Racing to Invest?
The Dynamics of Competition in Ethical Drug Discovery.

Iain Cockburn, U.B.C.
Rebecca Henderson, M.I.T.

WP # 3710-94 June 1994

Forthcoming, Journal of Economics and Management Strategy,
Fall 1994, Vol.3., No. 3.

This research was funded by the Sloan Foundation and by four pharmaceutical companies. Their support is gratefully acknowledged. We would also like to express our appreciation to all of those firms that contributed data to the study, and to Allan Afuah and Andrew Hoffman, who provided exceptional research assistance. We thank the editor and two particularly helpful referees, together with participants in seminars at the NBER, the UBC Summer IO Conference, Stanford, MIT, UCLA and Berkeley for helpful comments and suggestions. The conclusions and opinions expressed in this paper are, however, our own, and any errors or omissions remain entirely our responsibility.

Abstract

This paper draws on detailed internal data to explore the usefulness of the modern game theoretic literature as a source of insight into the dynamics of competition in pharmaceutical research. We find that research investment is only weakly correlated across firms once common responses to exogenous shocks are accounted for, and that rivals' research results are positively correlated with own productivity. While we cannot reject the hypothesis that investment behavior in the industry is driven by strategic considerations, these results suggest that the more extreme forms of rent dissipation identified in the literature are probably poor characterizations of the dynamics of competition in the industry.

1. Introduction

What drives a firm's decision to invest in research and development? Traditional industrial organization theory focussed on market structure, demand, technological opportunity, and appropriability as determinants of the intensity and direction of R&D investment, and several empirical studies have demonstrated the fruitfulness of this approach (Reiss and Levin, 1988). More recent theoretical work has stressed strategic interaction among rivals as a primary determinant of investment decisions, and this approach has spawned a wealth of interesting and elegant theoretical models that have generated some powerful insights into the dynamics of competition in R&D. Reinganum (1989) provides an excellent summary of this literature. For more recent work, see for example Dasgupta and Maskin (1987), Dixit (1988), D'Aspremont and Jacquemin (1988, 1990), Fraja, (1993), and Suzumura (1992).

Despite the potential power of the game theoretic literature as a source of insight into the dynamics of competition, surprisingly little empirical research has attempted to build on its insights, and our understanding of the forces that drive R&D investment decisions in practice remains sketchy: Khanna (1993), Lerner (1991), Meron and Caves (1991) and Scherer (1992) are notable exceptions. One possible reason for this paucity of empirical work may be a lack of suitably detailed data. Whereas the early literature took the industry as its primary unit of analysis, more recent work focuses attention on the individual research project, or on the single-project firm, as the key competitive arena. The modern game theoretic literature says little about the determinants of aggregate investment in R&D at the level of the typical multi-product multi-project firm, and firm level data cannot be used to test its predictions without the use of some heroic assumptions.

In this paper we use unusually detailed data on research investments and outcomes gathered at the level of individual research programs conducted within ten pharmaceutical firms over a period of more than seventeen years to explore the usefulness of the modern literature as a source of insight into the dynamics of competition in ethical drug discovery. These highly detailed data are well-suited for examining the decision to invest in research, since they allow us to draw direct and meaningful comparisons between investment decisions made by different firms. The pharmaceutical industry also provides a particularly intriguing setting for this research, since competition in the industry has often been held up as a prime example of the types of strategic racing behavior predicted by the literature. The industry is a relatively "pure play" in technological competition, and firms invest heavily in research and development since successful research is a key contributor to commercial success. Moreover since most firms invest in a wide range of technologies, we are able to compare

competition across multiple "markets."

We begin the paper with a review of some of the modern literature on strategic competition in R&D. We argue that in general these models are very difficult to test. Investment behavior is critically dependent on a wide range of factors, including the nature of the payoff function, the spillover regime, the information structure of the game and the extent and nature of asymmetries between players, all of which are rather difficult to capture empirically. Moreover few of the models in the existing literature can be easily nested.

As a first step in the empirical analysis, we therefore focus on simple correlations in research investment and output across firms at the program level. We examine ethical drug *discovery* -- research intended to identify promising new drugs -- rather than drug *development*, the application of these discoveries in the clinic, since we believe that there may be important differences in the nature of competition in the two stages. We find investment levels are very weakly correlated across firms. This correlation is not robust to the inclusion of measures of technological opportunity, and is consistent with the belief that levels of investment represent equilibrium responses to common shocks in demand and opportunity. Firm effects are quite significant, and investment levels are very highly autocorrelated. We interpret this as consistent with the hypothesis that adjustment costs and unobserved firm heterogeneities play a significant role in determining investment patterns.

