The Determinants of Innovative Effort:
Evidence from the Pharmaceutical Industry

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Abstract: This paper is an empirical investigation of the determination of innovative effort in the pharmaceutical industry. A model of innovation is introduced which implies that more pharmaceutical innovation should occur to treat those conditions that are more debilitating and have lower costs of development. To test these implications, a dataset is constructed with both time series and cross sectional attributes (varying across medical conditions) that includes previously unexamined information on medical disability, R&D costs, and R&D effort. Two areas of particular interest are the effect that different government policies play in the choice of innovative effort and the degree to which industry researchers exploit new medical and pharmacological information.

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1. Introduction

<u>Motivation</u>

This thesis is an attempt to better understand the determination of innovative activity. That most economic growth comes from increases in the stock of knowledge has become the consensus among economists. An increase in the stock of knowledge that results in increased productivity can be called an innovation. It should be no surprise that policymakers are increasingly studying innovation issues in a growth context. Thoughtful innovation policy can have large economic growth effects. However, our understanding of the determinants of industrial innovation is quite limited. There is little doubt among theorists that potential innovators live in a Schumpeterian world, seeking rents through a new product or an improved production process. Empiricists, on the other hand, have not been able to directly verify how large of a role these rents have in the innovation process. This paper tries to verify empirically that rent seeking behavior is a major source of industrial innovation.

Our current understanding of economic growth centers on additions to an 'intangible' capital stock often called the 'stock of knowledge,' or the embodiment of this knowledge in workers or physical capital. Put simply, production can be increased by adding labor, adding capital, or applying either of these more efficiently. The third source, the more efficient use of existing resources, can be called innovation and comes about through increases in the stock of knowledge. Ever since Denison (1961) and Solow (1956) laid the foundations of modern growth theory, researchers have focused on increases in the stock of knowledge as the main source of economic growth. This seems reasonable when one considers the public good aspect of knowledge. Applying additional labor or capital to a given productive process necessarily entails their removal from another productive process. On the other hand, knowledge that is created in one sector of the economy often has applications elsewhere in the economy without a productive loss to the originating sector.

Much of the research in innovation has followed the seminal work of Schumpeter (1942). He developed a theory where in agents innovate in order to obtain monopoly rents from a superior product or a lower cost of production. Little empirical attention has been paid to the main implications that firms seek rents in the empirical literature[1]. Empirical

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[1] The growing theoretical patent race literature explicitly assumes that firms seek the monopoly rents from being the sole patent holder for an innovation. See Kamien and Schwartz (1982) for a survey of the relevant literature.

tests of this theory have usually concentrated on derivative implications regarding differential abilities of monopolists and competitive firms to undertake innovative activity. A better understanding of the manner and extent that market forces affect the level of innovative activity can help formulators of innovation policy.

Outline of the Problem

This study is an empirical investigation of the determination of innovative effort. The determinants for industrial pharmaceutical Research and Development (R&D) are explored in a framework that includes utility and profit maximization with respect to the production of health. While a significant amount of research has studied different aspects of R&D in this industry, few have performed their analyses in an explicit supply and demand context and the allocation of innovative effort has scarcely been studied. Also, this research has concentrated on the effect of one government program (FDA R&D regulation) without accounting for others. This paper attempts to correct these oversights. Besides a new methodology for studying this problem, data which were previously unexamined by this literature on medical disability, the costs of performing R&D, and R&D effort are included in the empirical investigation.

Two related aspects of pharmaceutical R&D that will be explored in detail are the effect of different government policies on industrial R&D intensity and the degree with which industrial researchers exploit new information regarding promising avenues of drug therapy. The federal government plays three large roles in pharmaceutical R&D: it subsidizes the demand for drug products by providing third party payments akin to medical insurance, it restricts entry into industrial R&D by imposing regulatory costs through FDA restrictions, and it subsidizes basic research by funding researchers primarily through the National Institutes of Health. Also, new medical knowledge could lower the cost of performing R&D as it focuses efforts toward the more promising lines of inquiry. Attempts will be made to measure the R&D allocation effects of new knowledge from both academic and industrial sources.

For profit maximizing firms, the level of innovative activity depends on the expected demand for the new product and the expected cost of undertaking the innovative activity to develop this product. Rank possible research projects from the most promising to the least promising (that is, by the expected net present value of revenues minus costs). The number of projects and the level of their funding is determined at the point at which the net present value of undertaking another project is zero. The level of revenues expected from a specific project depends on the total demand for goods in this market and the share of these revenues that this product can capture. The expected costs of this project are the

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sum of costs incurred before and after the product goes on the market. Before it goes on the market the costs are R&D expenses and after it goes on the market the costs are production and promotion costs. For the pharmaceutical industry, demand for new therapies and the costs of finding them differ in identifiable ways. Exploiting these differences allows one to measure the response of R&D outlays to the costs and benefits of innovation.

Conceptually, the pharmaceutical industry is well suited for testing these implications. In general, the level of expected demand for a new product is difficult to predict. By definition the new product has not yet been invented and so its attributes are unknown. Products have many attributes and innovation can occur along any combination of these attributes. Comparisons across industries, or even product classes within an industry, are not easily made since innovative activity is often directed toward finding new niches of unsatisfied demand. This, too, is true to some extent for the pharmaceutical industry, but arguably, the most important attribute for all products in this industry is the promotion of health[2].

Further, the level of health can be thought of as specific to a medical condition. Treatment for one medical condition rarely substitute for other conditions. Measures of the level of heath with respect to medical conditions can be obtained and used as proxies for the demand for new products treating the condition. Proxies for the level of health are the morbidity and mortality rates associated with a condition and the number of physicians practicing in the speciality that treats the condition. These measures of the level of health are condition specific and directly comparable across medical condition.

Likewise, measures of the cost of innovating in this industry are identifiable. Usually, measures of the cost of innovating are not easy to come by. The estimation of the existing costs of production by economists is itself an inexact science. The cost of innovating, or the costs of lowering one's cost function[3], are even more difficult to quantify. However, compliance with FDA regulations is among the larger costs of innovating in the pharmaceutical industry and these costs vary across medical conditions in identifiable ways. These costs include the time a new drug requires for market approval and the probability that it will never reach the market. Also, new medical knowledge

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[2]   Others could be ease of administration (tablet are generally preferred to intravenous injections) and frequency of administration (once a day versus three times a day). It is claimed here that, for many medical conditions, most consumers will be willing to trade away much of these other attributes for a little more effectiveness in the promotion of health.

[3]   See Spence (1986) on the theoretical equivalence between process and product innovation.

yielded by both academic or industrial sources can reduce the cost of developing new drugs.

The next section of this paper will briefly describe the relevant aspects of the pharmaceutical industry. The literature relating to this topic will be reviewed in section 3. Section 4 will lay out a model that incorporates the features discussed here and conclude with testable implications. The data considerations for testing of these implications will be discussed in section 5. Results are reported in section 6 followed by a conclusion and discussion of future research plans.

2.   Description of the Industry

Firms in the pharmaceutical industry produce both over-the-counter drugs and ethical pharmaceuticals. Ethical pharmaceuticals are drugs requiring a physician's prescription, but often included with them are over-the-counter ethical drugs (sold over-the-counter but primarily promoted to health professionals, not drugs marketed directly to consumers). Most of the attention of economists has been in the ethical pharmaceutical industry rather than the over-the-counter market for a couple of reasons. First, they account for the bulk of the industry revenue. Over-the-counter drugs account for less than a fifth of total industry revenue. Second, many of the most successful over-the-counter drugs are first marketed as ethical pharmaceuticals. Attention here will be with the ethical pharmaceutical industry.

The Industry in General

The drug industry has grown relative to the rest of the economy over the last quarter century. In 1989, U.S. sales of human-use dosage-form pharmaceutical products was $35.9 billion. This amounts to about 0.7 % of GNP in 1989, up from 0.4 % of GNP in 1966. The Pharmaceutical Manufacturers Association (PMA) firms account for over 90% of the sales and virtually all of the R&D. Of the PMA employees in the U.S., 36% worked in production, 28% worked in marketing, and fully 23% worked in medical R&D. The PMA reports that its firms spent $5.5 billion on R&D in 1987, up from $416 million in 1966.

The industry has become more international in nature in the past thirty or forty years. The PMA reported that its member firms employed 317,820 persons worldwide with 55.0% employed in the U.S. in 1987, down from 62.5% in 1965. The number of U.S. drug and medicine patents granted to sponsors of foreign origin rose from 39.2% during the 1963-1975 period to 49.0% during the 1976-1989 period. In the early 1960's,

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most of the drugs marketed in the U.S. originated in the U.S. Wardell, et. al. (1978) report that much of the initial industrial research had moved overseas during the 1963 to 1975 period (presumably in response to the more stringent FDA Amendments of 1962). Firms did their initial testing in humans in a less regulated foreign country and would apply for similar testing in the U.S. only for the more promising ones.

The pharmaceutical industry is very R&D intensive. A common measure of intensity is the ratio of R&D expenditures to sales. Table 1 shows the R&D to sales ratio for a number of industries. By this measure, only office, computing and accounting machines and scientific measuring equipment are more R&D intensive than the drug industry with the drug industry having an R&D to sales ratio three times that of the average firm.

R&D's role in the industry has been increasing over time. Real R&D expenditure has increased for each of the PMA therapeutic categories (see graph 1). The rate of growth of R&D expenditures over this period has outpaced that of sales (see table 2). Likewise, the number of drugs and medicines patented by the industry in a year has more than doubled over the past three decades (from 660 during 1963 to 1975 to 1446 during 1976 to 1989).

