

Competitive advantages from in-house scientific research: The US pharmaceutical industry in the 1980s *

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Final version received July 1991

The public nature of science may lead to the simplistic conclusion that firms can at no cost avail of the scientific knowledge generated by academia or other non-profit institutions. This paper offers empirical evidence that in-house scientific research raises the ability of the firms to take advantage of “public” science. Case studies of a few large US drug manufacturers show that firms with better in-house scientific research programs have exploited more effectively outside scientific information. Statistical analysis reinforces this conclusion. Using data on the 14 largest US-based drug manufacturers between 1973 and 1986, I find that company patents are positively correlated with the scientific publications of the firms even after controlling for the scale of R&D.

1. Introduction

It is well known, at least since the works of Nelson [47] and Arrow [1], that science exhibits some features of public goods. This may lead to the simplistic conclusion that firms can take ad-

vantage at no cost of the information produced by academia and other non-profit research institutions.

A few authors have argued against this view. Cohen and Levinthal [19] distinguish between two facets of R&D: The two “faces” of R&D. They argue that firms undertake R&D not only as a direct input to innovation, but also as a means of absorbing external knowledge. Using a comprehensive data set on US R&D expenditures, they show that the second face of R&D plays an important role in the decision of the firms to invest in new knowledge. Although they use data on total R&D, Cohen and Levinthal also speculate about the incentives of the firms to invest in basic research:

... firms may conduct basic research less for particular results than to be able to identify and exploit potentially useful scientific and technological knowledge generated by universities or government laboratories, and thereby gaining a first-mover advantage in exploiting new technologies [19, p. 593].

Rosenberg [58] claims that, even though scientific knowledge circulates in the outside environment, firms have to undertake their own basic research in order to understand and utilize external science. In-house basic research is the price “to plug into the outside information network”. Pavitt [56] suggests that scientific research provides “skills, methods, and a web of professional contacts”, which makes the firms better equipped

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* I wish to thank Nathan Rosenberg, Tim Bresnahan, Paul David, Ashish Arora and Ed Steinmueller for continuous encouragement and suggestions. Of course, they are not responsible for the contents of this paper. I also thank Steven Gass of the Terman Engineering Library, Stanford University, for conducting the on-line search on patent data, and Francis Narin and Kimberly Steven of CHI/Computer Horizons for providing me with the data on the publications of the pharmaceutical companies.

Research Policy 21 (1992) 391–407
North-Holland

to exploit outside scientific findings. Again, we are dealing with the “costs” of external science.¹

This paper focuses on the relations between the in-house scientific research of the large US pharmaceutical firms and external scientific knowledge.² More precisely, it explores whether, in spite of the public nature of science, large US drug manufacturers have differed in their ability to exploit the public good. The investigation is based upon case studies of a few of the largest US drug companies. The case studies are complemented by statistical analysis which tests whether measures of scientific capability have a significant influence upon innovation even after controlling for R&D.

One must highlight two important points.

First, it is always difficult to define basic research. It may be easier to think of in-house scientific research in terms of how much the research environment of the companies resembles that of academia or other non-profit scientific institutions, particularly with respect to the autonomy of industry scientists in pursuing research topics, and in the decision to publish or share findings [20,21]. The question of this paper can then be rephrased as follows: To what extent are the capabilities for exploiting science positively associated with firms that organize, at least in part, their internal research in ways that parallel the ambience of academic departments or other scientific institutions?

Second, this paper focuses on the upstream segment of the drug innovation cycle. It neglects important issues, such as the length, costs and risks of the clinical trials, regulation, the role of commercialization and marketing assets. In view of the substantial time lag between scientific research and profitability in the drug industry, these are evidently relevant factors, which may affect the innovation and marketing performance of the firms.

However, this paper focuses on some of the largest pharmaceutical companies in the world. They have broadly similar financial capabilities and commercialization assets; they are US firms, which implies that they face a similar regulatory environment. Moreover, as we shall see, they are all firms that in one way or another have placed great value on innovation during the 1980s. One can claim that, after all, they are fairly homogeneous except in their attitudes towards scientific research. This paper does not assert that this was the only source of heterogeneity among them during the past decade; but it was certainly an important one, and possibly the most important one.

The next section presents the firms in the case studies. Sections 3 to 7 discuss the cases of Merck, Eli Lilly, Bristol-Myers/Squibb, SmithKline and Rorer. Section 8 presents the results of the statistical analysis. Section 9 concludes the paper.

2. The firms in the case studies

The case studies focus on the following firms: Merck, Eli Lilly, Bristol-Myers, Squibb, SmithKline, and Rorer. These are six of the major competitors in the US drug market (table 1).

These firms typify the different strategies of the large US pharmaceutical companies. Merck and Eli Lilly are highly research-intensive firms with strong in-house scientific capabilities. Bristol-Myers is a firm with strong marketing assets and a sound competitive position in non R&D-intensive products; it invested heavily in research during the 1980s to enter the market for patented drugs. Squibb and SmithKline are firms with good in-house research; their marketing position, however, relies only upon the sales of one major product (“one-drug-companies”). Rorer is a medium-sized firm with modest in-house research; during the 1980s, it expanded its research operations to break into the market of R&D drugs.

I believe that these stories span all interesting cases for the purposes of this study. One could add other major US pharmaceutical companies (e.g. American Home Products, Pfizer, Syntex, Upjohn, Warner-Lambert). These cases, however, would only reiterate the arguments developed for the firms that have been investigated.

¹ Among the studies that examined how industrial scientists gain access to public science, [31] and [57] also deserve special mention.

² Science plays an important role in drug research, which makes this sector especially apt to address this topic. There is a fair amount of evidence of the importance of science in pharmaceuticals. For instance, drug patents present the highest citation rate of the scientific literature among all three-digit SIC US industries [12].

3. Merck

Merck was probably the most successful US pharmaceutical firm in the 1980s. It introduced a host of new drugs, and has a number of compounds in late clinical trials (table 2) [14,63].

Merck's high performance rests upon superior in-house research skills. These, in turn, are associated with an internal organization of research that resembles academic departments or other scientific institutions.³ Merck's laboratories are highly informal, and scientists have easy access to one another, a feature which is explicitly meant to attract top-ranking scientists from university, and make them feel comfortable in an academic-like environment.

Research at Merck is divided into 12 therapeutic areas, which are organized into projects. The projects typically correspond to compounds that have shown some promise in early experimental stages. Each research project, including apparently successful ones, has no budget granted by authority. This is an interesting feature of Merck's research organization. If the head scientist of a particular project believes that his or her work needs additional resources, he or she has to convince researchers in other fields or projects to commit part of their budgets and time to the program. As a result, resources are allocated according to the scientists' own evaluation about the relative potential of different research lines [5,63].

The organization of research at Merck resembles that in the scientific community. In the scientific community, research performance is controlled by peer group evaluation (e.g. journal referees). Moreover, within the scientific community, early research breakthroughs lead many scientists to invest time and resources in the new areas. They are motivated by the pecuniary and non-pecuniary rewards (e.g. priority) that may derive from research in relatively unexplored directions which normally show higher potential

for successful discoveries. The key features are the relative autonomy of academic scientists to choose their research topics (and therefore to shift to new research programs), and the pecuniary and non-pecuniary rewards from undertaking research in "uncontaminated" realms. The system as a whole benefits from a social allocation of the scientists' time and resources that is chosen by the best experts to judge the scientific potential of different research lines, viz. the scientists themselves.