To capture out of equilibrium behavior, we measure changes in investment levels using both first differences and a measure of "news" in investment. In contrast to previous studies that have explored correlations in first differences of investment across firms, we find no evidence of correlation in either first differences or "news" in investment across firms at the program level. We also find no evidence of correlation in the residuals of our best fitting investment equations across firms. These results suggest that simple reaction function or "tit-for-tat" models are not useful descriptions of competition in pharmaceutical research.

We then turn to an exploration of possible correlation in outputs across firms. We find, for example, that the assumption that competition is for a single "prize" is probably not a useful one in this context. Our quantitative results suggest that research outputs are significantly positively correlated across firms, and that this correlation is robust to the inclusion of a number of measures of technical opportunity. Our qualitative work confirms that competing projects may well be complementary. The industry is characterized by substantial spillovers of knowledge and similar research can lead to related but significantly different outcomes.

These results have implications for both our understanding of competition and for public

policy. Our finding that the modern game theoretic literature is of only limited usefulness as an empirical guide points to the need not only to model R&D as a race with multiple prizes, but also to develop theories that incorporate richer models of adjustment costs and firm heterogeneity and to collect data that is comprehensive and detailed enough to enable one to test them.

Our results also throw new light on the relationship between investment behavior and social welfare. Many of the models that focus on strategic interaction raise the concern that free entry into R&D competition will result in overinvestment relative to both the private or social optima. Intuitively, these results are driven by the assumption that in deciding to invest research, firms consider only their own marginal return, and do not take into account the externality that they impose on other firms in reducing their chances of success. In the extreme, these models suggest that entry will occur until all expected profits are dissipated (Dasgupta and Stiglitz, 1980b; Loury, 1979 and Reinganum 1982, 1989). While we cannot say anything definitive about the relationship between the level of private investment in research and social welfare in the pharmaceutical industry, our results suggest that the more extreme forms of rent dissipation identified in the literature are rather poor characterizations of the reality of competition in pharmaceuticals.

The paper begins with a review of the literature. Section 3 outlines our data, and Section 4 describes the history of the discovery of the ACE inhibitors as a source of qualitative insight into the nature of R&D competition in the industry. Section 5 presents our quantitative results, and the paper closes with a discussion of their significance and of possible directions for further work.

2. Literature Review

A large and lively theoretical tradition that traces its roots back to Schumpeter (1934), (1950) and Arrow (1962) has explored the relationship between market structure, strategic interaction, and R&D investment, and has identified a number of conditions under which competitive markets may over-invest in R&D. Baldwin and Scott (1987) and Reinganum (1989) provide excellent surveys of a voluminous though disappointingly inconclusive literature.

Recent work has modelled R&D investment largely as games of timing. Two broad classes of model can be distinguished. The first, and most stark, are deterministic "auction" models (Scherer (1967), Dasgupta and Stiglitz (1980a,b)). In these models, if firm i spends x_i on research, it will complete the invention at date $T_i = T(x_i)$. Assume that Π_m is the value of "winning" and that every other firm receives no return on its investment. Then if all firms have the same discount rate, r, a Nash equilibrium for the game involves two or more firms bidding x^*, where x^* is the largest value of

x such that $\Pi_m e^{-rT(x)} - x = 0$. If the "winner" can appropriate all of the social returns to the invention, or if $\Pi_m = \Pi_s$, then all potential social returns from the invention will be dissipated through "overbidding."

Notice that within this framework there is no "racing" per se, since at equilibrium only one firm will actually invest x^*. However this class of models is unlikely to be a useful source of insight into the dynamics of competition in ethical drug discovery since it relies on a grossly inadequate characterization of the research technology. Pharmaceutical research is subject to enormous uncertainties (only 23% of all compounds entering clinical trials are eventually approved, and of the thousands of candidate compounds identified in the discovery phase, only a very small percentage enter the clinic (DiMasi et al., 1991), and thus the deterministic R&D function fundamental to these models is an unsatisfactory characterization of the dynamics of research in the industry.