Once a drug is marketed, often there is very little competition with other drugs. Telser (1981) studied competition within certain drug categories. One of his results is that when a drug goes off patent and generic drugs become available to the public, often at one third of the brand name price, the price of the original drug declines little, if at all. Also, the PMA reports that less than ten percent of its firms' R&D expenditures go toward process development for manufacturing and quality control, while nearly eighty percent go toward new product development. Firms do not compete as much on price or production costs, but rather at the innovation stage of product development, especially relative to other industries.

Industrial Drug Development

An understanding of the process of new drug development will shed light on some of the issues involved in pharmaceutical innovation. Initially, a new compound will be synthesized to treat a specific medical condition. This will lead to the synthesis of new derivative compounds that can be tested in animals. Satisfactory results with animals is at best a poor indicator of eventual marketability and the drug must undergo extensive clinical tests on humans before the FDA will approve a drug for sale. A drug which is a candidate for clinical tests are again tested in animals to find (a) the highest dosage that causes obvious side effects but does not kill the animal, (b) the dosage that causes borderline side

effects, and (c) the maximum dosage that causes no side effects. Once these are completed, an Investigational New Drug Application (IND) is required to begin testing on humans. At the time of the IND application, much of the information about the drug will become public knowledge. Therefore, most drugs reaching the IND phase as well as some that do not will be patented.

The clinical tests are divided into phases I, II, and III. Phase I tests are only concerned with the safety of the drug and are performed on around 10-20 volunteers. Phase II tests are more extensive (often two to two and a half years) and test for efficacy under different dosage regimes. If a drug survives these tests, Phase III entails a series of still wider scale (500-1500 patients) studies for proof of efficacy and acceptable levels of side effects. Although these are in sequence, the timing may overlap to some extent. It is only at this point that the New Drug Application (NDA) is complete and may be approved or disapproved.

To get an idea of the risks and costs involved in developing a new drug, one need only look at the numbers of drugs at various stages of development and the costs associated with each stage. The PMA reports that its members synthesized and extracted for medical purposes 126,060 substances and pharmacologically tested 703,900 substances in 1970. The total number of IND's per year since 1963 has ranged between 800 to 2200. IND sponsors have determined that only a 50-100 of these merit applications for marketing, with about 15-40 of these NDA's finally being approved.

The Impact of the Government on Innovative Incentives

The federal government plays three important roles in the development of new drugs. The government subsidizes the cost of basic research through the NIH, subsidizes demand for health care products and services through Medicare, Medicaid, Veterans Administration and various other programs, and enforces a barrier to entry into industrial R&D through the FDA regulations. Each of these roles can have a large influence on the amount of industrial R&D undertaken and attempts are made to measure these in this study.

First, the government subsidizes industrial R&D by sponsoring basic research through the NIH and, to a lessor extent, other federal organizations. The various institutes of the NIH both perform research and underwrite research conducted at mainly academic institutions. This research tends to be of the most basic nature with little applied research undertaken. Only recently have the institutes begun to patent chemical entities that are the product of their research or been able to so. Knowledge created by the NIH is freely and nearly costlessly used by industrial researchers.

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Second, programs such as Medicare, Medicaid, and the Veterans Administration provide large subsides to health care in general. Many of these do not pay directly for pharmaceutical products. However, pharmaceuticals are just one input into the production of health. The theory of derived demand for inputs implies that pharmaceuticals receive an effective subsidy.

Third, the costs of complying with the FDA requirements for safety and efficacy represent a formidable barrier to into to performing industrial R&D. Various studies have estimated that the R&D costs per new drug introduced have risen dramatically in response to increased regulatory stringency by the FDA. Further, the PMA reports that close to half of its R&D expense goes toward testing of new drugs in compliance with the FDA regulations.

3. Past Studies

Empirical investigations of innovation in the pharmaceutical industry are more common than in most other industries. The industry spends a larger fraction of its revenues on research than most other industries and, since much of the firms' activities are regulated, a great deal of data exist for empirical study. The three areas of research to be summarized below are: the effect of government regulation on R&D output, estimations of rate of return to pharmaceutical R&D and possible returns to scale in performing R&D.

The first branch of to be summarized has to do with the effect of the 1962 FDA Amendments on the production of new drugs. Most of the research to date has been in the estimation of a reduced form production function for New Chemical Entity (NCE) introductions. Invariably, this literature finds that the 1962 FDA Amendments had a large negative effect on NCE production, although the magnitude of the effect differs from study to study. A second research project discussed in the literature is the computation of the rate of return on R&D. The Hansen studies (1979, 1981)[4] were an attempt at estimating the costs of different phases of drug development. Other studies complement this work by tracking the sales of NCE's to come up with a net present value or rate of return for drug research. While there has been disagreement over what the rate of return is, there is general consensus that drug development is extremely risky at the individual NCE level. A third strain in the pharmaceutical R&D literature that is somewhat less related to the present topic is whether or not there are increasing, decreasing or constant returns to scale in

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[4] For a more recent version of this type of study and a summary of past R&D cost studies see DiMasi, Hansen, Grabowski, and Lasagna (1991).

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pharmaceutical R&D. This is a test of one of the Schumpeterian hypotheses that larger firms have an advantage in creating innovation. The results from this literature are still less conclusive and seem to depend on the time period in question.

The Effect of Regulation on NCE Introductions

Baily (1972) employed a production function for NCE introductions over the 1954 to 1969 period to find the effect of the stricter regulatory environment that began midway through this time period. He regressed the NCE to R&D ratio against a dummy variable for the post-1962 period and the number of new drugs introduced from all sources. The first of these was meant to capture the effect of the stricter regulations while the second was intended to measure the depletion of opportunities for drug research. He concluded that the cost to introducing a given number of NCE's has more than doubled due to the 1962 FDA Amendments. Grabowski et. al. (1978) followed the same methodology with a larger sample and controlled for the possible depletion of opportunities by fitting United Kingdom data to a year trend and restricting the U. S. regression to the same coefficient. They also measured the effect of regulations both with a post-1962 dummy variable and with the time of the average NDA approval for that year. They concluded that, while the rate of introductions in the U. K. fell by a factor of three, in the U.S. it fell by a factor of six.

The cost-benefit analysis done by Peltzman (1973) received considerable attention in both the economic and policy circles. He derived demand schedules for NCE introductions for both the pre- and post- 1962 periods in order to get consumer surplus measures of the gains and losses from the 1962 FDA Amendments. The supply of new drugs was postulated to be a function of demand parameters including the number of out-of-hospital prescriptions and expenditures on physician services. Peltzman's conclusions that the number of new drugs brought to the market each year was cut in half with no corresponding reduction in inefficacious drugs. This imposed a net cost on society from increased mortality and morbidity (estimated to have a value of at least $330 million per year) that would not have been incurred had the 1962 FDA Amendments not been in place.

Wardell and Lasagna (1975) confirmed Peltzman's contention that the new regulation had imposed substantial costs to U.S. drug development by comparing new drug development in the United Kingdom to that in the U.S. They found that from 1962 to 1971, nearly four times as many new drugs became available in the U.K. as in the U.S. Further, for those drugs that became available in both countries, twice as many drugs were first introduced in the U.K. than in the U.S. Further confirmation came when pharmaceutical firms were surveyed regarding specific NCE's by Wardell, et. al. (1978). They collected data on 1,103 NCE's that were tested in humans by 46 firms between 1963

and 1975. Of these 1,103 NCE's, 1,029 IND's were filed, 99 NDA's were applied for and 59 NDA's were approved. In general, they report a dramatic shift of initial drug research abroad and cite that 'an inhibitory influence was operating selectively on U.S. firms.' Presumably this influence was caused by the FDA Amendments of 1962. The average time in IND phase rose from 17 months in 1966 to 40 months in 1971 and remained at about that level through 1974. The average time in NDA phase rose from 14 months in 1966 to a peak of 43 months in 1969 and then declined to about 21 months thereafter.

Wiggins (1981) decomposed the total regulatory effect on NCE production into the direct effect of regulation on NCE production holding the level of research constant and the indirect effect of regulation on the level of research. His study also differs from previous research in that he looked at NCE production by therapeutic category although he was able to do so only for the 1970-1976 time period[5]. He measures the effect of regulation as the time in NDA phase at a point in time and for a particular category. The presumption being that approval time differences across categories and time were caused by the 1962 FDA Amendments. He concludes that regulation reduced introduction rates by 60%. Finally, Jensen (1987) studied firm specific NCE introductions for 28 firms from 1969 to 1979. Since the number of introductions in a given year take on only small positive values, estimation techniques more sophisticated than OLS may be warranted. She compared OLS, Tobit, and Poisson distribution estimation procedures and finds that the 'fit' of her equation is best for the Poisson estimation technique and confirms that regulation had a large effect in reducing NCE introductions.

In the course of studying the effect of regulation on R&D, researchers necessarily must study the various determinants of R&D. Except for Wiggins' studies (1981,1983,1987), the attention has been exclusively on the level of R&D output rather that the level of R&D expenditures or inputs. Since all of these reduced form NCE production functions include a measure of R&D regulatory stringency, they all have at least one proxy variable for the cost of performing R&D. Some of these studies account for the level of demand for new products while others take demand as exogenous (or constant). The most common demand parameter is the level of pharmaceutical sales which, of course, is the equilibrium between supply and demand. Only Peltzman (1973) uses a suitable demand proxy variable (physician services). The present study attempts to decompose R&D determinants into those that shift supply and those that shift demand.