Merck's research organization follows a similar model. The company's scientists are the main judges of the validity of different research programs. They have some (albeit not full) discretion to move across projects, and therefore also, to offer their contribution to projects that they deem to be of some value. The incentives to move into potentially successful projects are, of course, the pecuniary and non-pecuniary rewards that may arise from being part of a fruitful research endeavor.⁴

The story of the anti-cholesterol drug Mevacor best illustrates the effectiveness of a research organization that draws in many ways from the model of academia. It also exemplifies Merck's high skills in applying a deductive, "scientific" method to drug research. "Discovery by design" is gradually replacing traditional inductive procedures of drug research based upon random screening of hundreds or even thousands of compounds. Basic research on human pathologies and the structure of proteins help the scientists conceptualize an ideal compound that, according to *a priori* scientific theories, is expected to

³ This is not independent of the fact that a few top executives of the company come from academia. Roy Vagelos, the current CEO, was Dean of the Biological Chemistry Department at Washington University before joining Merck in 1975 as Director of Research. Alfred Albert, who directed the Mevacor research project (see below), was also hired from Washington University in 1975 [5].

⁴ The organization of research at Merck also fosters systematic relations with the scientific community. Merck's library has a reputation comparable with that of the best academic centers. The company regularly organizes internal seminars of world's top academic scientists. Recently, Merck issued a new research award (Scientific Award of the Board of Directors) to be bestowed for major scientific findings in areas related to pharmaceuticals. The prize also includes a 50,000 dollar grant to a school chosen by the winner. Finally, Merck's scientists are not prevented from developing their own research links with academia or other non-profit research institutions, even when this concerns projects not officially approved by the top management. *Business Week* [5] reports the case of a top Merck scientist who, apart from his duty at the company, also spends 10–20 percent of his time doing research with the National Cancer Institute on anti-cancer agents.

Table 1
1986 Pharmaceutical sales and 1983–88 average R&D to sales ratio of the 8 firms in the case studies

Company	Rank of the company in terms of 1986 US pharmaceutical sales	1986 US pharmaceutical sales (million \$)	1986 World pharmaceutical sales (million \$)	Average 1983–88 R&D/sales ratio (%)
Merck	2	1749.0	3441.0	11.3
SmithKline-Beckman	3	1626.3	2502.2	9.8
Bristol-Myers	4	1592.5	3598.0	5.9
Eli Lilly	6	1493.8	2120.0	11.8
Squibb	11	1016.9	1529.6	10.8
Rorer	23	471.0	845.0	7.1

Source: 1986 Sales and company ranking from [43]; Average R&D/sales ratio from R&D and sales data in [44].

counter a certain pathology. This restricts applied research to molecules with features as close as possible to the ideal compound.⁵

Early studies showed that cholesterol, a substance naturally produced by the body, can clog the arteries, thereby causing heart attacks. Merck's scientists first studied how cholesterol is formed within the human body. During the 1970s, they isolated an enzyme (HMG-CoA) which is responsible for starting the production of cholesterol. This, in turn, directed pharmacological research towards the design of a drug that could either inhibit HMG-CoA or prevent cells from using it. The company's scientists eventually isolated lovastatin, the Mevacor compound, which blocks the production of cholesterol [5,29].

The story of Mevacor also highlights Merck's skills in building new scientific findings upon publicly available science. Mevalonic acid, a chemical link in the cholesterol chain, was first isolated by Merck's scientists in 1956. The research on anti-cholesterol drugs, however, was spurred by later findings in the 1970s. Between 1972 and 1974, Michael S. Brown and Joseph L. Goldstein of the University of Texas identified the key steps in the production of cholesterol, a work for which they were awarded the Nobel Prize in 1985. These results motivated Merck's scientists to launch cell culture assay research for cholesterol inhibitors as early as 1975. This led to the discovery of lovastatin. Mevacor was ap-

proved for marketing by the Federal Drug Administration (FDA) in 1987. Its commercialization has been a complete success. The drug reached a record 260 million dollar sales in 1988, the first full year of marketing, and it is expected to grow further at sensational rates [2,5,29].

The point to be emphasized is that Brown and Goldstein's findings became immediately available to the public. Yet, Merck proved to be the only company to effectively exploit the new knowledge. Other firms had interests in this field. Bristol-Myers, for instance, had an anti-cholesterol product, Questran. We shall see that Bristol-Myers had modest in-house scientific skills, especially in the early 1980s. Unlike Merck, it was unable to lever the new (publicly available) findings to improve Questran, and it has yet to come out with a major new anti-cholesterol product.⁶

As also shown by table 2, Mevacor is by no means the only success of this company. In 1985, the FDA approved Pepcid, an anti-ulcer drug, and Vasotec, the second ACE-inhibitor anti-hypertensive drug after Squibb's Capoten. In 1988, Vasotec captured 46.6 percent the hypertensive market against 49.3 percent of Capoten [9]. Merck's research strategy includes building upon previous research successes. At present, it is developing Zocor, the second-generation Mevacor, and it is launching (jointly with ICI) Prinvil, the second-generation Vasotec. It is on the verge of

⁵ I discussed elsewhere the present shift of drug research from random screening to discovery by design [30]. See also [4,24,26,32].

⁶ Sankyo, a Japanese pharmaceutical company, was also carrying out research on anti-cholesterol drugs concurrently with Merck. Sankyo's compounds, however, proved to be much less successful than Merck's lovastatin [5].

Table 2

Merck, major new drugs in the market or in the pipeline, late 1980s

Drug	Category	Year approved for marketing/ status	Notes
Primaxin	Antibiotic	1985	
Pepcid	H2 antagonist	1985	
Vasotec	ACE-inhibitor (anti-hypertensive)	1986	2nd ACE-inhibitor drug in the market after Squibb's Capoten
Mevacor	Anti-cholesterol	1987	First anti-cholesterol drug; spectacular sales growth in first 2 years of marketing
Prinvil	ACE-inhibitor	1988	2nd generation Vasotec; marketed with ICI
Losec	Anti-ulcer	1990 (?)	Expects approval also for therapies other than ulcer (Zollinger-Ellison syndrome and gastro- esophageal reflux disease)
MK 538/ Prodiac	Aldose reductase inhibitor	In late clinicals	

Source: [2] and other trade magazine sources.

launching Losec, a new anti-ulcer drug. Losec exploits the previously accumulated knowledge in the field of anti-ulcers (which led to the introduction of Pepcid), and it is also believed to be effective in treating the Zollinger-Ellison syndrome (a hypersecretory disease) and a gastro-esophageal reflux disease.

4. Eli Lilly

Eli Lilly is another high research-intensive firm. Its in-house scientific capabilities are best exemplified by its current involvement in biotechnology. Eli Lilly has been one of the first corporations worldwide to undertake biotechnology research [54]. It is responsible for two of the seven biotechnology-based human therapeutics approved for marketing in the US during the 1980s, human insulin (jointly with Genentech) and the human growth hormone.⁷ Moreover, Eli Lilly is the second-ranking institution (after the University of California), and the first firm (including both large firms and the small/medium new biotechnology companies), in terms of number of

US patents in genetic engineering granted by December 1987 [55].

Eli Lilly is undertaking important investments in computer-based molecular modelling. It plans to install, in the early 1990s, a supercomputer, worth a few million dollars, to design complex molecular structures [17]. Moreover, in 1988, it entered into a research agreement with Agouron Pharmaceuticals, a small biotechnology concern specialized in computer-based drug design [3,15]. Eli Lilly is investing both in equipment, and in learning the new technique from Agouron. Computers are the fundamental tool of discovery by design. They enable the scientists to conceptualize and design the structure of ideal new drugs of increasing molecular complexity [50,51]. Eli Lilly's strategy thus emphasizes not only the attention paid by the company to frontier technology in drug research; it also underscores its interest in new scientific methodologies of drug discovery. The company aims at taking full advantage of the new potential of discovery by design. It uses both scientific methods and new advances in instrumentation as basic strategic tools for innovation in future years.

