may be available to the same researchers who were given subsidies.[2]

Another rationale for providing government grants for basic research is the belief that more basic research is not only beneficial in its own right, but also stimulates private-sector applied research, which produces economic growth. This rationale is often explicitly cited by policy makers to justify government spending,[3] and there is some empirical evidence indicating that government-funded scientific research is an important input into patentable applied research.[4]

However, there is a downside to this policy as well. With government funding of basic research, the results of which are to be publicly available,[5] the private returns to basic re-

[2] In the U.S., this has been the case especially since the passage of the U.S. Patent and Trademark Amendments Act of 1980 (the "Bayh-Dole Act") and subsequent amendments in 1984.

[3] 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).

[4] See, for example, Narin, Hamilton, and Olivastro (1997).

[5] 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 math-

search are reduced, for two reasons. First, if the government is funding research and making the results available for free, there is little benefit to a private firm's spending money to do 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-reporting 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 its 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 extreme situation will not occur.

ematician with a 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.

Causal links between government basic science and technological progress have been difficult to establish empirically. Some "spillover" studies attempt to link universities and government laboratories to firms that are geographically nearby and appear to benefit from having the scientists nearby (Jaffe, Trajtenberg, and Henderson 1993). Others focus on some sort of link through which information flows; for example, Adams, Chiang, and Jensen (2003) study the Cooperative Research and Development Agreements (CRADAs) between national laboratories and private firms, and Jaffe, Fogarty, and Banks (1998) measure spillovers by the number of citations of patents issued to federal labs in other patents issued to private inventors. A series of studies (Narin and Olivastro 1992; Narin, Hamilton, and Olivastro 1997; Deng, Lev, and Narin 1999) measures the impact of university research by counting citations to journal articles in patents owned by firms.

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

Crowd-out effects have been found by Joglekar and Hamburg (1983, 1986), Irwin and Klenow (1996a, 1996b), and Lach (2000). Wallsten (2000) found nearly dollar-for-dollar crowding out of private expenditures by government grants in the Small Business Innovation Research Program (SBIR) program, and Gans and Stern (2000) found that the performance of projects funded by SBIR is highest in industries that also have the highest level of venture capital financing.[6]

[6] For a further survey of the literature, see David, Hall, and Toole (2000).

These last two findings 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. In the case of medical research, an internal NIH study (NIH, 2000) makes this nearly explicit: it summarizes the major events in the development of the "top five" drugs, as measured by worldwide sales in 1994, and examines the role of NIH funding in the basic research (and scientist training) that can be linked to those drugs. The government's funding of medical research projects is explicitly justified on the grounds that it leads to top-selling drugs.

Although "basic science" projects are, by definition, undertaken without a specific commercial product in mind, 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. In both the SBIR and NIH cases, the projects touted for their profit potential are *ipso facto* 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 and NIH program administrators have the effect of minimizing the actual impact of their programs on R&D expenditures, since they induce funding decisions that selectively crowd out, rather than complement, private investment.

Levy and Terleckyj (1983) find that while contract spending has a large and statistically significant complementarity with privately-funded R&D, the effect of grant R&D on private R&D has a regression coefficient that is small and statistically insignificant – and initially negative, but turning positive after a lag of three years. Levin and Reiss (1984) found a small positive effect and a small decrease in the elasticity of unit cost in the same year, with no consideration of lagged effects. 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.

David and Hall (1999) construct a theoretical model of interaction between public and private R&D which predicts that 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. Also, 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.

Several studies have focused on the benefits of biomedical research subsidies by themselves. Reaves (1995) investigated the effects of the Orphan Drug Act (ODA), which provides market exclusivity and a 50% tax credit for clinical trials of drugs used to treat rare diseases. She reports that in the decade prior to enactment, only ten drugs that would have qualified as orphan drugs were introduced. In the first decade after ODA, over 400 substances received the orphan drug designation, and over 100 designated orphan drugs were approved by the FDA. Lichtenberg (2001) is one of the few studies that do not take government funding to be exogenous; 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 (2001) survey a number of studies of the effects of public research on the pharmaceutical industry and conclude that the social 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 those of Murphy and Topel (2003).

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. They report that a 1% increase in the budget of a constituent institutes of the NIH corresponds to a cumulative increase in private spending in a linked research category 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 and expanded version of the same data for industry R&D, but a much more detailed set of data for government-sponsored R&D. With 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 therapeutic categories that do not have corresponding NIH institutes, and to avoid the problem of classifying funding in the wrong category when a project is funded in the "wrong" institute,[7] as might happen for political or budgetary reasons, or when a research program has subcomponents that cut across categories. 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, do not adjust for inflation at all.[8] 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

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

[8] 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).

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.

3 Models of Scientific Research

3.1 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, technological progress is produced by a simple three-step process:

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

The first step is "basic research," which is scientific inquiry oriented toward understanding natural processes rather than toward producing marketable products or making profits.[9] 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

[9] 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.

a potentially marketable product or service that makes (potentially) profitable use of the technology.

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 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 9, 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.

3.2 Economic Models of Research

We are concerned primarily with incentives that encourage firms to undertake costly research and development. 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. There is also the risk that a competitor will develop a drug with similar therapeutic properties, in which case two patent-protected monopolies will function in the market as a duopoly, reducing profits to both firms.[10]

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

BR = Basic Research expenditure

C = Unit Cost of Research (including wages of researchers)

R = Firm's (utility) of return, i.e., risk-adjusted expected return

A = A measure of the degree and likelihood of appropriability of discoveries

Clearly, $f'(C) < 0$, $f'(R) > 0$, and $R'(A) > 0$. However, the firm's return $R(A)$ may

[10] This has been the case with several recently-developed drugs, including histamine-2 blockers (Tagamet and Zantac) and COX-2 inhibitors (Celebrex and Vioxx).