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[5]   Wiggins (1981, 1983,1987) are the only studies to analyze drug development at the therapeutic category level.

Only Wiggins (1981) performs his analysis at the drug category level. It will be shown below that different categories of drugs behave quite differently over time. The NDA approval time varies significantly over time and by category even before the 1962 FDA Amendments (rendering Wiggins' measure of regulation stringency tainted) as do NCE introduction rates and R&D expenditures. Aggregation across categories may cloud much of the effect that the researchers looked for.

The Rate of Return to R&D Investment

The earlier studies suggest that the returns to R&D investment have not covered the cost of capital, while the later, more comprehensive studies do not find that at all. The earlier studies stand in stark contrast to the sharp increases in R&D investment that have been sustained over the past three decades (as shown in graph 1). The model to be presented below assumes that firms know what the expected returns to different types of R&D investment are and allocate funds accordingly. It is reassuring that the later studies do not find evidence of the misallocation of R&D funds.

Baily (1972), Schwartzman (1975), and Statman (1983) derived average NCE R&D costs and sales from total R&D expenditures and sales in the industry, which can tend to aggregate new NCE's with older NCE's and sometimes non-pharmaceutical products. Grabowski and Vernon (1982) were able to use Hansen's (1979, 1980) estimates of the cost of NCE development and tracked individual NCE's, but were limited to just 37 over ten years. Often, these analyses depended on crucial assumptions regarding the timing of costs and revenues associated with a typical NCE or the expected foreign sales of pharmaceuticals. Baily (1972) estimated a nominal, pretax return under 15% for the post-1962 period and 30% pre-1962. Schwartzman (1975) found a real after-tax return of between 3.3% and 7.5% for the 1966-1972 period and Statman (1983) found that that the average internal rate of return (IRR) on drugs introduced in the U. S. declined from 22% to 10.3% from 1965 to 1978, ultimately lower that his estimate of the cost of capital of 12.7% in 1978.

Joglekar and Paterson (1986) performed the first comprehensive study in that it tracked 218 NCE's for up to 24 years of sales. They were able to provide estimates of the distribution of returns as well as a mean return and their results were somewhat robust to a sensitivity analysis. They also reported net present values (NPV) and break even points as alternative measures to the real rate of return to R&D. They conclude that the average NCE's real IRR outperformed matching corporate bonds (6.1% versus 2.3% in real rates) and had a net present value in 1976 dollars of $49 million. The more dramatic finding was that the range of IRR's varied from 14.25% (NPV = $472 million) for the 3.67 percentile

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NCE to -14.11% (NPV = $-19 million) for the 86.7 percentile NCE with the median NCE actually losing money (NPV = $-4.8 million)[6]. Given the apparent risk involved in pharmaceutical R&D, the authors state that a 6.1% average real IRR seems 'modest.'

Grabowski and Vernon (1990) use essentially the same methodology as Joglekar and Paterson (1986) for a sample of 100 NCE's which includes NCE's introduced in the 1970's with sales information into the 1980's. They conclude that the new drug product introductions in the 1970's realized returns in line with the 9% cost of capital. They also find that the distribution of returns is quite varied with the top decile of the present value of returns more than five times the average.

Returns to Scale in R&D

It has been argued that a higher degree of internal liquidity, firm diversification, and other features of larger firms all are conducive to R&D performance and therefore larger firms in an industry should be more research intensive than smaller firms. However, this result has not been found with any degree of regularity. Grabowski (1968) looked at firm data from 1959 to 1961 for firms in the chemical, drug and petroleum industries. He tested for returns to scale for only the chemical and drug industries and found decreasing returns for chemical and increasing returns for drugs. Angilley (1973) analyzed R&D output for a sample of 20 drug firms measured as sales weighted or therapeutic value weighted NCE production and found no significant deviation from constant returns to scale. Vernon and Gusen (1974) studied 50 drug firms and found that 'larger firms have decided advantages over smaller ones in accomplishing technical change.' In her work, Jensen (1987) could find no statistically significant deviation from returns to scale.

4.   A Model of Innovative Effort Determination

The model presented here is among the simplest that still captures the essence of R&D determination in a maximizing environment. This is achieved by making no explicit allowances for the intertemporal or probabilistic nature of pharmaceutical R&D described above. The average time from the first research of a drug to its eventual marketing has been rising steadily over time and now stands at well over ten years. Likewise, only a small fraction of research projects will ever become marketed and, even then, only a third will cover their development costs. While these features of the innovation process are

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[6]   The NPV to corporate bonds at these same percentiles were: the 3.67 percentile yielded $48.9 million, the 86.7 percentile yielded $22.6 million and the median yielded $19.3 million.

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important, their inclusion is unlikely to alter the model's conclusions and are likely to complicate the exposition.

Health is the underlying and common good being produced in this industry. People wish to buy products that will improve their health. Pharmaceutical firms and other agents (the government, hospitals, physicians, etc.) try to satisfy this demand by providing drugs, medical procedures, medical devices, etc. Some therapies that improve one's health are condition specific in that they are designed to alleviate a single medical condition (products such as insulin or a burn treatment centers) while others are more general in the sense that they deter a wider assortment of different medical conditions (products such as an emergency rooms, general practitioners, or a multi-vitamins). For this study, we will consider health respective of a specific medical condition and look at the factors that affect the supply and demand of therapies for that condition.

A production function for condition specific health would include inputs of many different kinds. The major inputs will not be limited to only pharmacological products, but will also include such things as medical devices, medical procedures, and public health measures designed to combat this condition. The production function used here is:

(1) $\quad h^i = h^i \, (\mathbf{q}^i, \mathbf{z}^i)$

where $\mathbf{q}^i$ is a vector of the quantities of products that promote health and $\mathbf{z}^i$ is a vector measuring the state of knowledge embodied in the current products[7]. The elements of $\mathbf{q}^i$ are (q^{iD}, q^{iM}, q^{iP}, q^{iH}, . . .) and the elements of $\mathbf{z}^i$ are (z^{iD}, z^{iM}, z^{iP}, z^{iH}, . . .) with the first superscript representing the condition and the second superscript representing either drugs, medical devices, medical procedures, and public health. The element z^{iJ} measures the state of knowledge embodied in the Jth type products treating condition i. There may only be one product of type J treating condition i at a time and that product treats only condition i. The vectors $\mathbf{q}^i$ and $\mathbf{z}^i$ completely characterize the products treating condition i.

The production function, h^i, will be assumed to have two certain regularity conditions. First, it will be assumed that h^i is concave and increasing in both $\mathbf{q}$ and $\mathbf{z}$.

(2) $\quad \dfrac{\partial h^i}{\partial q^{iJ}} > 0 \quad$ and $\quad \dfrac{\partial^2 h^i}{\partial q^{iJ}\partial q^{iJ}} \leq 0$

$\quad \dfrac{\partial h^i}{\partial z^{iJ}} > 0 \quad$ and $\quad \dfrac{\partial^2 h^i}{\partial z^{iJ}\partial z^{iJ}} \leq 0 \quad$ for all i and J = D, M, P, H

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[7] Bold face will be used to denote multi-dimensional vectors throughout the paper.

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Increasing the amount of treatment at the current state of knowledge will increase health, but at a decreasing rate. Likewise increasing the state of knowledge embodied in a treatment will increase health, but at a decreasing rate. Second, we will assume that increasing the state of knowledge will increase the marginal product of a given treatment.

(3) $\quad \dfrac{\partial^2 h^i}{\partial q^{iJ} \partial z^{iJ}} > 0 \quad$ for all i and J = D, M, P, H

Utility is generated by health with respect to all potential medical conditions and by the consumption of other goods $\mathbf{x}$:

(4) $\quad U = U(\mathbf{x}, \mathbf{h}(\mathbf{z}, \mathbf{q}))$

Utility is maximized subject to a budget constraint involving the elements of $\mathbf{x}$ and $\mathbf{q}$. Consumers do not pay directly for $\mathbf{z}$, the state of knowledge. It will be assumed that U is concave and increasing in its arguments or $U_i > 0$ and $U_{ii} \leq 0$ (where it is unambiguous we will use subscripts to denote partial derivatives). These assumptions guarantee an interior solution to the consumers' maximization problem and necessary first order condition for a maximum yields:

(5) $\quad U_i \dfrac{\partial h^i}{\partial q^{iJ}} = \lambda \ P^{iJ} \qquad$ for J = D, M, P, H

where λ denotes the usual Lagrangian multiplier. The price, P^{iJ}, will denote the price of treatment J at the current state of knowledge. Letting $\alpha = 1/\lambda$ we can solve for the price as:

(5') $\quad P^{iJ} = \alpha U_i \dfrac{\partial h^i}{\partial q^{iJ}}$

Up to a scalar constant, the price of a health product equals marginal utility times its marginal product in producing health.

Pharmaceutical firms maximize profits by supplying drugs to consumers. Their profits are the sum of revenues from health promoting products minus the cost of production and the cost of performing research.

(6) $\Pi = \sum_i (P^{iD} q^{iD}) - C(\mathbf{q}) - R(\mathbf{dz})$

where $\mathbf{dz}$ is the increment to the stock of knowledge chosen by the firm. It is important to include research costs as well as production costs since, in the pharmaceutical industry, $R(\mathbf{dz})$ seems to be quite large relative to $C(\mathbf{q})$. The production costs will be assumed to have non-increasing returns to scale to guarantee an interior solution.