Table 3 summarizes Eli Lilly's market performance. The company has 11 drugs with 1989 sales above 100 million dollars. Moreover, in 1987 Eli

⁷ The other five products are alpha-interferon, OKT-3, hepatitis B vaccine, TPA and EPO [16].

Table 3
Eli Lilly's drugs with 1989 sales above 100 million dollars

Drug	1989 sales (million \$)
Ceclor (oral antibiotic)	715
Prozac (anti-depressant)	350
Humulin (human insulin)	300
Keflex-Keftab (oral antibiotics)	190
Animal-insulin	165
Dobutrex (heart failure drug)	150
Tylan	145
Vancocin (injectable antibiotic)	130
Darvon	125
Axid (anti-ulcer)	100
Nebcin (injectable antibiotic)	100

Source: [53].

Lilly obtained marketing approval for an important new drug, Prozac, an anti-depressant. Prozac is a major example of discovery by design, which underscores Eli Lilly's felicitous use of scientific research to bring new products to the market. Prozac is a serotonin-based drug. Although the molecule of serotonin, a chemical in the brain, was first isolated in 1948, and scientists had long linked serotonin to depression, no firm had produced a new drug in this field for many years. Recent scientific advances in the field of protein receptors have shown how to correct and regulate pathological behavior of serotonin, thereby paving the way to the development of serotonin-based drugs.

The molecular structure of serotonin, its links to depression, and the new scientific advances in the field of protein receptors, as developed by researchers in various firms and academic institutions, have always been part of the stock of scientific information in the public domain. Indeed, the new knowledge of protein receptors has prompted many firms to work on the serotonin molecule. Various companies have had access to the new knowledge, and attempted to take advantage of it.⁸

Prozac, however, appears to be a superior discovery amongst all serotonin-based compounds, and it represents the first real breakthrough in this field. We have a further example of how, despite the public availability of science, some firms prove to be better equipped to avail themselves of the public good.

After serotonin is secreted in the brain, most of it is reabsorbed by the nerves. When serotonin is not completely reabsorbed, it improves the mood. Eli Lilly's scientists used this (public) scientific knowledge to design and develop a drug that slows the absorption of serotonin so that some of it remains in the brain [6]. The successful design of the molecule required, first, in-house scientific skills to understand the information in the public domain. Eli Lilly did not develop a new map of the structure of the brain receptor. The knowledge about the receptor sites and characteristics was part of earlier efforts, which poured into the public stock of scientific knowledge. Yet, in-house scientific research was necessary to properly understand the structure of the brain receptors, and to design a compound that could best fit the receptor targets and bind to the desired enzymes in the brain.

An important characteristic of the serotonin molecule is that it can be linked to various other conditions of the human body. Depending upon where serotonin turns up in the body, it can increase or decrease blood pressure, suppress migraine headaches, influence appetite and sexual activity, and of course anxiety and depression. Eli Lilly's scientists have observed that Prozac reduces weight. They are studying the compound to fight obesity. Interestingly enough, they have also observed that, with suitable modifications, the compound could treat the opposite problem, anorexia. The experience with Prozac thus gives Eli Lilly a lead in the development of serotonin-drugs. It enables the company to take full advantage of the heterogeneous applications that may result from "general" scientific principles, which

⁸ There are other serotonin-based drugs apart from Prozac. For instance, Bristol-Myers obtained approval for a serotonin-based anti-anxiety drug in 1986. In December 1989, Ciba-Geigy obtained approval for a serotonin drug. Glaxo is currently awaiting for approval of a similar compound [6,52].

of course has profound implications on its competitive strength and potential for innovation.⁹

Again, the numerous potential effects of serotonin are largely public science, and a considerable part of the current research on serotonin is undertaken by institutions of the scientific community.¹⁰ Similarly, research about the different structures of the human proteins responsible for the different effects of the chemical is to a large extent a public good [52]. However, what is not in the public domain is the research about how to design a compound that could best fit the different receptor structures to develop serotonin drugs that counter selected pathologies of the human body. It is here that the scientific capabilities of Eli Lilly are likely to give it a competitive edge.

5. Bristol-Myers / Squibb

In 1989, Bristol-Myers and Squibb merged to form a new company. During the 1980s, the two firms had somewhat diverse, but partially successful stories. The merger suggests that neither strategy was sufficiently effective in coping with the increasing competitive pressures of the pharmaceutical market.

Bristol-Myers was traditionally specialized in health care and consumer products; it had strong marketing capabilities, but a modest research base. In the 1980s, it took important steps to become a major research-oriented group.

It first started an extensive program to reorganize internal research. It concentrated its re-

search laboratories, which were previously scattered in three separate locations around the US, in one new research center in Connecticut. The location was chosen because of its proximity to Yale and other universities of the New England, which was explicitly meant to facilitate informal contacts between academic and industry scientists [66].

The company also carried out important investments in genetic engineering and molecular biology [66]. Apart from in-house research, it acquired scientific skills through external linkages. In 1982, it signed a comprehensive agreement with Yale University on anti-cancer research. The agreement, which was renewed in 1986, covers a relatively large number of scientific disciplines, and establishes that Bristol-Myers finance research at Yale in exchange for a first option on licenses [3,13,35]. Bristol-Myers also internalized research capabilities in biotechnology via acquisitions. In 1985 and 1986, it acquired Genetic Systems and Oncogen, two medium-sized firms specialized in biotechnology research [3,66].

The new strategy produced some results. Bristol-Myers now performs frontier research in a number of fields, including sophisticated basic research in the area of nerve and brain cell chemistry, and in biotechnology [35].

In spite of this successful shift towards research, Bristol-Myers' market performance did not show a significant improvement in the 1980s. The company has not yet marketed a fundamentally new drug, nor are radically new compounds in the pipeline. The sales of its major product, Buspar, a tranquillizer, have not been as successful as expected. Moreover, the company has been unable to capitalize upon its experience on anti-cholesterol drugs. Bristol-Myers was a pioneer in this field with Questar. Yet, Merck's Mevacor is rapidly taking the lead, and Bristol-Myers has yet to come out with major improvements of Questar.

Bristol-Myers' story suggests that rapid catch-up strategies are not sufficient to become leading innovators in this market. The discovery and development of new compounds require high research costs. Effective competitive strengths depend upon the capability of entering the market with at least one fundamentally new drug. Even without considering the time and costs of isolating a major new molecule, the clinical tests may

⁹ Eli Lilly's skills in furthering heterogeneous applications of the scientific basis of its own drugs is not limited to Prozac. Early research tests at Eli Lilly showed that the human growth hormone, used against dwarfism, slows the effects of aging [11,53]. Eli Lilly's scientists had a fairly accurate understanding of the characteristics of the protein, and how it is used by the human body. They knew that dwarfism is caused by the fact that the human body does not produce the growth hormone. Similarly, they realized that aging slows down the production of the protein, and successfully tested the molecule for this new application.

¹⁰ For example, nutritional biochemists at MIT and neuropharmacologists at Rockefeller University are studying how serotonin influences depression and appetite. Psychopharmacologists at the National Institute on Alcohol Abuse and Alcoholism are studying the links between serotonin and aggressive behavior [6].

well take a decade before new drugs can be marketed. The ten-year time span since Bristol-Myers has reorganized its internal research is probably only a modest fraction of the time actually needed by this strategy to pay off.