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 (perhaps only slightly so) 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, 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, 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, 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.[11]

[11] Kealey (1995, pp. 226-230) has dubbed this the "second-mover advantage," citing the case of SmithKline, which spent years doing basic research on stomach ulcers, discovered the role of histamine-2 in producing them, and introduced the first drug to block it (Tagamet). A Glaxo scientist attented a lecture by SmithKline's leading ulcer researcher, and shortly thereafter Glaxo began work on what became a more potent

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.

histamine-2 blocker (Zantac). Zantac turned out to be much more profitable than Tagamet, and David Jack of Glaxo admitted publicly that, "The original thinking had been done by Jim Black [of SmithKline]."

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.[12] Furthermore, 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 no change or an increase in private spending, *ceteris paribus*.

A firm's optimal expenditure on applied research is a function of the above variables

[12] 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 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.

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, if the short-run effect is the opposite of the long-run effect, then j is the lag at which the effect reverses (i.e., where the sign of the derivative changes).

4 Data

4.1 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[13] and publishes data on R&D spending by therapeutic category. These therapeutic categories correspond to the five-digit Standard Industrial Classification (SIC)

[13] 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 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.

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 1.

4.2 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. Although CRISP includes more recent project, it does not include funding levels after 1996. The bulk of the funding (over 80%) 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,[14] the thesaurus terms can be

[14] 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

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 1). 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 based on its thesaurus terms. Following Lichtenberg (2001), 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

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.

spending at the category level since a project that impacts multiple therapeutic categories will affect private research decisions in all those categories.Figure 1 displays the level of public ("Grants") and private ("PhRMA") funding for each of the seven therapeutic categories for the period 1972-1996.

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 U.S. 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.

5 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 19). 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.

5.1 Basic Results

Table 2 shows the results of the distributed-lag regressions (2) 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 correspond-

ing regression.[15]Figure 2 displays, 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 2 that for all categories, the cumulative

[15] Note that each number in parenthesis in Table 2 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:

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

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 Table 2.

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-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.

5.2 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 five or more years into the future — but the combination of negative and positive results requires a more subtle explanation. Recall that government grants are primarily intended for basic research. These grants crowd out private basic research, because a private firm will not

be willing to spend its resources doing basic research in a particular field if the government is doing it anyway and will publish the results for both itself and its competitors, essentially for free. However, 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 (the returns to) *applied* research by that firm. 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 is consistent with the prediction of any reasonable theoretical model that distinguishes between basic and applied research (a distinction that is less problematic 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 6.

5.3 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 3 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 4 and are plotted in Figure 3. 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 as a proxy for 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 5 and 6 shows the results of the distributed-lag regression (4) with various 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 4.

In order to quantify the significance of the '$\cup$-shaped" pattern of coefficients, Table 7 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 8 and Figure 5. 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 '⋃-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 "⋃-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 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 9 and Figure 6. 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.

5.4 Medical Research and Drug Sales

Medical 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 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.[16] 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.[17]

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.

Table 10 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 11 shows comparable results with x_t as PhRMA research spending. Figure 7 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. 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

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

[17] Unfortunately, for reasons described on p. 19, 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.

result in the loss of too many degrees of freedom. Autoregressive effects of drug sales show no particular pattern.

6 A case in point: The case of COX-2 inhibitors

To supplement the theoretical and statistical links between government-funded research and pharmaceutical development, it would be useful to confirm the link with specific evidence indicating that government and private research efforts interact in the way we think they do. 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.[18]

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 under trade names such as Advil and Motrin, for example), naproxen (sold as Naprelan and Aleve), and indomethacin (sold as Indocin). Some common NSAIDs and COX-2 inhibitors are illustrated in Figure 8.

[18] 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.

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.[19]

The initial discovery took place when Vane, Smith, and Willis were all in the Department of Pharmacology at the Royal College of Surgeons of England. Their work was funded by the Medical Research Council a British Government organization roughly equivalent to

[19] 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 October 31, 1973; reprinted in Eugene Garfield, ed., *Essays of an Information Scientist*, ISI Press, 1977, pp. 496–499).

the National Institutes of Health in the U.S. Vane also received funding from The Wellcome Trust, a private charitable foundation.[20] 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,[21] 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 founded 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 cyclooxygenase-1, or COX-1. The second, ("inducible") form is involved in the inflammatory process, and is known as cyclooxygenase-2, or COX-2.[22]

[20] 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.

[21] 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).

[22] More recently, some researchers speculated that there might be a third form of cyclooxygenase, which

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."[23]

The third group, led by Professor Harvey R. Herschman at the University of Califor-

would have a role in producing fever; and Simmons' group at BYU has in fact isolated a third form. See, for example, Botting (2000), Simmons et al. (1999), and Willoughby et al. (2000) and Chandrasekharan et al. (2002).

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

nia, 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 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 12.

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, it is a fairly accurate description of 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.

The success of the linear model in this case does not carry an unambiguous public-policy message. 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 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, such as that in the previous section, is an essential line of inquiry.

7 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 is for government to provide subsidies for basic research, in the hope that an increased stock of basic scientific knowledge will stimulate the private sector to increase its investment in more-appropriable applied research, and thus ultimately stimulate private-sector innovation. But since basic research is at least partly appropriable and 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, I find 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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Table 1: 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.

Table 2: 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.

Table 3: 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 4: 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

Table 5: 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 6: 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.

Table 7: 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 8: 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.

Table 9: 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*.