Turning to research costs, we allow firms to investigate potential new products through the choice of $\mathbf{dz}$. The function $R(\mathbf{dz})$ denotes the total expense incurred by the firm by adding $\mathbf{dz}$ to the stock of knowledge and we will assume that R is increasing and convex[8] in its arguments, or that $R_i > 0$ and $R_{ii} \le 0$. Successful innovation either lowers the cost of existing products (process innovation) or creates a new product that delivers more services at the same cost (product innovation). Theoretically, these are equivalent and are simply different sides of a numeraire problem. Here, we will denote successful innovation as the ability to increase the magnitude of z^{iJ} at the same production cost.

After substituting (5') into (6) we get:

(6') $\Pi = \sum_i \left(\alpha U_i \frac{\partial h^i}{\partial q^{iD}} q^{iD} \right) - C(\mathbf{q}) - R(\mathbf{dz})$

The first order condition for profit maximization with respect to production for the ith medical condition is:

(7) $\left[\alpha U_i \frac{\partial^2 h^i}{\partial q^{iD} \partial q^{iD}} + \alpha U_{ii} \frac{\partial h^i}{\partial q^{iD}} \frac{\partial h^i}{\partial q^{iD}} \right] q^{iD} + \alpha U_i \frac{\partial h^i}{\partial q^{iD}} - C_i(\mathbf{q}) = 0$

The expression in the brackets is the sufficient second order condition for a maximum to the utility maximization problem and both terms in the brackets are negative. The second term is the price, P^{iD}, and the last term is the marginal cost of production. The first two terms together represent the marginal revenue of drug treatment and equation (7) gives the classical result that firms maximize profits by setting marginal revenue equal to marginal

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8   Decreasing returns may be a strong assumption for research. In ongoing work, Telser has found that R&D exhibits either constant returns to scale or increasing returns to scale for capital intensive research programs in Chemistry and Physics. For the model presented here, convexity is a sufficient and not a necessary condition. So long as the concavity is not too strong the model is qualitatively unchanged.

cost. As the second term is the price of the treatment, the first measures how much marginal revenue deviates from price. Another classical price theory result is that, as marginal revenue approaches price, profits fall. Thus, the first term is a measure of the economic rents generated in this market.

The first order condition for profit maximization with respect to research for the ith condition is:

$$(8) \qquad \left[\alpha U_i \frac{\partial^2 h^i}{\partial q^{iD} \partial z^{iD}} + \alpha U_{ii} \frac{\partial h^i}{\partial q^{iD}} \frac{\partial h^i}{\partial z^{iD}} \right] q^{iD} - R_i(\mathbf{dz}) = 0$$

The first term is the marginal revenue from doing drug research and the second is the marginal cost. The term involving $\partial q^{iD}/\partial z^{iD}$ drops out due to an envelope theorem argument. To interpret equation (8), we can decompose the term in brackets into its parts. Literally, the first term is the marginal utility of health with respect to condition i times the change in the marginal productivity of a drug treatment due to an increase in the stock of knowledge in drug therapy. The second is the change in the marginal utility of health with respect to condition i times both the marginal product of health with respect to both the drug treatment and the stock of knowledge. Comparing these two terms to equation (5') however, reveals that it is also the change in the price of drug therapy due to an increase in the stock of knowledge in drug therapy.

Pharmaceutical firms take levels of q^{iJ} and z^{iJ} as given for J = M, P, and H. These levels may have come from a maximization problem, as with the drug industry, or from some other determining process. For N different conditions there are 2N different equations and 2N unknowns. With the standard regularity conditions we can guarantee a unique solution to this problem.

To see how this solution changes due to changes in other parameters, we can fully differentiate (7) and (8). We are only concerned here with the effects of different parameters on the level of drug research. By ignoring third derivative terms[9], from (8) we get:

$$(9) \qquad \left\{ \left[2\alpha U_{ii} \frac{\partial h^i}{\partial z^{iD}} \frac{\partial^2 h^i}{\partial q^{iD} \partial z^{iD}} + \alpha U_{ii} \frac{\partial h^i}{\partial q^{iD}} \frac{\partial^2 h^i}{\partial z^{iD} \partial z^{iD}} \right] q^{iD} - R_{ii}(\mathbf{dz}) \right\} dz^{iD} + \left(\alpha U_{ii} \frac{\partial^2 h^i}{\partial q^{iD} \partial z^{iD}} \right) dh^i = 0$$

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[9]   In this model, it is impossible to sign third derivatives.

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The term in braces is the sufficient second order condition for a maximum with respect to drug research and is negative. The other term in parenthesis is negative since U_{ii} is negative and the change in the marginal product of drug treatment due to an increase in the stock of drug therapy knowledge is positive. Thus, an increase in health will tend to decrease the incentives to research new drug therapies, or $dz^{iD}/dh^i < 0$.

To see how the level of drug research is affected by the costs of doing research let $R = R(\mathbf{dz}, y^i)$, where y^i is an exogenously determined cost parameter such that $\partial^2 R/\partial z^{iD}\partial y^i > 0$. That is, an increase in y will increase the cost of increasing the stock of knowledge in drug therapy. Differentiating equation (8) with respect to y gives us:

$$(10) \quad \left\{ \left[2\alpha U_{ii}\frac{\partial h^i}{\partial z^{iD}} \frac{\partial^2 h^i}{\partial q^{iD}\partial z^{iD}} + \alpha U_{ii}\frac{\partial h^i}{\partial q^{iD}} \frac{\partial^2 h^i}{\partial z^{iD}\partial z^{iD}} \right] q^{iD} - \frac{\partial^2 R}{\partial z^{iD}\partial z^{iD}} \right\} dz^{iD} + \frac{\partial^2 R}{\partial z^{iD}\partial y^i}dy^i = 0$$

As before, the term in braces is negative, leaving $dz^{iD}/dy^i < 0$. The obvious implication is that as the cost of drug therapy research rises, the level of drug research falls.

The two main implications of the model to be tested are that: (1) the level of research for a condition should fall as the level of health of its victims rises ($dz^{iD}/dh^i < 0$) and (2) the level of research for a condition should fall as the costs of undertaking research rises ($dz^{iD}/dy^i < 0$). The basic regression equation is:

$$(11) \quad z^{it} = \beta_0 + \beta_1 h^{it} + \beta_2 y^{it} + \beta_3 X^{it} + \varepsilon^{it}$$

where $z^{it}, h^{it}, y^{it}, X^{it}$ and ε^{it} are the level of drug research, the level of health, the cost of research, other explanatory variables and an error term for condition i at time t. In general, the level of health and the costs of research are proxies for demand and cost shifters.

The model derives results for profit maximizing agents. However, the main source of medical research expenditures in the U. S. for at least the last three decades has been the NIH, a government agency. While economists do not fully understand the decision-making processes of government agencies, to the extent that the objectives coincide with those in the pharmaceutical industry (delivering a greater level of health with a minimum of cost), the decisions should mimic those of the industry. The allocation of research effort by the NIH can also be tested to see how well the process outlined above describes the government decision process.

5. Data Considerations

Data from a number of different sources can be brought to bear on this problem. Although there were some problems in constructing this dataset arising from the differing definitions of a medical condition from different data sources, the dataset to be used varies across medical condition and year. The three main areas of interest are research intensity, the level of health, and the costs of performing R&D. Each one will be discussed in turn below.

Research Intensity

Two different measures of industrial innovative effort will be explored: R&D expenditures and the number of U.S. patents granted. Likewise, government sponsored R&D expenditures can be measured[10]. The construction and implications of these measures are discussed here.

The PMA's Annual Survey Report groups total member sales and R&D expenditure into eight broad therapeutic categories[11] and are summarized in table 3. These data run from 1966 to 1987, however these specific data were not collected in three separate years. Values for these years were interpolated. The R&D numbers are somewhat suspect for two reasons. First, the survey asked U.S. firms for both overseas and domestic R&D expenditures but asked foreign firms for only U.S. based R&D expenditures. R&D growth may be understated since research has increased at a faster rate overseas. Second, research programs sometimes overlap medical categories or there is some joint or common cost between categories requiring an allocation into the competing categories.

The other major source of health related R&D is research undertaken by the NIH. While industrial R&D tends to be mostly development of products with some applied research, research done by the NIH tends to be mostly basic research and is not confined to pharmaceutical research. The NIH Almanac publishes expenditures by institute since 1938 while the NIH Data Books provide more detail for a particular year. An NIH database has

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[10]   The NIH has only recently has become interested in patenting drug products that result from their research. Subsequently, there are very few government sponsored and patented drugs.

[11]   Therapeutic categories define the broad markets within the drug industry. These therapeutic categories are: Anti-infectives, Central Nervous System and Sense Organs, Cardiovasculars, Neoplasms, Endocrine System and Metabolic Diseases, Gastrointestinal and Genitourinary System, Repiratory System, Dermatologicals, and Vitamins and Nutrients. The PMA also reports figures for Diagnostics and Biologicals, but these are not consistent throughout the sample.

recently been constructed by Rebecca Henderson at MIT from the NIH Data Books which, among other things, aggregates R&D expenditures into medical condition categories based on the actual institute[12] for the period 1962 to 1988.

Another measure of innovative effort is being derived from drug patents granted to the pharmaceutical industry. Patents play an important role in protecting property rights that firms have over the product of their R&D effort. Patenting usually occurs just prior to filing an IND application or, on average, nine or ten years prior to marketing. As many as ten to twenty times the number of drugs that are marketed in a year will be patented. Most of the new molecular entities that do reach the market have been patented. Between 1963 and 1989, over 28,000 patents have been granted for pharmaceutical products. Therefore, while a patent represents the culmination of some industrial research effort, a great deal more development lies ahead for a newly patented drug to reach the market.