Squibb's story during the 1980s is somewhat different from Bristol-Myers'. The company had a good research base, and internal scientific skills. Squibb's success during the past decade rested upon the discovery, development and marketing of the first angiotensin-converting-enzyme (ACE) inhibitor anti-hypertensive drug Capoten.

The origins of Capoten date back to the 1960s, and involve two different lines of research.

The first was concerned with the genesis of hypertension. Researchers working on hypertension realized that renin, a chemical released by the kidneys, causes blood to produce another chemical, angiotensin I, which in turn produces angiotensin II. Angiotensin II is the ultimate regulator of blood pressure. Overproduction of angiotensin II is a major cause of hypertension as it sharply increases blood pressure. Scientists then realized that they had to find a drug that blocked the action of the enzyme responsible for releasing angiotensin II.

The second line of research was related to the causes of death from the venom of the Brazilian viper. Researchers found that the victim dies because the venom contains an extract that reduces the blood pressure by inhibiting the production of angiotensin II. Understanding the chemical structure of the venom then represented a major opportunity for re-producing a compound that could treat hypertension [65].

John Vane, a British pharmacologist, brought these findings to Squibb. The company was working on heart medicines. Building upon the previous knowledge of the causes of hypertension and the action of the viper's venom, Squibb's scientists constructed a molecule that mimicked the function of the viper's compound. Captopril, the chemical compound of Capoten, effectively blocked the enzymes responsible for the conversion of angiotensin, and Capoten became the first ACE inhibitor anti-hypertensive drug [65].

Once again, the discovery of a major new drug was spurred by scientific knowledge available in the external environment. The knowledge about angiotensin conversion, the properties of the chemicals to influence blood pressure, as well as

the properties of the viper's venom were not proprietary information. Yet, the information was best exploited by a company with adequate in-house scientific skills. First, since Squibb was undertaking scientific research in related fields, it was able to monitor effectively the outside environment, and recognize the potential of the new scientific advances. Second, Squibb's in-house scientific skills in drug design enabled the company to lever the external knowledge to generate a compound with unique therapeutic properties.

Despite Capoten's success, Squibb's position in the market during the 1980s was not completely safe. Although it had a few drugs in the pipeline, Squibb was a "one-drug-company". Capoten accounted for about 40 percent of its total sales [9]. The risks of one-drug-companies are apparent. As competitors come out with important competitive drugs, they erode market shares of the company's basic product, thereby affecting a substantial fraction of its profits.¹¹ Squibb needed to escape its one-drug-company status. However, as shown by the "stories" of Merck and Eli Lilly, steady flows of new products rest upon heavy investments in research, particularly in scientific research. The reliance upon Capoten as the sole major source of profits was unlikely to provide sufficient financial stability to plan long-run scientific research.

The 1989 merger integrated two major complementary assets. Squibb brought research capabilities. Bristol-Myers brought marketing skills and an extended marketing network. Moreover, Bristol-Myers' financial resources, which come primarily from its base of health care and consumer product business, will help Squibb escape the problems typically associated with one-drug-companies. They provide the necessary stability for further research, thereby diminishing the risks of relying only upon the financial flows generated by Capoten [69].

¹¹ Indeed, Capoten currently faces intense competition from Vasotec and Prinivil. It is important to mention that the latter have been introduced by Merck. Competitive challenges to Capoten come from another firm with high quality in-house scientific research, i.e. capable of exploiting the public scientific knowledge on the enzymes that regulate blood pressure and the chemicals that inhibit the overproduction of angiotensin II.

6. SmithKline

SmithKline's story during the 1980s is largely associated to Tagamet, the anti-ulcer drug it introduced into the market in 1977. Tagamet, like Mevacor, Prozac and Capoten, is another example of the application of a deductive, scientific method to drug discovery [25].

SmithKline enjoyed a virtual monopoly in the anti-ulcer market between 1978 and 1983. In 1983, Glaxo, a British company with a modest presence in the US at the time, introduced a competing product, Zantac. Zantac had a few advantages over Tagamet, such as a twice per day dose against the four time dose of Tagamet, and less severe side effects. Moreover, Glaxo undertook an aggressive marketing strategy. In a few years, Zantac overcame Tagamet, and became the leading anti-ulcer drug in the market [7,25].

SmithKline reacted by attempting to improve Tagamet. It successfully reduced its daily dosage to twice per day. Moreover, SmithKline sought to develop various "sons" of Tagamet to diminish its side effects. These attempts however proved to be unsuccessful, and the company has not yet come out with a significantly better version of the drug [7,67,68].

In 1988, Tagamet's sales fell by 16 percent. SmithKline is another one-drug-company. Tagamet accounts for about 25 percent of its sales,

and 40 percent of its profits. The drop in Tagamet's sales had a major impact on SmithKline's financial performance. Moreover, in 1987, the patent of Dyazide, SmithKline's blood pressure drug, expired. Dyazide sales dropped by 51 percent because of generics competition. In 1988, the company's net income fell to 229.2 million dollars from 570.1 million dollars in 1987 [8,44,68].

Its future perspectives are also staggering. In fact, SmithKline has now 28 drugs under development, from a handful in the early 1980s. Moreover, in the 1980s it marketed a genetically engineered vaccine against hepatitis B. Yet, its most important new drugs have not performed as expected. The sales of its new antibiotic, Monocid, have been modest. Its new anti-arthritis drug, Ridaura, showed some non-trivial side effects in clinical tests, which are likely to dampen its potential for sale [3,8,68].

Industry analysts suggest that SmithKline's low performance is largely due to its inability to establish major in-house research capabilities during the 1980s [7,8,68]. Figure 1 reports the ratio of SmithKline's R&D expenditures to sales between 1959 and 1988. The R&D to sales ratio has two peaks during the late 1960s and the early 1970s. These are the years of Tagamet's research. They are years of strong scientific and intellectual ferment at the Welwyn (UK) research laboratory, where Tagamet was discovered [59]. SmithKline's

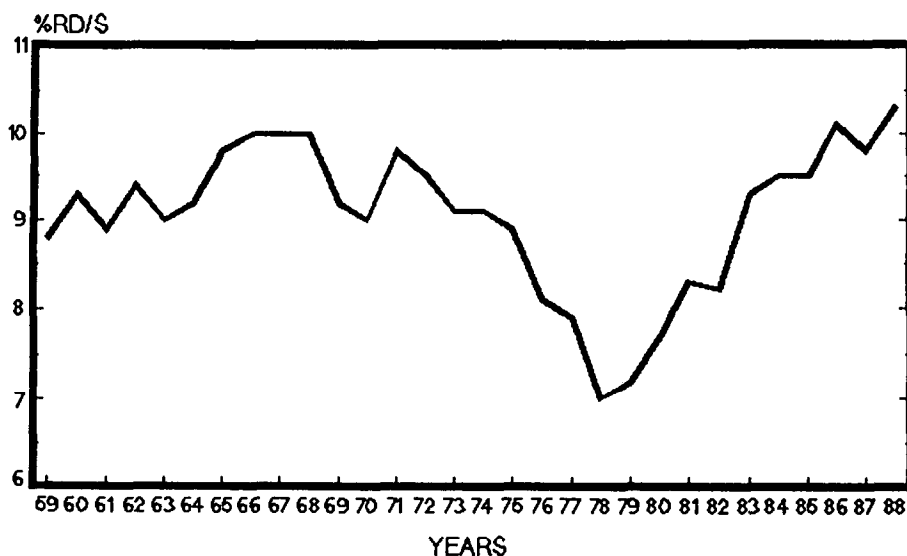


Fig. 1. SmithKline's R&D to sales ratio, 1959–88. Source: R&D and sales data from NBER Compustat Files [33]; 1986–88 data from [44].