Table 10: 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 11: 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.

Table 12: 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			

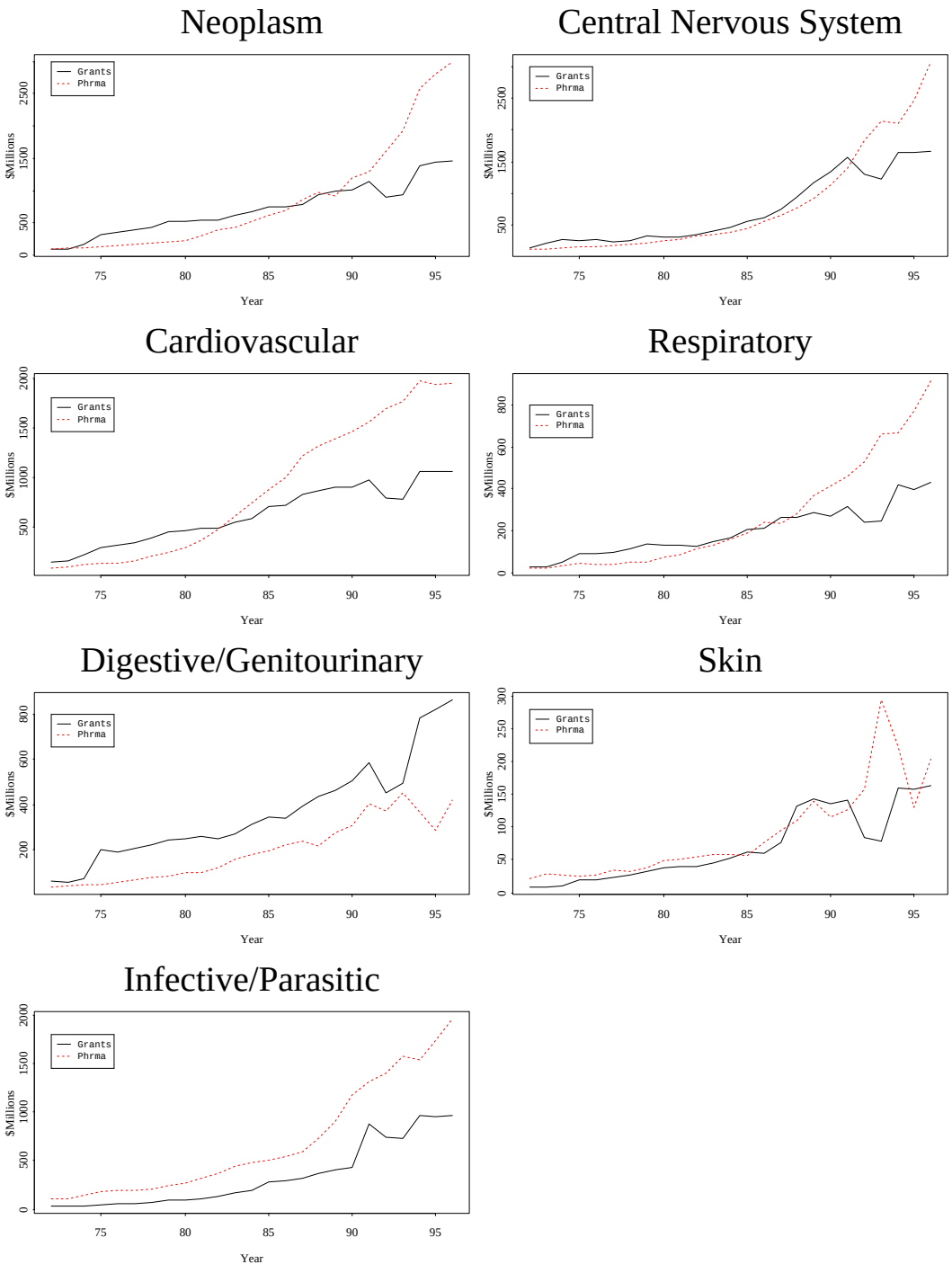

Figure 1: Federal Research Grants ("Grants") and Private R&D of PhRMA members ("PhRMA"), by Therapeutic Category.