The U.S. Patent and Trademark Office assigns each patent to a six digit class and sub-class. For drugs and medicines there are over 500 subclasses indicating a large degree of specificity in the classification system. Counts of patents can be a misleading indicator of innovative effort for two different reasons. First, counts of patents put the same weight each patent while patented drugs have a wide range of potential therapeutic values or expected profitability and different amounts of R&D effort in their discovery. Second, it is claimed that firms in this industry often patent drugs without the intention of ever marketing the drug but as a mechanism to protect the monopoly rents of a previously marketed or soon to be marketed drug. These are common criticisms of the use of patent data, however they are less applicable to the present study since patent comparisons are made not between industries with different institutions but within the industry and often only within a class of drugs in the industry where a greater degree of homogeneity of patents is to be expected.

Level of Health

Measures of the level of health are derived from mortality and morbidity statistics and statistics on the number of physicians by specialty. These data have the advantage of being comparable across the different markets within the drug industry. Attempts were made to find sources that report statistics for all of medical conditions analyzed here in order to insure comparability of the measures. Using measures with different condition

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12   There are five broad categories that have consistent time series for a number of years. These conditions (Institutes) are: Allergy and Infectious (NIAID), Arthritis, Musculoskeletal, Skin, Diabetes, and Digestive and Kidney (NIAMD, NIAMS, NIADDK), Cancer (NCI), Heart (NHI, NHLBI), and Neurology (NINDS, NINCDS).

severity implications (physicians versus deaths) allows one to see the effect not only of a higher incidence of the condition, but also of a more severe condition.

Mortality rates by disease (ICD classification) are published in U.S. Vital Statistics for about 60 disease groupings for the period 1950-1989 and are summarized in table 4. Different revisions of the ICD classification system during this period require some care in constructing a consistent time series. For broader categorizations, as with the PMA or NIH categories, insuring consistency is not difficult.

The Center for Health Statistics publishes morbidity measures collected from the National Health Interview Survey. The survey has been conducted annually since 1961 and the published data from the survey distinguish between acute and chronic conditions. For acute conditions, this series runs from 1961 to 1988 and include the incidence of the condition, the number of days of restricted activity, and the number of days of bed disability by category[13]. The published data underwent a revision in 1980 which make a consistent time series difficult to create. For chronic conditions, the series is shorter, beginning in 1979 and continuing to the present and only the prevalence of the condition is reported. Another limitation of the published sources is that they are for selected conditions and not all possible conditions. Notably absent are cancer and neurological diseases.

A measure of morbidity (or, more generally, the demand for health) that is readily available is the number of physicians by speciality. Peltzman (1973) used the total number of physicians as a proxy for the demand for new drugs. Here, we have matched the number of physicians in a particular specialty with the demand for new drugs treating conditions addressed by the physician speciality. A little over a quarter of the physicians analyzed in "Physician Characteristics and Distribution in the U.S." could be placed into categories comparable with the PMA categories. Almost half of all physicians claim General Practice, Family Practice, General Surgery or Internal Medicine as their specialty. The remaining physicians fall into specialties such as Aerospace Medicine and Emergency Medicine.

The decision about the patient's consumption of a drug is primarily in the hands of the attending physician and not the patient. Other than choosing not to have a prescription filled or, more recently, filling it with a generic equivalent, the end consumer has little latitude in deciding which prescription drug or how much of it to purchase. The implicit assumption in using the number of physicians as a proxy for demand is that physicians and drugs are compliments in the production of health and not substitutes. If a particular

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[13]   The broad categories are: Infectious, Respiratory, and Digestive conditions as well as injuries. Data are also available for certain sub-categories.

medical condition is treatable, a physician has at his disposal any of a number of options: surgery, radiation therapy, physical therapy, a medical device, diet, or a solely pharmaceutical treatment. Most of these options include drugs in the production of the final therapy to some degree.

<u>Costs of Performing R&D</u>

Finding direct measures of the costs of performing R&D is difficult. The two broad measures to be used here, drug development times and the changes in the stock knowledge, imply changes in costs but are not direct measures. FDA monitoring of the drug development process mandated by the 1962 Amendments provides measures of development time costs. The fraction of drugs that are never marketed can also be calculated. Of those that are eventually approved, the time in research phase has risen considerably between 1960 and 1980 and varies across drug categories. Increases in either the drug category's attrition rate or approval time can increase the costs of innovation significantly. Alternatively, the costs of performing R&D are related to the unexploited stock of knowledge in existence at the time of the research. That is, when a breakthrough occurs in our understanding of a medical condition, pharmaceutical researchers can limit their attention to those treatments advanced by the breakthrough. This measure is of particular interest in that most medical basic research is funded through the NIH. The effect of this measure also has the interpretation of being a knowledge or technology spillover. These two types of R&D cost measures are explored below.

The FDA's list of drugs approved for marketing from 1950 to 1987 has been obtained in order to measure development times. The information contained in this list include the NDA application and approval dates, dosage form, applicant, and therapeutic category. Second, for those drugs that were patented, the patent dates have been merged to this list. Third, for a sub-sample of drugs, the date of the IND application has been added. These dates allow us to get three measures of the drug development time (from patent, IND or NDA application to NDA approval). Other researchers indicate that the time in IND phase and the time in NDA phase tend to be positively correlated.

The FDA claims to speed up the approval process for important new drugs. Likewise, if a pharmaceutical firm thought that it had an important new drug it would tend to speed up the the pre-NDA investigations. If important drugs are more concentrated in specific categories or years than expected, then an unadjusted approval time may lead to a biased measure of the expected time to approval. To solve this problem, the time of approval will be regressed against measures of importance of the drug and the residual will be used as the adjusted time to approval. The measures of importance to be explored are

the number of patent and medical journal citations, the number of countries in which the drug was marketed, whether or not the drug spawned a new category of drugs, and whether or not the drug is referenced by pharmaceutical textbooks[14].

From the information on drug approval times and information on the total number of IND and NDA applications in a year, it is possible to construct a measure of the probability of eventual marketing from both the IND application and the NDA application. In any year, there are four times as many NDA's applied for and nearly 20 times as many IND's applied for than are ever introduced. Again, the attrition rates depend on the therapeutic category and year of introduction of the drug. This allows two different measures of the probability of eventual market introduction.

Finally, some areas of medical research have witnessed more successful basic research than others. When the level of medical or pharmacological understanding is increased substantially, drug researchers can better allocate their resources toward the more promising treatment strategies and eliminate research on newly apparent blind alleys. Measuring the stock of knowledge is problematic. Two measures to be explored here are the number of medical articles published in a particular category and year and patents of major breakthrough drugs.

The National Library of Medicine (NLM) abstracts over a quarter million medical journal articles each year and adds them to the Medline Database. A unique feature of this data base is the medical subject heading tree structure that the librarians have used to categorize articles. This allows one to search for articles pertaining to different diseases with a relatively high degree of confidence that the search will be exhaustive and that there will be little double counting. The search performed for this thesis narrowed the article search further by including articles pertaining only to drug therapy. The NLM has increased its coverage by adding abstracts from journals not previously in the database. These could either be entirely new journals or previously marginal journals. In either case, it is not clear that the increase in the number of new articles represents new knowledge or rather a lower cost of publication. To correct for this possible bias, the article count was adjusted by dividing by the total number of medical journal articles for the year and multiplying by the average number of articles over all years.

Since most of the medical research is funded by the government (primarily through the NIH but other agencies contribute as well), this variable can be interpreted in part as a knowledge spillover from the government to the industry. In 1988, the NIH spent nearly

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[14]   These importance measures are currently being investigated in the context the effect of FDA regulation on new drug development in work by Dranove, Meltzer and Ward.

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seven billion dollars on medical research. More than 80% of this sum funded extramural projects (R&D grants and contracts and research training) making the NIH by far the largest sponsor of medical research.

About the time that an IND application is submitted to the FDA by a pharmaceutical firm, a patent application is also submitted to the Office of Patents and Trademarks. Industry insiders who track the progress of competitors can glean information from these filings. They will often be able to discern which of these filings represents a significant breakthrough in the treatment of a particular medical condition and direct their own R&D efforts accordingly. To capture this effect, a variable will be constructed to indicate when an important new drug was patented. Importance will be judged by the degree to which the new drug was subsequently cited in patent applications or medical journal articles. This variable will reflect an increase in the stock of knowledge and, to a certain degree, an interfirm spillover of information.

Other Explanatory Variables

The level of drug research depends also on the income of drug consumers. It is possible to calculate the usual income elasticity with the inclusion of an real income variable. Both real disposable income and R&D expenditures have been trending up over time with that rate of R&D expenditures outpacing income by more than two to one. This is likely to introduce spurious correlation between these two variables. To solve this problem, two different measures of income, public expenditures on health from the OECD: Health Data File, 1989 and personal consumption expenditures on medical goods and services from the National Income and Product Accounts, are examined. The rationale for using these measures is that final consumers in the health sector do not pay directly for most of the services that they receive. Third party providers such as health insurance and government health subsidies pay the bulk of the direct medical costs[15]. Subsequently, the share of income devoted to health care is often not chosen directly by the consumer. The federal government, through Medicare, Medicaid and like programs, has become the largest single payer for health expenditures.