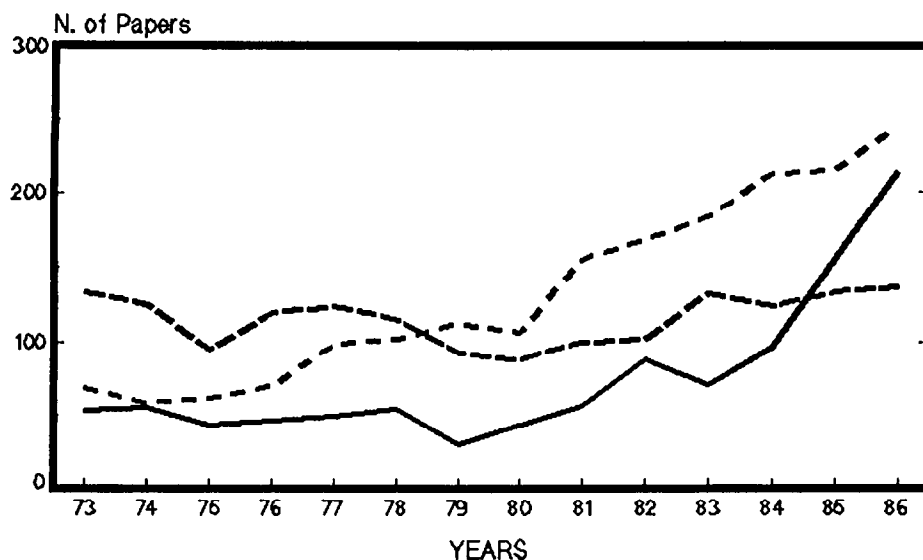


Fig. 2. Number of company papers SmithKline, Eli Lilly, Merck, 1973–86. — SmithKline, — — — Eli Lilly, Merck. Source: CHI Research/Computer Horizons.

R&D to sales ratio declines immediately after 1974. Tagamet was under regulatory revision for marketing approval, and the bulk of research on the product had ended.¹² The R&D to sales ratio, however, starts rising again in 1978, when Tagamet's sales increase sharply, and it rises all the way up to 1988. This suggests that the company did reinvest its profits in research. Therefore, accounts that SmithKline's problems rest upon its inaction in translating Tagamet's high surplus into new research appear to be partly inaccurate.

Rather than low research expenditures, I maintain that SmithKline's poor research performance during the 1980s rests upon the type of research investments carried out by the company. In particular, SmithKline did not reinvest resources into upstream scientific research.

Figure 2 presents the 1973–86 trend in the number of scientific papers published by SmithKline's scientists, and compares it with Merck and Eli Lilly. The number of publications is only an approximate measure of in-house scientific capabilities. Publications, however, are the common

means by which the scientific community diffuses its research findings. They can then be taken as evidence of how much company scientists are plugged into the scientific network. SmithKline's papers show a moderate trend between 1973 and 1984. Merck shows a significant upward trend. Eli Lilly's papers are around 100–120 papers per year. SmithKline scientists published about 50 papers per year up to 1981, and only in 1985–86 we observe a major upswing from below 100 to more than 200 papers.

Apart from the number of papers, the two scientists most responsible for Tagamet's success, Sir James Black and William Duncan, left the company right after the end of Tagamet's research. Black left in 1973; Duncan in 1979 [59]. Black and Duncan were quite a valuable asset. Not only did they lead the Tagamet project, but they also contributed to the creation of an environment of great intellectual fervor, and especially congenial to scientific research [59]. When Black and Duncan resigned from their posts, the company did not strive to hire other leading scientists that could replace not only their research skills, but also their capabilities in furthering an intellectually stimulating atmosphere. Tagamet's profits were used, for instance, to acquire Beckman Instruments in 1982. Beckman had a good research basis in the field of instrumentation. The acquisition, however, was to a

¹² This is also confirmed by the fact that Sir James Black, the scientist responsible for the discovery of Tagamet, left SmithKline in 1973. He said: "I left because, once I know the problems are solved in principle, I quit. And I'm happy to quit, once I know they are solved in principle" [59, p. 5].

large extent an investment alternative to scientific research. SmithKline chose to acquire Beckman's research capabilities rather than recreating a research environment with characteristics similar to the one that Black and Duncan had helped shape.

In sum, SmithKline failed to use the proceeds and the market position acquired with Tagamet to establish as early as the mid-1970s a strong in-house scientific research basis, or at least to continue the research tradition initiated by Black and Duncan. As suggested by the rise in the number of scientific papers in 1985–86, SmithKline did attempt to boost its in-house scientific capabilities after a few years that Tagamet was on the market. Moreover, the 1988 drop in profits prompted the managers to undertake a major reorganization of research. They concentrated various research divisions in one major facility. They also sold part of the stakes in Beckman Instruments to raise funds for research [8,68] – which also suggests that this was not the best allocation of Tagamet's surplus back in 1982.

These initiatives, however, appear to be spurred by external events. The rise in scientific papers during 1985–86, viz. in scientific research two or three years earlier, corresponds to the first threats from Glaxo's Zantac. The reorganization of research followed evident needs for restructuring after the drop in performance. These moves are unlikely to yield immediate results. In this industry, research, and particularly scientific research, pays off after a decade or so. Tagamet had been the top world selling drug, and SmithKline had a virtual monopoly in the anti-ulcer market, for five years. The company could have established strong in-house scientific research capabilities well before Glaxo entered the market. It was unable to find such stimuli internally, and waited until competitive pressures rendered the reorganization of research a necessary condition for market survival.

7. Rorer

In the mid-1980s, Rorer had a modest research base. Its major operations were cosmetics and over-the-counter (OTC) medicines. It had an important OTC drug in the market, Maalox, the leading consumer antacid product in the US.

However, it had practically no prescription drug line.

In 1986, Rorer undertook an aggressive strategy to enter the market for R&D-based drugs. It acquired the ethical pharmaceutical business of Revlon, which raised its sales by more than two times, from 313.7 and 338.1 million dollars in 1984 and 1985 to 844.6, 928.8 and 1041.6 million dollars in 1986, 1987 and 1988. Its R&D expenditures increased almost four times, from 16.3 and 17.9 million dollars in 1984 and 1985 to 69.7, 81.8 and 102.8 million dollars in 1986 and 1987, viz. a rise in the R&D to sales ratio from slightly more than 5 percent in 1983 and 1984 to above 8 percent in 1986 and 1987 and to almost 10 percent in 1988 [44]. Rorer also embarked on a program to focus on its most promising lines of research. It concentrated research in five areas (cardiology, gastroenterology, hypersensitivity, bone metabolism and hematology) [64].

Rorer's strategy, although a courageous one, was certainly not free from risks. Rorer needed to achieve a quick breakthrough. Maalox was producing some cash flow. Indeed, the profits from Maalox provided the necessary funds to carry out Rorer's research restructuring. Yet, Maalox, an OTC drug, was certainly unable to generate as many funds as a major prescription drug. An important success in the field of patented drugs was necessary to enable the firm to enter a positive spiral of self-reinforcing advantages, namely obtain a major boost in sales and profits to support further research on a long-term basis.

Rorer was unable to come out with a major new discovery in relatively short time. In 1990, it was acquired by Rhone-Poulenc. The acquisition integrated various complementary assets of the two companies, and it was explicitly aimed at reinforcing both firms in the research-intensive segment of the drug business [10].