A second class of stochastic racing models which may be more appropriate for thinking about exploratory research allow the date of success to be stochastically related to the firm's level of R&D investment. These models yield qualitatively the same results as the deterministic auction model (Harris and Vickers, 1987; Lee and Wilde, 1980; Loury, 1979; Reinganum 1982, 1989), but also rely on strong assumptions about the information available to the players and the stochastic nature of invention. In these models uncertainty leads to multiple entry, so that many firms invest in research. In the absence of effective barriers to entry or of collusion between firms in the industry, entry occurs until the expected returns from innovation are driven to zero, and all available private returns are dissipated through excessive entry.

These models capture some important aspects of competition in pharmaceuticals. This is an industry which is driven to a great extent by non-price competition in R&D, and one of the few in which patents provide a high degree of appropriability. Regulatory approvals or patent grants for new compounds represent particularly well-defined "prizes" in the R&D game, and the first and second firms to discover drugs usually capture the lion's share of the market. Since many major breakthroughs are triggered by advances in fundamental science and since this knowledge is freely available, it is not unreasonable to believe that firms start each "race" in a symmetric position.

In the simplest version of one model representative of this tradition, n firms compete to perfect innovations from a common pool of undiscovered inventions, receiving the "leader's" payoff P_L if they are first to succeed, and the "follower's" payoff P_F otherwise (Reinganum, 1982). Two important features which add to the realism of this model are that rivals are free to change their level of investment over time and in response to changes in the state variables, and that the probability of

success is a function of accumulated knowledge. Given that knowledge accumulates according to the expression:

$$\frac{dz_i}{dt} = u_i(t, z(t)) \tag{1}$$

where $z_i(t)$ is firm i's knowledge stock at t, and $u_i(t,z)$ is firm i's rate of knowledge acquisition at (t,z), and assuming that $z_i(0)=0$, and that the probability of success given a knowledge stock of z or less distributed is exponentially so that:

$$F(z) = 1 - e^{(-\lambda z)} \tag{2}$$

then it is possible to explicitly compute each firm's payoff for any given strategy and aggregate rival hazard rate, and with some restrictions, to derive feedback Nash equilibrium strategies for each firm as functions of payoffs, elapsed time, and the number of players. For our purposes, the most significant propositions arising from these models are that:

(1) provided $P_L >> P_F$, increases in rivalry have a positive impact on own investment

and

(2) own success probability is negatively related to rivals' aggregate hazard of success.

However a disappointingly comprehensive set of observed outcomes are consistent with one or more of these stochastic racing models, particularly when we recognize incentives to drop out of, or not to enter, races once a rival has established a big enough lead. Rival firms' optimizing responses to each other's moves could be to increase investment, decrease investment, or do nothing, depending on the structure of the "true" behavioral model, the determination of payoffs, the distribution of success probabilities, the nature of costs and so on (Harris and Vickers, 1987; Scherer, 1967, 1992).

Discriminating empirically amongst these models is a daunting prospect, since theoretical models that attempt to account for the interactions between all possible factors simultaneously quickly become intractable. Equilibrium strategies for R&D investment can be computed, but signing the comparative statics results for, for example, the effect of an increase in rivalry upon equilibrium investment levels is difficult without knowing a great deal about payoffs in the product market and the nature of the asymmetries among players. Conclusions from these types of models are also rather fragile: small changes in the timing of moves, the information structure of the game or the treatment of spillovers can easily reverse or weaken any given theoretical result.

Notice, moreover, that these models are essentially models of industry equilibrium: firms

formulate R&D strategies based on anticipations of rival investment and underlying demand and cost parameters. With perfect information, and absent any shocks to underlying demand and cost conditions, firms will not deviate from their equilibrium strategies. Investment will only be correlated across competitors as a common response to exogenous shocks. The simple tit-for-tat responses suggested by the anecdotal literature require a much more complicated framework incorporating, for example, heterogeneity of beliefs or private information.

Prior empirical research in this area has used firm level investment data to test for reactions between "leaders" and "followers" in an industry. Grabowski and Baxter (1973), for example, found that in the chemical industry, the two largest firms responded quickly to changes in each other's R&D policies, while rivalry amongst the smaller firms in the industry was less clear cut. Meron and Caves (1991) found that in a sample of 28 U.S. manufacturing industries, leaders and followers reacted positively to each others' increases in R&D expenditures, while fringe firms' investment decreased with their larger rival's investment and Scherer (1992) found that firms with greater domestic sales in more concentrated U.S. markets were likely to react much more aggressively to increasing import competition than smaller firms or firms in less concentrated markets.