Also included in the regression equations are therapeutic category dummy variables and the lag of the dependent variable. The dummy variables are meant to capture any idiosyncratic differences between the therapeutic categories. Note that the inclusion of

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[15] While final consumers pay about 25% of total health care costs, they pay about 70% of the costs of pharmaceutical preparations. However, pharmaceuticals are just one input into the production of health. The theory of derived demand for inputs implies that pharmaceuticals receive an effective subsidy.

category dummy variables implies that the results are not derived from cross category comparisons and only reflect time variation within the categories. That is, even though more people suffer, and suffer greater disability, from cardiovascular conditions than dermatological conditions, this difference will not be reflected in the results. The lagged dependent variable is to correct for autocorrolation in the error terms.

6. Results

In order to estimate equation (11), estimates of the drug development time must be made first. These estimates were made using the data on drugs approved for marketing by the FDA. The other variables used in estimating equation (11) are directly at hand.

Estimates of the Drug Development Time

The goal of these estimates is to construct measures of the expected drug development time from the point of view of the potential innovator. Ward (1991) details the estimation of different measures of the drug development time. We will summarize some of those results here. Generally, there has been an increase in the drug development time during the sample period of this study (1966 to 1987), however these increases vary considerably across categories.

The time from NDA application to NDA approval for drug applications falling between 1960 to 1987 period averaged 2.23 years with a standard deviation of 1.75 years. OLS estimates were obtained by regressing NDA approval time on a polynomial in year of NDA application interacted with a therapeutic category dummy variable[16].

The time from first worldwide patent application to NDA approval for drugs patented between 1945 and 1987 averaged 8-13 years with a standard deviation of about 8-12 years. This development time measure captures much more of the time that a drug spends in development. This sample exhibits a serious truncation problem requiring maximum likelihood estimation techniques[17]. In this procedure, both the mean time to approval and it's standard deviation were estimated as functions of observable data.

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[16] The sample consisted of 922 New Molecular Entities introduced since 1966 and the estimated regression equation had an adjusted R^2 of .05. No one variable is statistically significant at even the 10% level, however the F-statistic for the model with 26 degrees freedom was 5.174 which is significant at the 0.01% level.

[17] The sample includes all drugs given NDA approval by 1989. Therefore, a drug that had its patent application filed in 1979 is in the sample only if it is given NDA approval within the 10 years of the

Estimates of Industry Research and Development Expenditures

Here, we explore statistical estimates of determinants of industry R&D expenditures. Explanatory variables included therapeutic category dummies, the lagged value of industry R&D expenditures, the mortality level, the number of physicians, real personal consumption expenditures on medical goods and services, the predicted length of time for an NDA to be pending at the FDA and various measures of the number of drug therapy articles. Personal consumption expenditures do not vary across conditions in the same year. Also, multicolinearity between disposable personal income, public health expenditures for health care and personal consumption expenditures on medical goods and services (correlation coefficients of more than .98) prohibit the inclusion of more than one of these variables in the same regression equation.

Some values of the number of physicians and the number of deaths would have required taking the natural log of zero which, of course, is undefined[18]. An established procedure for including these observations in a regression is to compute the mean value of the independent variable for the non-zero valued observations, assign this value to the zero valued observation and include a dummy variable for those observations for which this procedure was used. In this way, the zero valued observations add no value to the estimated parameter and the effect of a zero value is captured by the dummy variable. Since the estimation to be used here already has category dummies, no new ones were included and the estimated dummy variables are re-interpreted.

From table 5 presents results for the basic regression equation. The number of physicians seems to be good proxy for demand while the mortality rate does not. Increases in income, as defined here, increase demand. While only significant in equation (6), the coefficient of the NDA approval times is always negative. The coefficient of the average number of articles over increasing lengths of time just prior to the R&D expenditure is positive and increasing in magnitude as the length of time increases. In moving from equation (1) to equation (6), the length of time for this average is increased. Also, although the number of observations decreases, the fit for all of the variables seems to improve. A word of caution is necessary in interpreting the adjusted R-squares. With only the dummy

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patent application. However, a drug that had its application filed in 1954 is in the sample if it was approved within 35 years of the patent application.

[18] There were too few deaths from central nervous system or dermatological diseases for U.S. Vital statistics to report implying that the true value was close to zero. Also, the AMA does not report a physician specialty that primarily treats infectious conditions.

variables and the lagged dependent variable in the regression, the adjusted R-square is greater than .80.

In moving from equation (1) to equation (6), the coefficient of the lagged dependent variable falls and its standard error rises. Thus, its contribution to the explained sum of squares is falling as better measures of the number of drug therapy articles are used. This is consistent with the notion that the lagged dependent variable proxies for omitted variables that are incrementally introduced as one goes across the table.

Drug research is directed toward products which are intended to be introduced well into the future. Table 6 reports a variant of equation (6) of table 5 with future values of the number of deaths as the independent variable rather than the contemporaneous value on the assumption that drug researchers could predict the mortality levels a few years hence. The coefficient for the future number of deaths is marginally significant at a four year lead but not at earlier leads. The coefficient estimates for the number of drug therapy articles increase as does that of the number of physicians. The number of observations drops even further due to the lead values as does the contribution of the lagged dependent variable.

<u>Estimates of NIH Research and Development Expenditures</u>

This section explores the determination of NIH R&D expenditure. The explanatory variables to be examined are the same ones as in the previous section. As mentioned earlier, it is not at all clear what the government's objective function is, although it is often claimed to be the maximization of total surplus. The maximization of total surplus has the same implications for the effects of demand and costs on R&D determination as does profit maximization. The measures for demand used above would be the same ones relevant for the government, however, the NDA duration time is probably only relevant for industrial R&D.

The results of these regressions are presented in table 7. The same procedure for dealing with zero valued observations presented above was applied here. Again, lagged R&D expenditures are the best predictor of current R&D expenditures. In contrast to the industry regression results, however, both the coefficient of number of physicians and of deaths are significantly positive. Moreover, the coefficient of the number of deaths is about twice that of the number of physicians. The income measure has essentially no effect. Except for equation (6), with only three quarter of the observations remaining, the predicted NDA approval time is also insignificant. As with table 5, averages of the number of drug therapy articles of increasing numbers of years were included as regressors. In contrast to table 5, they seem to have no effect on the determination of NIH R&D expenditures.

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In broad terms, these results are consistent with what one might expect the difference to be between industrial and government research. The industry is more interested in the number of people with the condition (as represented by physicians) while the government is more concerned with serious conditions (as represented by deaths). Moreover, the industry is sensitive to factors that might increase the costs of performing research while the government is not.

<u>Estimates of Medical Journal Article Production</u>

Table 8 presents estimates of a reduced form production function for medical journal articles. Special attention is placed on the role of NIH funding on the production of new knowledge (as represented by medical journal articles). The only variables which are statistically significant here are the lagged dependent variable, income, and lagged NIH expenditures for lags over three years. The coefficients of physicians and deaths are positive but generally only one standard error away from zero. Income, or real personal consumption expenditures on medical goods and services, enters into the regressions negatively. This may be an artifact of how the number of articles variable was adjusted for an upward trend not associated with a quickened pace of knowledge creation. The positive coefficient on four and five year lagged NIH expenditure confirms the governments role in the creation of new knowledge.

Table 9 is the analog of table 6 in that the number of deaths in future years is used instead of the contemporaneous number of deaths. Also, NIH expenditures from the fourth and fifth years lagged are averaged. Moving from equation (1) to equation (5), the lead on deaths increases and so does the coefficients and significance of both physicians and deaths.

7. Conclusions and Discussion of Further Research

A better understanding of the determinants of innovative effort is important as innovation policy is being developed. This paper presented a model of innovation based on rent seeking behavior by firms. The model that predicts that industrial pharmaceutical R&D expenditures should decrease with the level of health and with the costs of performing R&D. Preliminary empirical results bear this out. Measures of health disability increase R&D expenditures and measures of decreased R&D costs, both in terms of shorter drug development times and increases in the stock of knowledge, increase R&D expenditures. Moreover, government funding of basic research tends to be an important source of new knowledge to the industry.

Plans for future work will are focused on two areas. First, will be the investigation of a different measure of R&D intensity derived from the patent statistics. It is hoped that analysis of this measure will confirm the results presented here. Second, the proxies for costs of R&D from both different development time measures and measures of the stock of knowledge will be refined. Measures of the drug development time from IND and patent application to NDA approval will be created and tested along with the NDA approval time. A change in the stock of knowledge variable will be created from the patenting of new important drugs. That is, when an important drug is patented by one firm, it becomes public knowledge to all drug firms. This measure of interfirm technology spillover should complement that of the government spillover.