8. Test of interfirm differences in exploiting public science

The case studies suggested that, although science is a public good, pharmaceutical companies with better in-house scientific capabilities have been able, not only to exploit internal science, but also to avail themselves more effectively of external science. This section tests this hypothesis

using data for the largest 14 US pharmaceutical companies during 1973–86 (table 4).¹³

In order to conceptualize this test, one can think of the following “search” framework [22–24,27,28,48,49]. Applied research can be thought of as the sampling of balls from urns that contain black and red balls in different ratios. The urns are families of compounds; black balls are inactive compounds, and red balls are active compounds. Scientists choose an urn from which to sample. Scientific knowledge guides the scientists to the choice of urns that are more likely to contain a higher fraction of red balls.¹⁴

Suppose that science is freely available, and all firms have access to the same information set about which urns contain relatively more active compounds. All firms choose the same urns for sampling. Then, successful discoveries depend only on the scale of the search (i.e. the number of draws, or, out of metaphor, the expenditures on applied research). After controlling for the scale of the search, one ought to observe no systematic interfirm differences in the number of successes. In particular, measures of in-house scientific capabilities ought to be uncorrelated with the number of discoveries.

Instead, suppose that although science is publicly available, firms with better in-house scientific capabilities are better informed about which urns are more likely to contain a higher number of red balls. These firms conduct a more efficient search. Measures of in-house scientific capabilities are now correlated with the number of discoveries, even after controlling for the scale of search.

I use the number of US patent applications of the firms as a proxy for innovation. As suggested by many authors, patents are an effective means of protection in pharmaceuticals [18,39,41,42,62], and the drug companies normally patent their new chemical entities. Moreover, because the firms patent the new compounds that come out of laboratory research, patents are not only a good proxy for innovation, but they are also a good

Table 4
Descriptive statistics, 14 firms, year 1981

Variable	Mean	Standard error	Minimum	Maximum
Patents (number of)	74.4	35.2	33	155
Scientific papers (number of)	63.8	42.6	19	155
R&D exp. (constant 1972 million \$)	75.7	34.9	32.6	140.7

measure of the output of basic and applied research, i.e. of the number of red balls drawn from the urns.

I use the number of scientific papers of the firms as a proxy for in-house scientific capabilities. Publications are only an approximate measure of the companies’ scientific research capital. For one, the number of papers does not account for quality differences in the publications. Moreover, the bulk of papers published by pharmaceutical industry scientists are in clinical research (about 45 percent of papers published by drug industry scientists [45]). Clinical medicine is mostly concerned with “hands-on” analysis of patients, and is a field somewhat distant from basic research [61]. Publications, however, are a common means by which scientific knowledge circulates. Thus, even though they do not provide an exact measure of in-house scientific research, they proxy for the extent to which company scientists are linked to the scientific community. After all, a significant part of what this paper really means by internal scientific capital of the firms is the extent to which the companies are plugged into the scientific network.

The exercise of this section is not the first attempt to analyze the relations between patents, publications and research expenditures in pharmaceuticals. Narin et al. [46] addressed this topic using data for 17 major US pharmaceutical companies between 1975 and 1982. They found that patents are highly correlated with both the number of scientific papers, and the research budget of the firms. Narin et al., however, calculate simple correlation coefficients, which does not enable one to distinguish whether the effects of publications and research on patents actually span different dimensions: Their analysis does not

¹³ The data are described in the Appendix.

¹⁴ This framework is especially apt to characterize the relations between scientific knowledge and laboratory research in pharmaceuticals. I discussed this topic at some length elsewhere [30].

clarify whether publications have an impact upon patents also after controlling for R&D.

This section uses event count regression procedures, which are especially apt for statistical analysis when the dependent variable (patents in this case) takes only non-negative integers [34,36–38]. Define PAT_{it} (patents) to be the number of successes of the i th firm at time t . Assume that PAT_{it} follows a Poisson distribution, i.e.

$$PAT \sim \exp(-\mu \cdot n) \cdot (\mu \cdot n)^{PAT} / PAT! \quad (1)$$

In (1), μ is the Poisson parameter, and n is the number of draws from the urns. Both μ and n have subscripts (it), which have been dropped for convenience. In (1), n proxies for the scale of the search, whilst μ proxies for the “productivity” of the search. I interpret interfirm differences in μ to imply that firms draw balls from urns with different probability of success.

Given (1), the expected number of successes of the i th firm at time t (viz., the mean of the Poisson distribution) is $E(PAT/\mu, n) = \mu \cdot n$. Assume that the number of draws n (the scale of the search) can be approximated by the size of R&D operations of the firm (in real terms).¹⁵ The Poisson parameter μ accounts for interfirm differences in selecting the “best” urns from which to sample. If scientific capabilities provide the firms with information about the urns with higher probabilities of success, μ is to be correlated with measures of internal scientific knowledge. Assume a log-linear relation. One can write

$$\log E(PAT_{it}/\mu_{it}, n_{it}) = \beta_t + \beta_{sp} \cdot \log SP_{it} + \beta_{rd} \cdot \log RD_{it-1} \quad (2)$$

where SP is the number of scientific papers of the i th firm at t , RD is R&D expenditures in constant dollars, β_{sp} and β_{rd} are elasticity parameters, and the β_t 's are time dummies. I use scientific papers at time t . Publications normally reflect research carried out two or three years earlier. Thus, SP at time t reflects research per-

Table 5

OLSQ Poisson and negative binomial estimation, eqn. (2) in the text

Parameters	OLSQ	Poisson	Negative binomial
β_{rd}	0.568 (0.058)	0.508 (0.062)	0.538 (0.062)
β_{sp}	0.250 (0.056)	0.305 (0.058)	0.269 (0.057)
δ	–	–	2.086 (0.162)

(overdispersion parameter for NB)

Number of obs. = 181 Heteroskedastic consistent standard errors in parenthesis. In OLSQ, dependent variable is $\log PAT_{it}$, and regressors are $\log SP_{it}$ and $\log RD_{it-1}$. In Poisson and negative binomial, expected value of patents is defined in eqn. (2) in the text. Adjusted R^2 for OLSQ is 0.53. Log-likelihood functions are 58435.6 (Poisson) and 58943.6 (negative binomial). All equations include time dummies. The overdispersion parameter δ in the negative binomial equation is such that the variance of the process is equal to its expected value times $(1 + \exp(\delta))$.

formed before the innovation has occurred.¹⁶ I use RD at time $t - 1$. Innovations depend on the number of draws in the previous period.¹⁷ Expression (2) can be estimated by maximum likelihood [34,36–38,40]. The hypothesis that internal scientific capabilities guide the firms to the choice of better urns can be tested by assessing the magnitude and the statistical significance of β_{sp} .

The empirical results are in table 5.¹⁸ Apart from Poisson, table 5 also shows the results from ordinary least square estimation of (2) (i.e. with $\log PAT_{it}$ as the dependent variable), and the results obtained under the assumption that PAT_{it} follows a negative binomial distribution. The Poisson distribution has a few restrictive proper-

¹⁶ Patents are applications at time t . (See the Appendix.) Hence, one can assume that they reflect innovations at time t .

¹⁷ The results of the estimation are quite robust under different time lags of both SP and RD. I also estimated (2) after including various other regressors – investment, advertising, capital stock, as well as the ratio of drug sales to total sales of the company to account for the possibility that, scientific papers are nothing else than another measure of the companies' involvement in the pharmaceutical business. All these variables are statistically insignificant, and the results are practically identical to the ones with only SP and RD (and time dummies) as regressors.

¹⁸ The number of observations is 181, and not 196, as there are missing values for the number of papers.