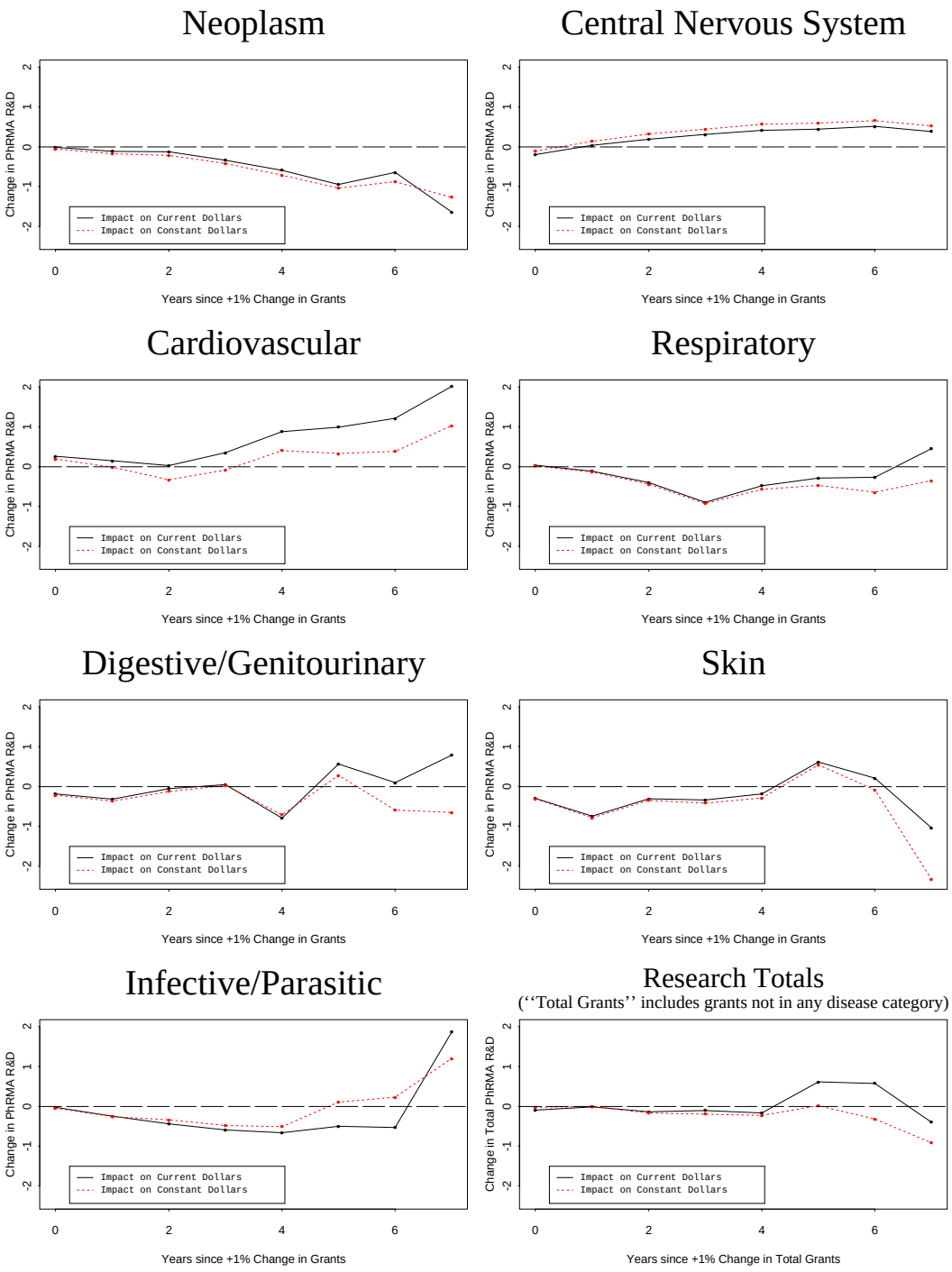

Figure 2: Cumulative predicted percent change in Private (PhRMA) R&D corresponding to a one-time +1% change in Federal Research Grants, by Therapeutic Category. In each plot, the solid line represents the response in current dollars; and the dashed line in constant dollars according to the Biomedical Research and Development Price Index (BRDPI).