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Graph 1
R&D Expenditure by Therapeutic Category
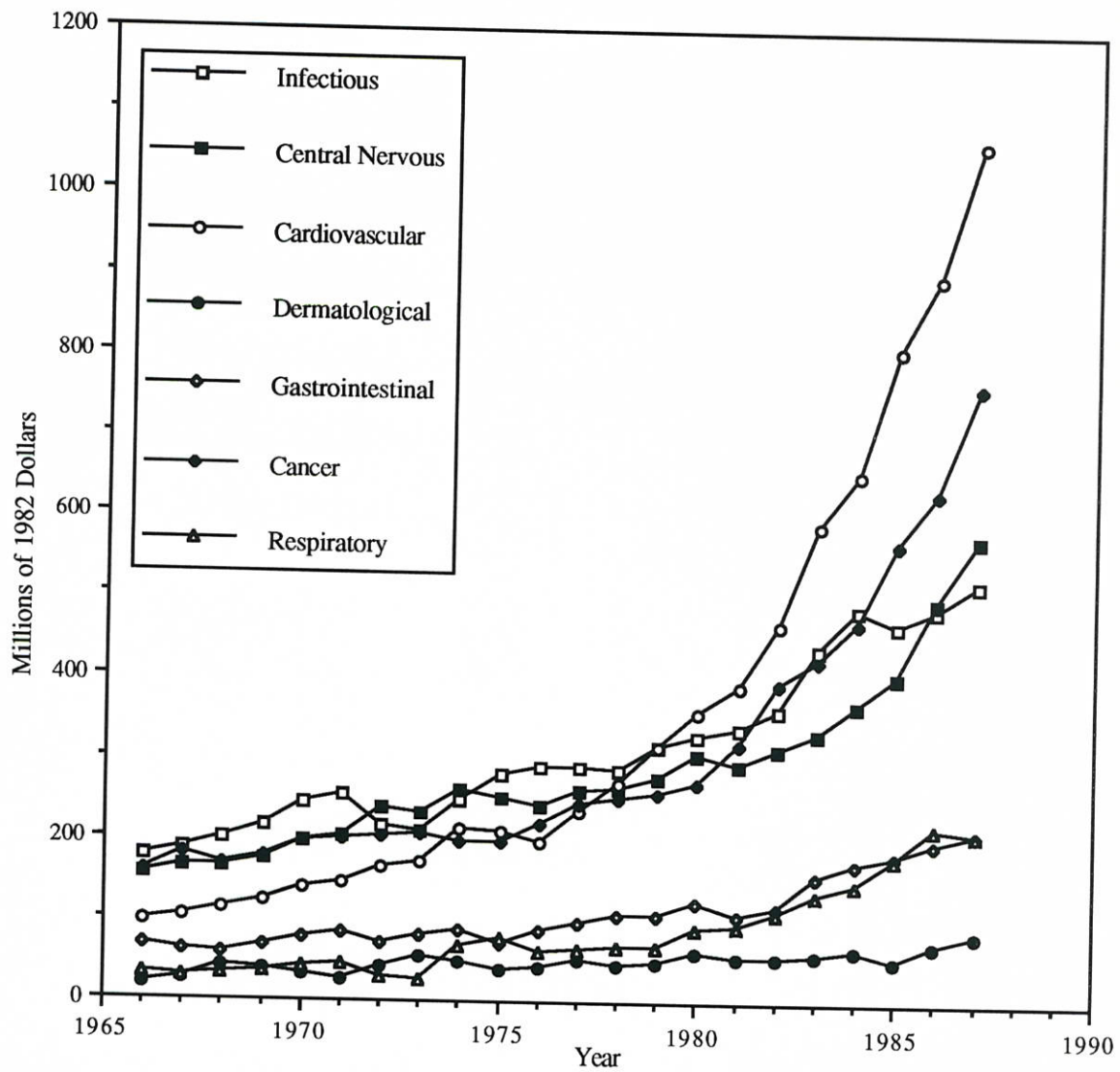
From Annual Survey Report, PMA, various years

Table 1
Companies own funds for industrial R&D in 1987 by industry
percentage of sales and percentage of total R&D

Industry	SIC codes	R&D/Sales	Fraction of all R&D $
Food and kindred	20,21	0.7%	2.2%
Textiles and apparel	22,23	0.4%	0.3%
Lumber, wood products and furniture	24,25	0.6%	0.2%
Paper and allied products	26	0.7%	0.9%
Chemicals and Allied Products	28	5.2%	14.9%
Industrial Chemicals	281-282,286	4.6%	5.7%
Drugs and Medicines	283	8.5%	6.3%
Other Chemicals	284-285,287-289	3.3%	2.9%
Petroleum refining and extraction	13,29	1.0%	2.9%
Rubber Products	30	1.8%	1.2%
Stone, clay and glass	32	2.6%	1.6%
Primary Metals	33	0.8%	1.1%
Ferrous metals and products	331-332,3398-3399	0.6%	0.5%
Non-ferrous metals and products	333-336	1.2%	0.7%
Fabricated metal products	34	1.6%	1.6%
Machinery	35	7.6%	17.6%
Office, computing and accounting machines	357	12.6%	13.1%
Other machinery, except electrical	351-356,358-359	3.5%	4.5%
Electrical Equipment	36	5.4%	17.0%
Radio and TV receiving equipment	365	3.2%	0.2%
Communications equipment	366	5.4%	8.5%
Electronic Components	367	8.7%	5.6%
Other electrical equipment	361-364,369	3.0%	2.7%
Transportation equipment	37	3.4%	20.7%
Motor vehicles and equipment	371	3.3%	11.2%
Other transportation equipment	373-375,379	2.4%	0.6%
Aircraft and missiles	372,376	3.7%	9.0%
Professional and scientific instruments	38	8.4%	8.0%
Scientific and mechanical measuring instruments	381-382	8.1%	2.5%
Optical, surgical, photographic, and other instruments	383-387	8.5%	5.5%
Other manufacturing industries	27,31,39	1.1%	0.6%
Non-manufactoring industries	08,10-12,14-17, 40-67,72-73, 806-807,891	N/A	9.1%
Total		3.2%	100.0%

From National Science Foundation, *Research and Development in Industry: 1987*

Table 2
Global Sales and R&D for PMA member firms ($ million)

Year	Sales	R&D	Percent R&D/Sales
1989	51,492	7,271	14.1%
1988	46,197	6,461	14.0%
1987	41,635	5,505	13.2%
1986	37,137	4,748	12.8%
1985	32,026	4,078	12.7%
1984	29,854	3,579	12.0%
1983	27,506	3,218	11.7%
1982	25,654	2,774	10.8%
1981	23,530	2,340	9.9%
1980	22,513	1,977	8.8%
1979	18,939	1,627	8.6%
1978	16,431	1,404	8.5%
1977	14,155	1,276	9.0%
1976	13,035	1,164	8.9%
1975	11,769	1,062	9.0%
1974	10,361	942	9.1%
1973	8,839	825	9.3%
1972	7,930	726	9.2%
1971	7,605	684	9.0%
1970	6,637	619	9.3%
1969	6,008	550	9.2%
1968	5,482	495	9.0%
1967	4,941	461	9.3%
1966	4,509	416	9.2%
1965	4,136	365	8.8%
1964	3,643	310	8.5%
1963	3,399	292	8.6%

From Annual Survey Report, PMA, various years

Table 3
PMA U. S. Sales and R&D
by Therapeutic Category in 1966 and 1987

	Anti-Infectives	Central Nervous System	Cardio-Vascular	Dermato-logical	Gastro-Intestinal	Cancer	Respir-atory	Vitamins and Nutrients
Millions of Current Dollars								
1966 Sales	509	723	192	61	324	348	199	246
1987 Sales	4,139	5,324	4,962	532	2,593	2,922	1,541	823
1966 R&D	61.5	53.9	33.9	6.3	23.3	54.9	11.3	8.0
1987 R&D	605.4	670.1	1,247.7	97.0	244.9	891.9	244.9	9.2
Percent of Total								
1966 Sales	19.5%	27.8%	7.4%	2.3%	12.5%	13.4%	7.7%	9.5%
1987 Sales	18.1%	23.3%	21.7%	2.3%	11.4%	12.8%	6.7%	3.6%
1966 R&D	24.3%	21.3%	13.4%	2.5%	9.2%	21.7%	4.5%	3.2%
1987 R&D	15.1%	16.7%	31.1%	2.4%	6.1%	22.2%	6.1%	0.2%
Percent R&D/Sales								
1966	12.1%	7.5%	17.7%	10.3%	7.2%	15.8%	5.7%	3.2%
1987	14.6%	12.6%	25.1%	18.2%	9.4%	30.5%	15.9%	1.1%
Average Annual Rate of Growth 1966-1987								
Sales	11.1%	10.5%	17.7%	11.4%	11.0%	11.2%	10.8%	6.2%
R&D	12.1%	13.4%	19.8%	14.6%	12.5%	15.0%	16.6%	0.7%

From Annual Survey Report, PMA, various years

Table 4
Mortality Rates by Category
for 1950 an 1987

	Infectious Diseases	Cancer	Cardio-Vascular Disease	Respir-atory Disease	Gastro-Intestinal Diseases	Other Causes	Total
Deaths per 100,000							
1950	38.0	139.8	510.8	33.3	40.2	201.7	963.8
1987	19.9	195.9	395.9	60.8	26.9	173.0	872.4
Percent of Total							
1950	3.9%	14.5%	53.0%	3.5%	4.2%	20.9%	100.0%
1987	2.3%	22.5%	45.4%	7.0%	3.1%	19.8%	100.0%
Percent Change 1950 to 1987	-47.6%	40.1%	-22.5%	82.6%	-33.1%	-14.2%	-9.5%