¹⁵ Total R&D is not the best proxy here. One would rather use constant dollar expenditures on applied research. Unfortunately, these data are not publicly available.

ties, most notably that the mean and the variance of the process are equal. The negative binomial is a generalization of the Poisson. It allows for overdispersion, viz. the variance of the process is permitted to be higher than its mean. In the negative binomial model estimated here, the variance of the process is equal to its mean ($\mu \cdot n$) times a proportionality factor ($1 + \exp(\delta)$), where δ is a parameter to be estimated.¹⁹

From table 5, β_{rd} is positive and significant. As expected, the higher the scale of research (number of draws), the higher the number of successes. The parameter β_{sp} is also positive and well measured. Even after controlling for the scale of search, there seem to be important inter-firm differences in the number of successes. To the extent that the number of scientific papers proxy for in-house scientific capabilities, or more generally for the strength of the links with the scientific community, firms with better scientific capital draw balls from better urns. Their productivity of the search μ is higher.

9. Conclusions

This paper examined the relations between scientific research, drug discovery and the economic behavior of the large US pharmaceutical firms. It asked whether the public nature of science implies that all firms can exploit the public good at no cost. Case studies of a few large US pharmaceutical companies showed that firms with better in-house scientific capabilities have been able not only to make efficient use of internal science, but they have also been able to exploit more effectively external science. This result was confirmed by statistical analyses. Innovation (patents) is correlated with measures of the in-house scientific capabilities (scientific publications) even after controlling for R&D.

The conclusion of the case studies can also be read as follows. Best market and innovation performance is associated with firms that organize, at least in part, their research laboratories according to the spirit and the mores of the scientific community, particularly with respect to autonomy in pursuing research topics and disclo-

sure of research findings. This is, I believe, an important conclusion. Profit-seeking agents tend to restrict diffusion, as it encourages imitation. This appears to be no longer a profitable strategy. The “winning models” of the US pharmaceutical industry during the 1980s were firms like Merck, which organized their internal research like academic departments.

In view of the increasing complexity and multidisciplinary of knowledge, external information is critical to the development of innovations. The conclusions of this paper suggest that what is nowadays more and more important is not the production of information, but the dynamics and transformation of a larger pool of information. Information exchange, rather than retaining it within one's own organizational boundaries, is a major determinant of successful innovation. But this requires that one be prepared to diffuse research findings in exchange for the knowledge produced by others. To be part of a network, and to be able to effectively exploit the information that circulates in the network, has become even more valuable than being able to generate new knowledge autonomously.

Appendix – The data used in the empirical analysis

The empirical analysis in section 8 used data for 14 US pharmaceutical firms between 1973 and 1986. The 14 firms are Abbott Laboratories, American Home Products, Bristol-Myers, Eli Lilly, Johnson & Johnson, Merck, Pfizer, Schering-Plough, SmithKline, Squibb, Sterling Drugs, Syntex, Upjohn, Warner-Lambert. These are the first 14 US-based pharmaceutical firms in terms of 1986 pharmaceutical sales in the US market; if one includes the foreign-owned multinationals, they are 14 out of the first 19 firms in 1986 US pharmaceutical sales [43].

The empirical analysis employed the following variables.

Patents. The number of US patent applications of the firms between 1973 and 1986. Patent application data between 1973 and 1979 are from the National Bureau of Economic Research (NBER) Compustat File (for more details on these data, see [33]). Patent applications between 1980 and 1986 are from an on-line search on the Dialog

¹⁹ On the negative binomial distribution, see [34,36–38].

files 224 and 225 conducted at the Terman Engineering Library, Stanford University.²⁰

Scientific Publication. The number of publications by company scientists between 1973 and 1986. I obtained these data from CHI Research/Computer Horizon, Inc., Haddon Heights, NJ. The data are from an indicator of the top 100 US institutions in each sector generated for the Science Indicators unit of the NSF. The 1973–80 data are from a constant 1973 journal set of the *Science Citation Index* [60]. The 1981–86 data are from a constant 1981 journal set of the *Science Citation Index*.²¹

R&D. The yearly R&D expenditures of the companies in constant 1972 dollars. R&D expenditures are from the NBER Compustat File [33]. The deflator is a Price Index for R&D goods from the NBER Compustat File.

²⁰ Details on the on-line search are available upon request. The on-line search was conducted for patent applications of the firms between 1976 and 1986. The years overlapping with the Compustat File data were necessary to compare the two series. Comparison of the two series for the overlapping years indicates a perfect match for the patent applications of 12 out of 14 firms in the sample. For two firms (Bristol-Myers and Eli Lilly), the two series did not match perfectly. The Compustat data were systematically higher. The differences, however, were small (in the order of 5 percent for Bristol-Myers, and 20 percent for Eli Lilly). I then adjusted the 1980–86 data to match with the Compustat File by multiplying the data from the search by the average proportional difference between the 1976–79 patents of the two firms in the two series.

²¹ The *Science Citation Index* adds new journals each year from which the papers are collected. Constant journal sets thus provide a consistent basis for the number of papers. The 1981 journal set added to the 1973 one roughly 30 percent more US Clinical Medicine papers. In the empirical analysis of section 8, I tried to introduce various dummies to account for this “jump” in the variable after 1981. The results are practically identical to the ones shown here.

References

- [1] K. Arrow, Economics of Welfare and the Allocation of Resources for Invention, in: National Bureau of Economic Research, *The Rate and Direction of Inventive Activity* (Princeton University Press, Princeton NJ, 1962).
- [2] Bear Sterns, Merck & Co (Bear Sterns & Co. Inc. Investment Research, 17 February 1989).
- [3] Bioscan, *The Biotechnology Corporate Directory Service* (Oryx Press, Phoenix AZ, April and December 1988 editions).
- [4] *Business Week*, Eli Lilly: New Life in the Drug Industry (29 October 1979) p. 134.
- [5] *Business Week* The Miracle Company (19 October 1987) p. 84.
- [6] *Business Week*, Fighting Depression with One of the Brain's Own Drugs (22 February 1988) p. 156.
- [7] *Business Week*, How Glaxo's Eager Beavers Chewed Up Tagamet's Lead (10 October 1988) p. 40.
- [8] *Business Week*, SmithKline's Case of Ulcers (10 October 1988) p. 40.
- [9] *Business Week*, Don't Look Back Squibb – A Giant is Gaining on You (10 October 1988) p. 68.
- [10] *Business Week*, Rhone-Poulenc Finds Its American Connection (5 December 1990) p. 39.
- [11] *Business Week*, The Many Personalities of Gene-Spliced Drugs (30 July 1990) p. 68.
- [12] M. Carpenter, Patent Citations as Indicators of Scientific and Technological Linkages, paper presented at the Annual Meeting of the American Association for the Advancement of Science, Detroit MC, 30 May 1983.
- [13] *Chemical Marketing Reporter*, Bristol-Myers Opens New Research Center in Connecticut (30 June 1986) p. 5.
- [14] *Chemical Marketing Reporter*, Merck Expects its R&D to Produce a Continuous Flow of New Drugs (16 November 1987) p. 9.
- [15] *Chemical Week*, A New team in Three-Dimensional Drug Design (11 May 1988) p. 17.
- [16] *Chemical Week*, Biotechnology: On the Rebound And Heading for a Boom (27 September 1989) p. 31.
- [17] *Chemical Week*, Automating the Chemical Processing Industry, Special Report (25 October 1989) p. 16.
- [18] W. Cohen and R. Levin, Empirical Studies of Innovation and Market Structure, in: R. Schmalensee and R. Willig (editors), *Handbook of Industrial Organization*, Vol. II (Elsevier Science Publishers (North-Holland), Amsterdam, 1989).
- [19] W. Cohen and D. Levinthal, Innovation and Learning: The Two Faces of R&D, *Economic Journal* 99 (1989) 569–596.
- [20] P. Dasgupta and P. David, Information Disclosure and the Economics of Science and Technology, in: G. Feiwel (editor), *Arrow and the Ascent of Economic Theory* (New York University Press, New York, 1987).
- [21] P. Dasgupta and P. David, Priority, Secrecy, Patents and the Socio-Economics of Science and Technology, Working Paper No. 127, Center for Economic and Policy Research, Stanford University, Stanford CA, March 1988.
- [22] P. David, Integrated Strategies for Basic and Applied Research under Uncertainty, Stanford University, mimeo, 1978.