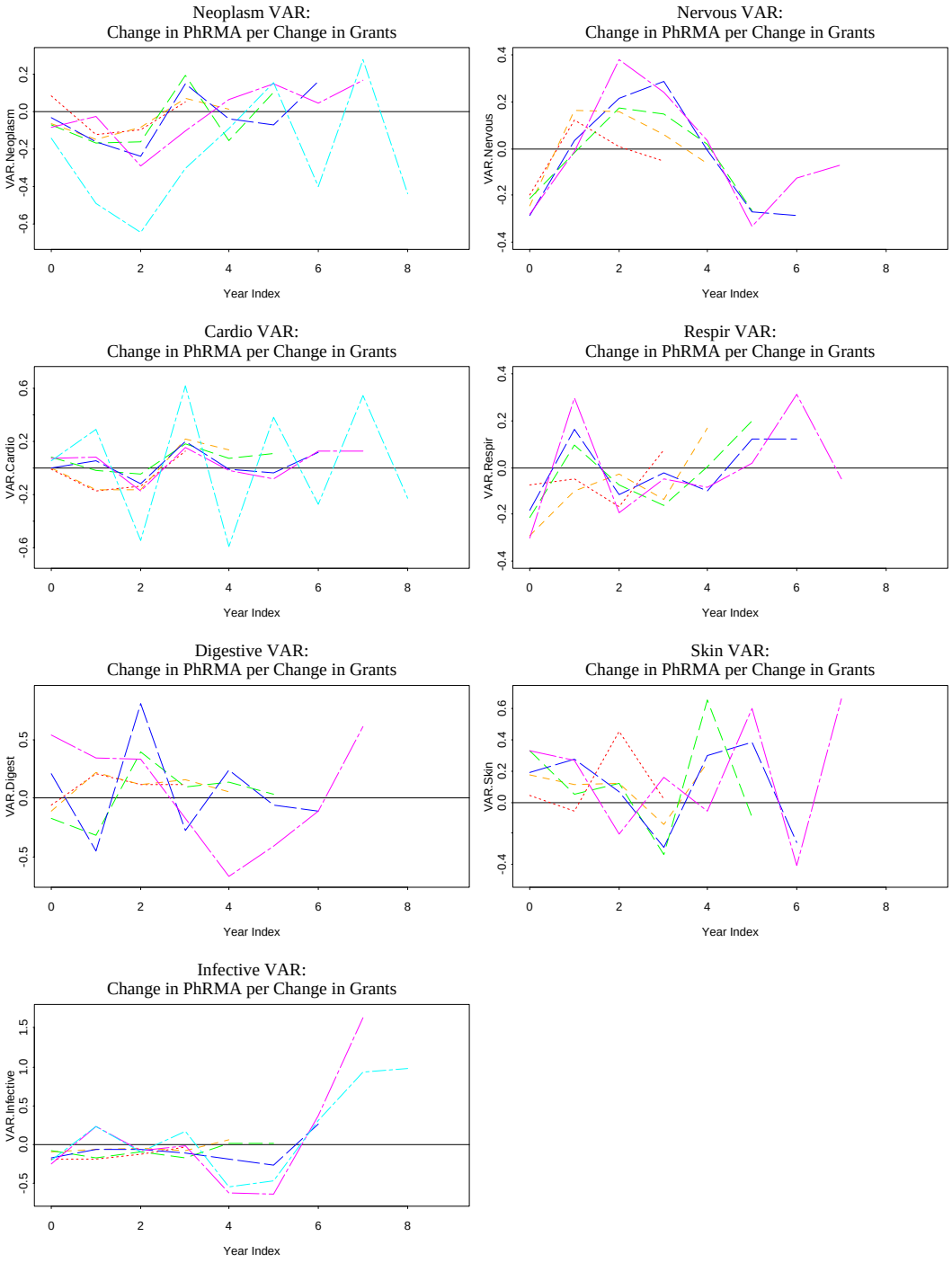

Figure 3: Cumulative Direct and Autoregressive Effects of Log of Annual Changes in Federal Grants, on Private R&D of PhRMA members, by Therapeutic Category. (Each line shows the cumulative change at each stage in a regression with a given number of lags; the number of lags is shown by the extent of the line. Thus, each chart has a line with three lags, a line with four lags, and so on.)

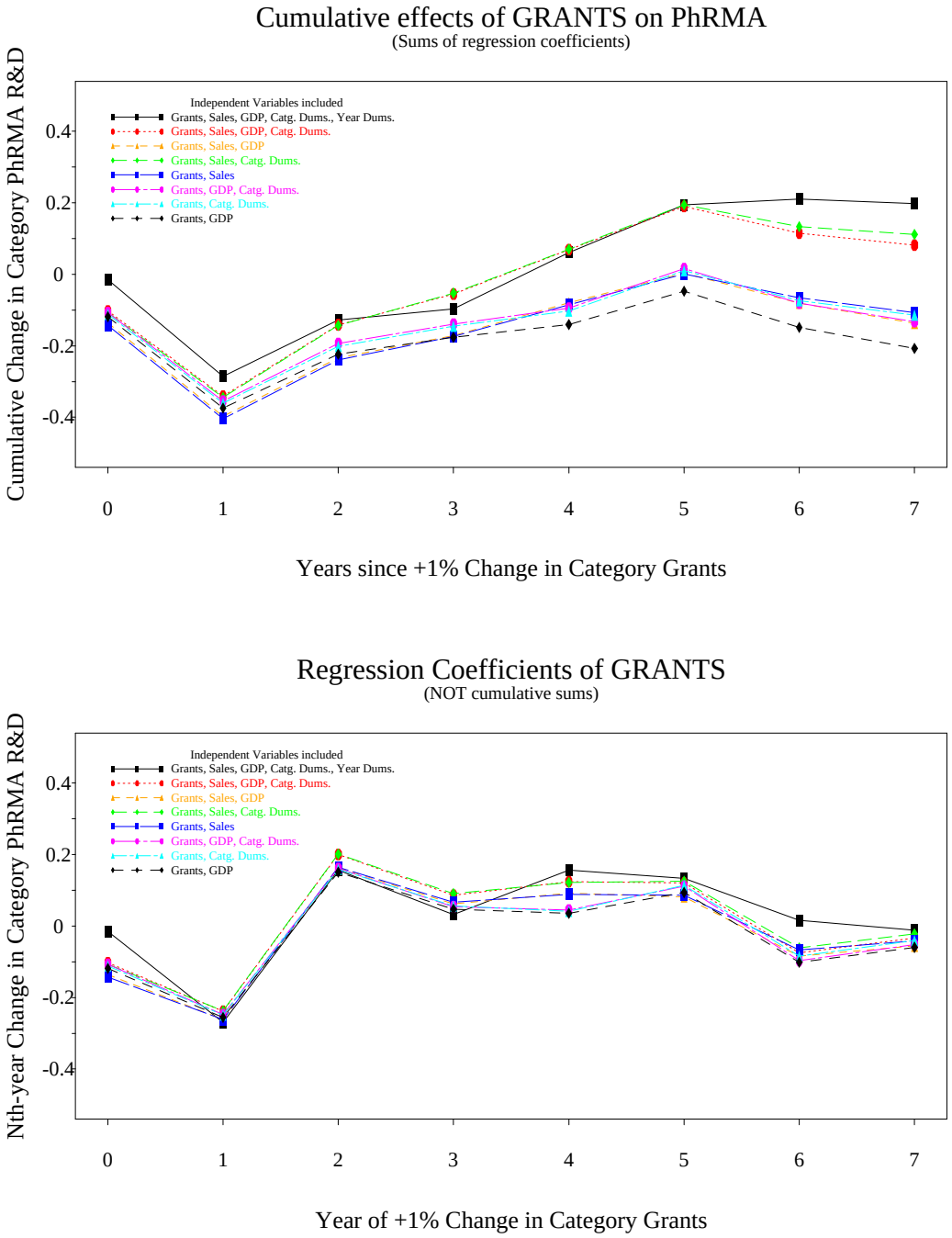

Figure 4: *Upper plot:* Cumulative predicted percent change in Private (PhRMA) R&D in a category, corresponding to a one-time +1% change in Federal Research Grants in that same category, controlling for the variables indicated.
Lower plot: Regression coefficients of Federal Research Grants used to generate cumulative predicted percent change in the upper plot. See Equation 4 on page 26 for the functional form of the regressions.