From U. S. Vital Statistics, various years

Table 5
Industry R&D Determination
Sample includes years 1967 to 1987

Dependent Variable: Log Real PMA R&D Expenditures	1	2	3	4	5	6
Log Lag Real PMA R&D Expenditures	0.70* (0.07)	0.69* (0.07)	0.66* (0.07)	0.63* (0.08)	0.58* (0.08)	0.52* (0.09)
Log of Number of Deaths	0.04 (0.11)	0.06 (0.11)	0.06 (0.12)	0.05 (0.12)	0.02 (0.13)	0.01 (0.13)
Log of Number of Physicians	0.23+ (0.10)	0.22+ (0.11)	0.23+ (0.11)	0.24+ (0.12)	0.23+ (0.12)	0.24+ (0.12)
Log of Real Pers. Cons. Expend. on Med Serv.	0.31* (0.09)	0.38* (0.22)	0.43* (0.11)	0.52* (0.13)	0.69* (0.14)	0.84* (0.16)
Log of Predicted NDA Approval Time	-0.18 (0.11)	-0.16 (0.12)	-0.10 (0.12)	-0.12 (0.13)	-0.18 (0.13)	-0.30+ (0.14)
Log of No. of Drug Therapy Articles	0.28+ (0.11)					
Log of 2 Year Avg. of Drug Therapy Articles		0.38* (0.13)				
Log of 3 Year Avg. of Drug Therapy Articles			0.37* (0.14)			
Log of 4 Year Avg. of Drug Therapy Articles				0.46* (0.16)		
Log of 5 Year Avg. of Drug Therapy Articles					0.63* (0.18)	
Log of 6 Year Avg. of Drug Therapy Articles						0.79* (0.21)
Number of Obs	147	140	133	126	119	112
Adjusted R^2	.97	.97	.97	.97	.97	.97

Standard errors of estimates are in parenthesis. Confidence levels for tests of whether the estimated coefficient is significantly different from zero are denoted by: (*) for 1%, (+) for 5%, and (#) for 10%. Dummy variables for each therapeutic category were included in the regressions but are not reported. The therapeutic categories included are for the following conditions: cancer, cardiovascular, dermatology, gastrointestinal, infections, nervous system, and respiratory.

Table 6
Industry R&D Determination
Sample includes years 1967 to 1987

Dependent Variable: Log Real PMA R&D Expenditures	1	2	3	4
Log Lag Real PMA R&D Expenditures	0.50* (0.09)	0.49* (0.09)	0.47* (0.09)	0.41* (0.10)
Lead 1 of Log of Number of Deaths	0.09 (0.11)			
Lead 2 of Log of Number of Deaths		0.13 (0.10)		
Lead 3 of Log of Number of Deaths			0.09 (0.11)	
Lead 4 of Log of Number of Deaths				0.22# (0.13)
Log of Number of Physicians	0.26+ (0.12)	0.28+ (0.12)	0.33+ (0.14)	0.39+ (0.16)
Log of Real Pers. Cons. Expend. on Med Serv.	0.82* (0.16)	0.81* (0.16)	0.82* (0.17)	0.81* (0.18)
Log of Predicted NDA Approval Time	-0.24# (0.13)	-0.22 (0.13)	-0.39+ (0.15)	-0.38+ (0.18)
Log of 6 Year Avg. of Drug Therapy Articles	0.84* (0.21)	0.87* (0.21)	0.88* (0.23)	1.00* (0.26)
Number of Obs	112	112	105	98
Adjusted R^2	.97	.97	.97	.97

Standard errors of estimates are in parenthesis. Confidence levels for tests of whether the estimated coefficient is significantly different from zero are denoted by: (*) for 1%, (+) for 5%, and (#) for 10%. Dummy variables for each therapeutic category were included in the regressions but are not reported. The therapeutic categories included are for the following conditions: cancer, cardiovascular, dermatology, gastrointestinal, infections, nervous system, and respiratory.

Table 7
NIH R&D Determination
Sample includes years 1967 to 1988

Dependent Variable: Log Real NIH R&D Expenditures	1	2	3	4	5	6
Log of Lag Real NIH R&D Expenditures	0.80* (0.05)	0.75* (0.06)	0.69* (0.06)	0.67* (0.06)	0.62* (0.07)	0.55* (0.08)
Log of Number of Deaths	0.28* (0.09)	0.32* (0.09)	0.33* (0.09)	0.37* (0.09)	0.45* (0.09)	0.53* (0.10)
Log of Number of Physicians	0.10# (0.06)	0.15+ (0.06)	0.17+ (0.07)	0.21* (0.07)	0.28* (0.07)	0.35* (0.08)
Log of Real Pers. Cons. Expend. on Med Serv.	0.03 (0.07)	0.04 (0.07)	0.07 (0.07)	0.04 (0.08)	-0.07 (0.08)	-0.12 (0.10)
Log of Predicted NDA Approval Time	-0.02 (0.12)	-0.03 (0.12)	-0.05 (0.12)	-0.10 (0.12)	-0.20 (0.12)	-0.27# (0.14)
Log of No. of Drug Therapy Articles	-0.04 (0.09)					
Log of 1 Year Lag of Drug Therapy Articles		0.03 (0.09)				
Log of 2 Year Lag of Drug Therapy Articles			0.06 (0.09)			
Log of 3 Year Lag of Drug Therapy Articles				0.05 (0.09)		
Log of 4 Year Lag of Drug Therapy Articles					-0.01 (0.09)	
Log of 5 Year Lag of Drug Therapy Articles						0.05 (0.09)
Number of Obs	110	105	100	95	90	85
Adjusted R^2	.97	.97	.97	.98	.98	.98

Standard errors of estimates are in parenthesis. Confidence levels for tests of whether the estimated coefficient is significantly different from zero are denoted by: (*) for 1%, (+) for 5%, and (#) for 10%. Dummy variables for each therapeutic category were included in the regressions but are not reported. The sample includes the five NIH therapeutic categories (NCI:cancer, NHI:heart, NINDS:neurological, NIAMD:arthritis, diabetes, and digestive & kidney, and NIAID:allergy and infectious conditions).

Table 8
Medical Journal Articles Determination
Sample includes years 1967 to 1988

Dependent Variable: Log Number of Drug Therapy Articles	1	2	3	4	5	6
Log of Lag No. of Drug Therapy Articles	0.76* (0.06)	0.76* (0.06)	0.75* (0.06)	0.74* (0.06)	0.70* (0.06)	0.66* (0.06)
Log of Number of Deaths	0.08 (0.06)	0.07 (0.06)	0.04 (0.06)	0.05 (0.06)	0.04 (0.05)	0.05 (0.05)
Log of Number of Physicians	0.05 (0.04)	0.04 (0.04)	0.03 (0.04)	0.04 (0.04)	0.05 (0.04)	0.06 (0.04)
Log of Real Pers. Cons. Expend. on Med Serv.	-0.09 (0.05)	-0.09+ (0.05)	-0.11+ (0.04)	-0.11+ (0.05)	-0.13* (0.04)	-0.16* (0.04)
Log of Predicted NDA Approval Time	0.07 (0.08)	0.07 (0.08)	0.07 (0.08)	0.07 (0.08)	0.06 (0.07)	0.07 (0.07)
Log of Real NIH R&D Expenditures	-0.04 (0.09)					
Log of 1 Year Lag of NIH R&D Expenditures		-0.01 (0.04)				
Log of 2 Year Lag of NIH R&D Expenditures			0.05 (0.03)			
Log of 3 Year Lag of NIH R&D Expenditures				0.04 (0.03)		
Log of 4 Year Lag of NIH R&D Expenditures					0.09* (0.03)	
Log of 5 Year Lag of NIH R&D Expenditures						0.13* (0.03)
Number of Obs	105	105	105	105	105	105
Adjusted R^2	.96	.96	.96	.96	.97	.97

Standard errors of estimates are in parenthesis. Confidence levels for tests of whether the estimated coefficient is significantly different from zero are denoted by: (*) for 1%, (+) for 5%, and (#) for 10%. Dummy variables for each therapeutic category were included in the regressions but are not reported. The sample includes the five NIH therapeutic categories (NCI:cancer, NHI:heart, NINDS:neurological, NIAMD:arthritis, diabetes, and digestive & kidney, and NIAID:allergy and infectious conditions).

Table 9
Medical Journal Articles Determination
Sample includes years 1967 to 1988

Dependent Variable: Log Number of Drug Therapy Articles	1	2	3	4	5
Log of Lag No. of Drug Therapy Articles	0.68* (0.06)	0.68* (0.06)	0.68* (0.06)	0.68* (0.06)	0.70* (0.07)
Log of Number of Deaths	0.04 (0.05)				
Lead 1 of Log of Number of Deaths		0.04 (0.05)			
Lead 2 of Log of Number of Deaths			0.05 (0.05)		
Lead 3 of Log of Number of Deaths				0.08 (0.05)	
Lead 4 of Log of Number of Deaths					0.12* (0.05)
Log of Number of Physicians	0.05 (0.04)	0.06 (0.04)	0.07 (0.04)	0.11+ (0.04)	0.15* (0.05)
Log of Real Pers. Cons. Expend. on Med Serv.	-0.15* (0.04)	-0.15* (0.05)	-0.17* (0.05)	-0.19* (0.05)	-0.24* (0.06)
Log of Predicted NDA Approval Time	0.07 (0.07)	0.06 (0.07)	0.07 (0.08)	0.03 (0.09)	0.01 (0.11)
Avg of 4 & 5 Yr Lag of Log Log NIH R&D Expend.	0.12* (0.03)	0.12* (0.03)	0.13* (0.03)	0.13* (0.03)	0.14* (0.03)
Number of Obs	105	105	100	95	90
Adjusted R^2	.96	.97	.97	.97	.97

Standard errors of estimates are in parenthesis. Confidence levels for tests of whether the estimated coefficient is significantly different from zero are denoted by: (*) for 1%, (+) for 5%, and (#) for 10%. Dummy variables for each therapeutic category were included in the regressions but are not reported. The sample includes the five NIH therapeutic categories (NCI:cancer, NHI:heart, NINDS:neurological, NIAMD:arthritis, diabetes, and digestive & kidney, and NIAID:allergy and infectious conditions).

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