- [23] P. David and J. Stiglitz, Analysis of Factors Affecting the R&D Choices of Firms, Center for Research in Economic Growth, Research Memorandum No. 232, Stanford University, Stanford CA, March 1979.
- [24] P. David, D. Mowery and E. Steinmueller, The economic Analysis of Payoffs from Basic Research: An examination of the Case of Particle Physics Research, Working Paper No. 122, Center for Economic and Policy Research, Stanford University, Stanford CA, January 1988.
- [25] *The Economist*, More Than a One-Drug Wonder? (20 December 1986) p. 87.
- [26] *The Economist*, Molecules and Market, Special Survey on the Pharmaceutical Industry (7 February 1987).
- [27] R. Evenson and Y. Kislev, *Agricultural Research and Productivity* (Yale University Press, New Haven, London, 1975).
- [28] R. Evenson and Y. Kislev, A Stochastic Model of Applied Research, *Journal of Political Economy* 84 (2) (1976) 265–281.
- [29] Federal Drug Administration (FDA), From Test Tube to Patient: New Drug Development in the United States, *FDA Consumer*, Special Report, Dept. of Health and Human Service, HHS Publication No. (FDA) 88-3168, January 1988.
- [30] A. Gambardella, Science and Innovation in the US Pharmaceutical Industry during the 1980s, Ph.D. Thesis, Stanford University, Stanford CA, 1991.
- [31] M. Gibbons and R. Johnston, The Roles of Science in Technological Innovation, *Research Policy* 3 (1974) 220–242.
- [32] H. Grabowski and J. Vernon, The Pharmaceutical Industry, in: R. Nelson (editor), *Government and Technical Progress* (Pergamon Press, New York, 1982).
- [33] B. Hall, C. Cummin, E. Laderman and J. Mundy, The R&D Master File Documentation, National Bureau of Economic Research, Stanford CA, 1988.
- [34] J. Hausman, B. Hall and Z. Griliches, Econometric Models for Count Data with an Application to the Patents–R & D Relationships, *Econometrica* 52 (4) (1984) 909–938.
- [35] *Journal of Commerce*, Bristol-Myers and Yale renew Previous Agreement (10 March 1988) p. 9B.
- [36] G. King, Statistical Models for Political Science Event Counts: Bias in Conventional Procedures and Evidence for the Exponential Poisson Regression Models, *American Journal of Political Science* 32 (3) (1988) 838–863.
- [37] G. King, *Unifying Political Methodology: The Likelihood Theory of Statistical Inference* (Cambridge University Press, Cambridge UK, 1989).
- [38] G. King, Event Count Models for International Relations: Generalizations and Applications, *International Studies Quarterly* 33 (2) (1989) 123–147.
- [39] R. Levin, A. Klevorick, R. Nelson and S. Winter, Appropriating the Returns from Industrial Research and Development, *Brookings Papers on Economic Activity* 3 (1987) 783–831.
- [40] G. Maddala, *Limited Dependent and Qualitative Variables in Econometrics* (Cambridge University Press, Cambridge UK, 1983).
- [41] E. Mansfield, Patents and Innovation: An Empirical Study, *Management Science* 32 (1986) 173–181.
- [42] E. Mansfield, M. Schwartz and S. Wagner, Imitation Costs and Patents: An Empirical Study, *Economic Journal* 91 (1981) 907–918.
- [43] *Medical Advertising News*, Top 50 Pharmaceutical Companies, Special Survey (1 September 1987).
- [44] *Moody's Industrial Manual*, Moody's Investor Service Inc., New York (various years).
- [45] F. Narin and R. Rozek, Bibliometric Analysis of US Pharmaceutical Industry Performance, *Research Policy* 17 (1988) 139–154.
- [46] F. Narin, E. Noma and R. Perry, Patents as Indicators of Corporate Technological Strength, *Research Policy* 16 (1987) 143–155.
- [47] R. Nelson, The Simple Economics of Basic Scientific Research, *Journal of Political Economy* 67 (1959) 297–306.
- [48] R. Nelson, The Role of Knowledge in R&D Efficiency, *Quarterly Journal of Economics* 97 (1982) 453–470.
- [49] R. Nelson and S. Winter, *An Evolutionary Theory of Economic Change* (Harvard University Press, Cambridge MA, 1982).
- [50] *New Scientists*, Computers Picture the Perfect Drug (16 June 1988) p. 54.
- [51] *New York Times*, Advances in Drugs, Courtesy of Computers (3 August 1988) p. C5.
- [52] *New York Times*, The Intriguing Potential of Molecular Switches (4 February 1990) p. F8.
- [53] *New York Times*, More Gilding for Lilly as New Drug Stars (17 July 1990) p. C1.
- [54] Office of Technology Assessment (OTA), *Commercial Biotechnology: An International Analysis* (US Congress, OTA-BA-218, Washington DC, 1984).
- [55] Office of Technology Assessment and Forecast (OTAF), *Technology Profile Report: Genetic Engineering* (U.S. Patents and Trademark Office, Office of Document Information, Washington DC, December 1987).
- [56] K. Pavitt, What Makes Basic Research Economically Useful, *Research Policy* 20 (1991) 109–119.
- [57] D. Price de S., The Science/Technology Relationship, the Craft of Experimental Science and Improvements of High Technology Innovation, *Research Policy* (1984) 13 3–20.
- [58] N. Rosenberg, Why Do Firms Do Basic Research?, *Research Policy* 19 (1990) 165–174.
- [59] A. Sapienza, The Paradox of a Successful Drug Discovery: The Story of Tagamet, mimeo, Harvard School of Public Health, Harvard University, Cambridge MA, 1987.
- [60] *Science Citation Index* (Institute for Scientific Information (ISI), Philadelphia).
- [61] J. Spangenberg, R. Starmans, Y. Bally, B. Breemhaar, F. Nijhuis and C. van Dorp, Prediction of Scientific Performance in Clinical Medicine, *Research Policy* 19 (1990) 239–255.
- [62] C. Taylor and A. Silberston, *The Economic Impact of the Patent System: A Study of the British Experience* (Cambridge University Press, Cambridge UK, 1973).
- [63] *USA Today*, Merck Would Like to Have the Leading Laboratory in Every Aspect of Medicine (27 December 1987) p. 1B.
- [64] *Wall Street Journal*, Rorer Aims to Become a Top Drug Firm (13 April 1987) p. 6.
- [65] *Wall Street Journal*, Star Performer: Hypertension Drug

- Boosts Squibb but also Stirs Criticism of Promotional Efforts (28 May 1987) p. 1.
- [66] *Wall Street Journal*, Bristol-Myers Boosts Laggard Drug Research Group (16 February 1988) p. 14.
- [67] *Wall Street Journal*, SmithKline Stops Tests of an Ulcer Drug That Was to Back Up Flagging Tagamet (14 November 1988) p. B4.
- [68] *Wall Street Journal*, Drop In Tagamet Sales is Putting SmithKline in Danger of Takeover (13 January 1989) p. 1.
- [69] *Wall Street Journal*, Bristol-Myers and Squibb Agree to Merge in a Stock Swap Valued at \$11.52 Billion (28 July 1989) p. A3.