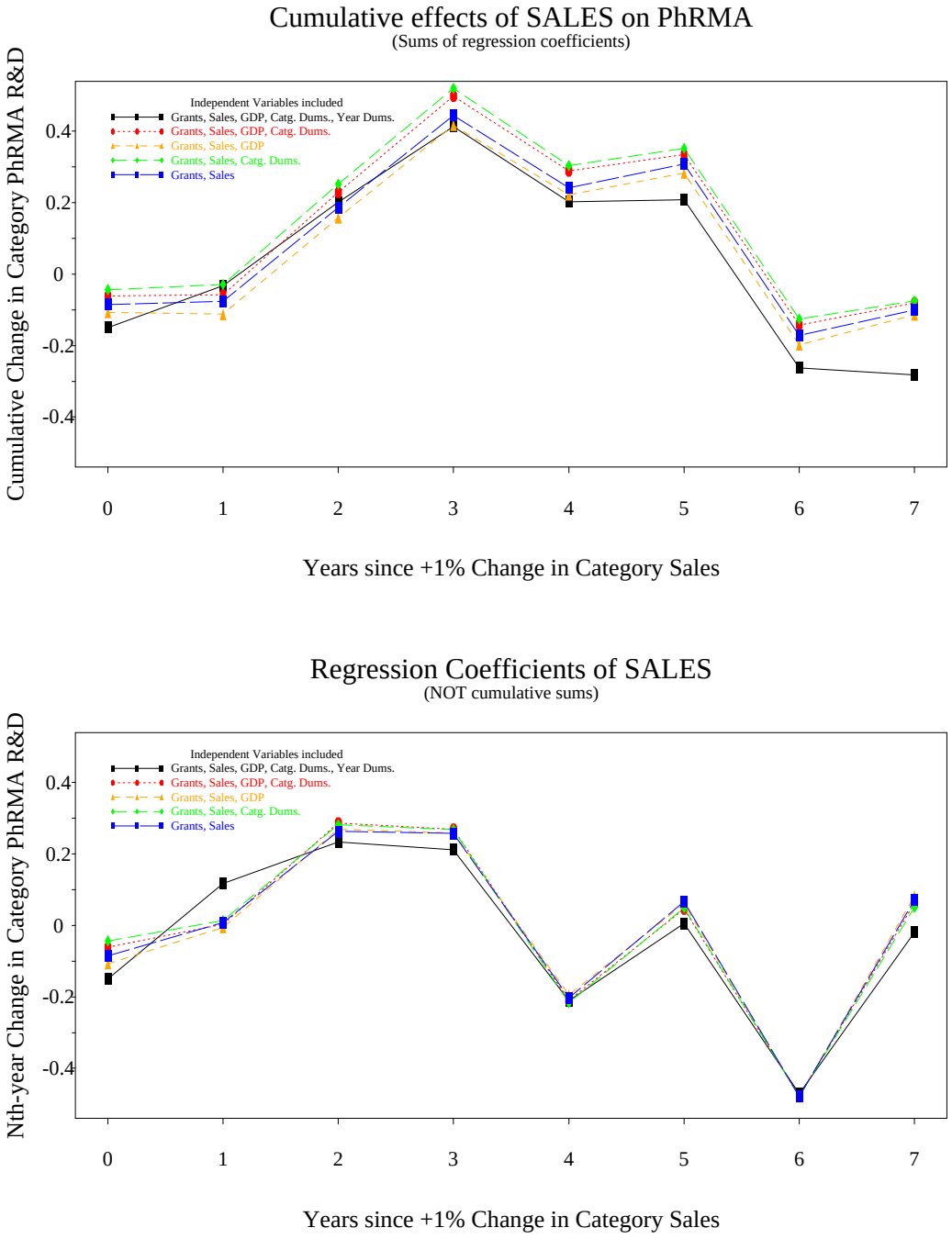

Figure 5: *Upper plot:* Cumulative predicted percent change in Private (PhRMA) R&D in a category, corresponding to a one-time +1% change in Pharmaceutical Sales in that same category, controlling for the variables indicated.
Lower plot: Regression coefficients of Pharmaceutical Sales used to generate cumulative predicted percent change in the upper plot. See Equation 4 on page 26 for the functional form of the regressions.

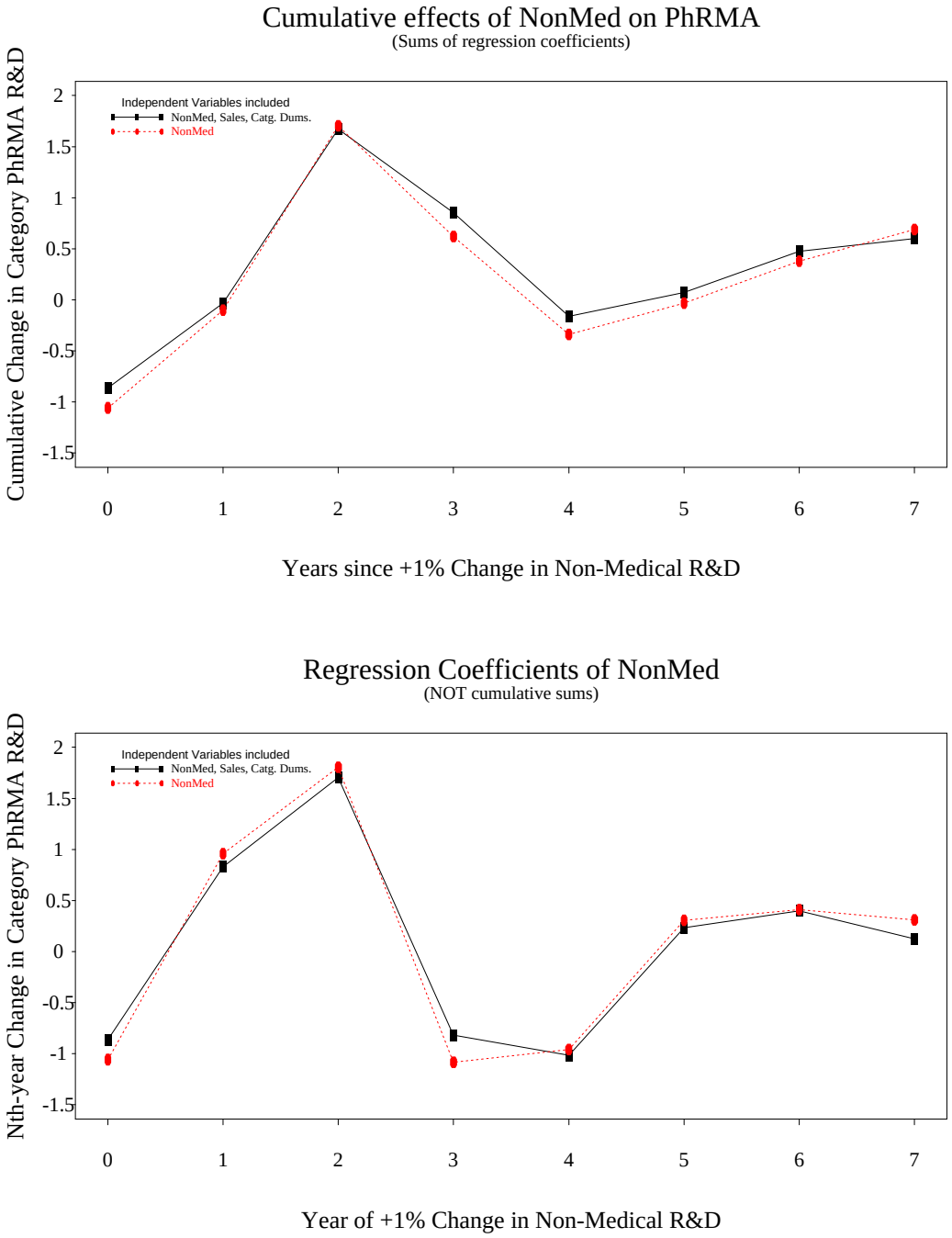

Figure 6: *Upper plot:* Cumulative predicted percent change in Private (PhRMA) R&D in a category, corresponding to a one-time +1% change in Non-Medical Federal R&D, controlling for the variables indicated.
Lower plot: Regression coefficients of Federal Non-Medical R&D used to generate cumulative predicted percent change in the upper plot. See Equation 4 on page 26 for the functional form of the regressions.

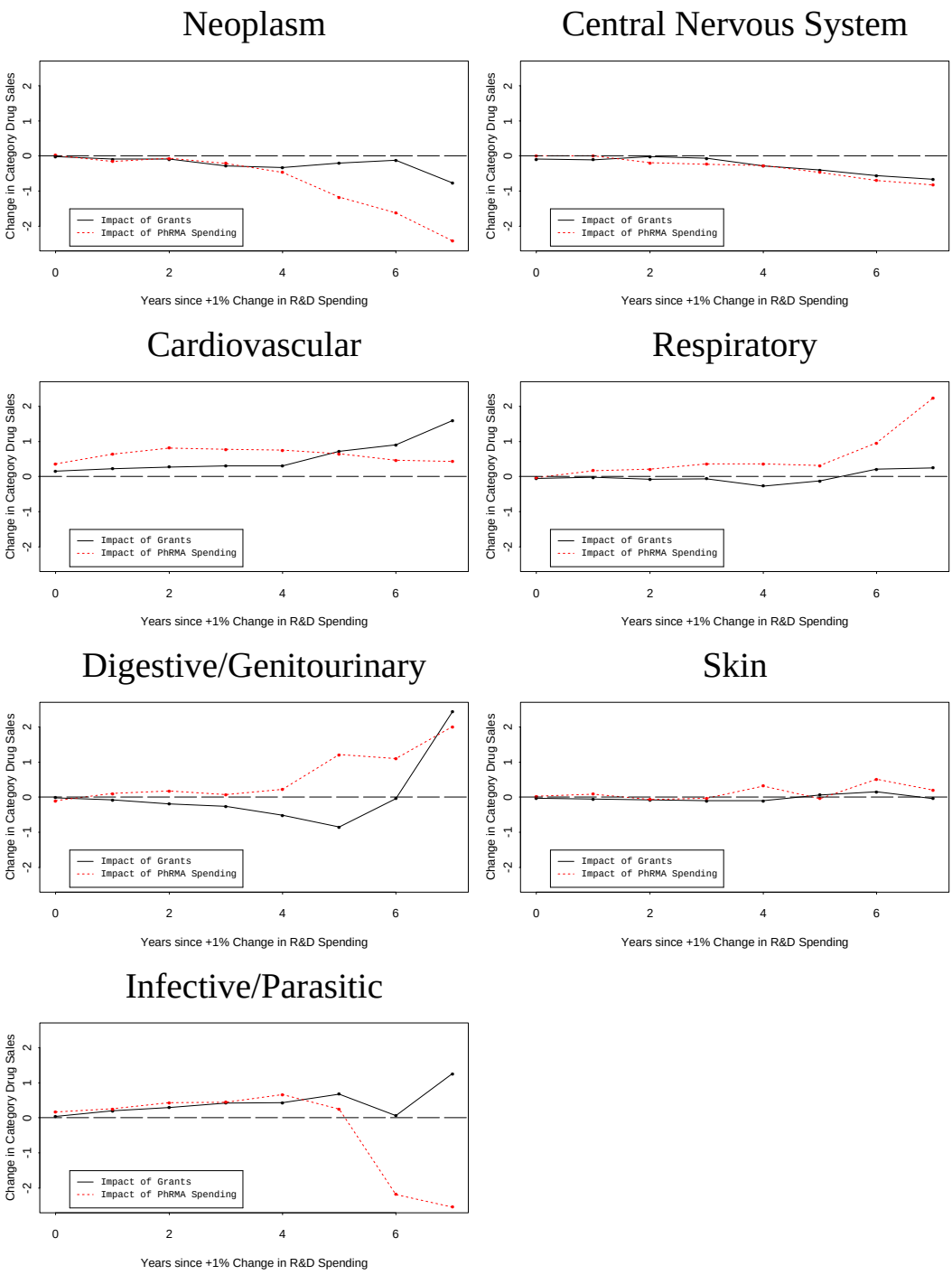

Figure 7: Cumulative predicted percent change in drug sales corresponding to a one-time +1% change in R&D, by therapeutic category. In each plot, the solid line represents the response to a change in federal research grants, and the dashed line the response to a change in private (PhRMA) R&D.

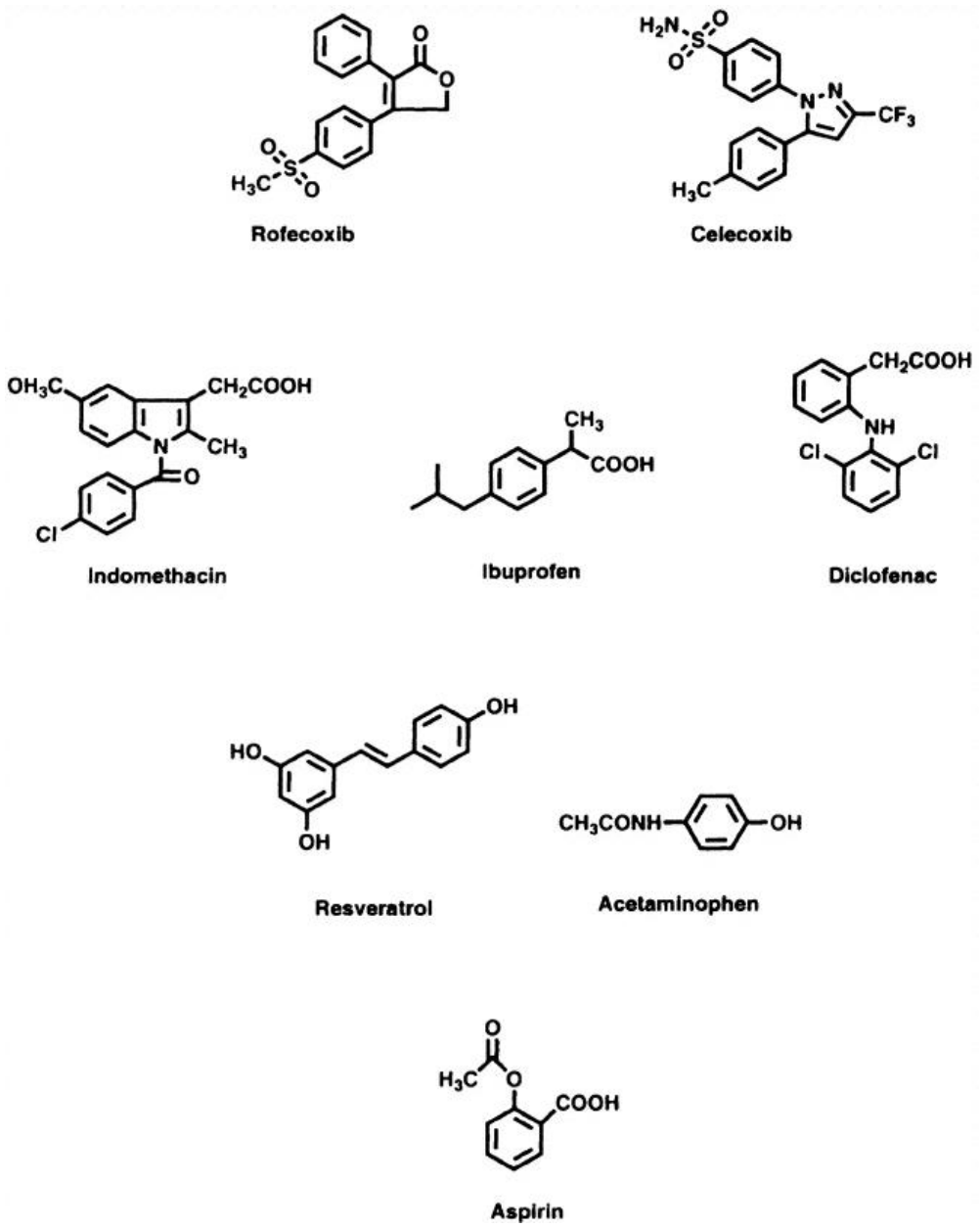

Figure 8: Chemical diagrams of important COX inhibitors and related drugs. Rofecoxib and Celecoxib are selective COX-2 inhibitors developed by Merck and Searle, respectively. Indomethacin, Ibuprofen, and Diclofenac are common non-selective COX inhibitors, known as Non-Steroidal Anti-Inflamatory Drugs (NSAIDs). Acetominophen has minimal anti-inflammatory properties, but is otherwise clinically similar to NSAIDs. Aspirin was the first large-scale commercially-produced NSAID.