In this paper we look for evidence of racing behavior using disaggregated data that on both investment and output at the research project or program level. This data set is described in the next section. We use the data to explore both correlation in investment levels and correlation in changes in investment levels across firms at the project level. We interpret the results of the first set of correlations as a test of the hypothesis that equilibrium strategies depend on underlying demand and cost parameters, rather than on rival's investment levels, while we interpret the results of the second as a test of the presence of simple minded reaction function or tit-for-tat strategies.

We also use our data to explore the validity of the assumptions on which many of the racing models rely. Much of the literature assumes, for example, that firms race for a single prize, so that payoffs to investment have a "winner take all" quality and outputs will be negatively correlated across firms. To the degree that investments in research lay the groundwork for several, related innovations, or that success in one area increases the market for all innovation in that area, payoffs across firms may be positively correlated.

The strong implication of many of these models that free entry into research is unambiguously welfare destroying is similarly subject to a number of caveats. Recent research has shown that it rests on at least five key assumptions: that there is total appropriability of consumer surplus and no spillover of knowledge between firms, that competing projects are perfect substitutes for each other,

that there are no efficiency gains to multi firm competition, and that entry will occur until marginal private return has been driven to zero. Models of competition in which these assumptions are relaxed yield outcomes that are fundamentally indeterminate: competitive industries may invest too much, too little or just about the right amount in research.

For example if firms pursue identical research projects, and if there is no transfer of information between firms, the entry of an additional firm into the industry unambiguously destroys social welfare. But if there are substantial spillovers of knowledge between firms, the entry of additional firms will increase the marginal productivity of existing players, reducing the negative externalities that lead to over investment. Spence (1984) shows that the effect on competition is difficult to predict, but in general, under plausible assumptions, the presence of spillovers will reduce R&D investments below their non spillover levels. This conclusion has been confirmed by later work (D'Aspremont and Jacquemin, 1988, 1990; Fraja, 1993 and Suzumura, 1992), which suggests that if the firms in an industry cooperate in setting their research investments, then the presence of spillovers may lead the industry to invest approximately the welfare maximizing amount. Similarly if competing projects are better characterized as complements to each other - if, for example, any one of several approaches to a desired end is possible in theory but there is great uncertainty as to which is likely to prove successful - then the entry of additional firms may enhance welfare as entry increases the odds that a discovery will be made (Dasgupta and Maskin, 1987).

Here we explore the validity of the assumptions on which the theoretical models rest using a combination of qualitative and quantitative data, focusing particularly on the degree to which competing projects are better characterized as substitutes or complements and on whether outputs are positively or negatively correlated across firms.

3. Sources and Construction of the Data Set

In order to explore these issues we rely on both qualitative and quantitative data drawn from a larger study of research productivity in the pharmaceutical industry. Data were obtained from public sources and from ten major pharmaceutical firms. Although for reasons of confidentiality we cannot describe the overall size or nature of the firms, we can say that they cover the range of major R&D-performing pharmaceutical manufacturers, and that they include both American and European manufacturers. In aggregate, the firms in our sample account for approximately 25-30% of worldwide R&D and sales, and we believe that they are not markedly unrepresentative of the industry in terms

of size, or of technical and commercial performance.

Pharmaceutical technology is enormously complex. Thus we tried both to develop a general understanding of the history of research and development in the industry and to focus in detail on the scientific and technical history of the development of cardiovascular drugs.[1] We made extensive use of secondary sources such as the national press, reference texts, published articles, academic textbooks, and reports by both consultants and the Office of Technology Assessment. We combined this data with a program of extensive field interviews within the ten firms that make up our sample. Appendix One summarizes our qualitative research strategy.

The quantitative study draws upon data about spending and output at the research program level obtained from the internal records of each of the ten pharmaceutical firms. The choice of the "research program" as our fundamental unit of observation is important. A "program" is a level of aggregation of the data somewhere between individual research projects and the level of therapeutic classes, as in, for example "Hypertension" as opposed to "Cardiovascular therapy" or "Compound 12345". We believe this is the most appropriate way of organizing the raw data provided to us by participating firms -- although some detail about individual projects is lost for some of our firms, it allows us to be consistent across firms, and it corresponds to the level of analysis at which firms organize their internal data and make strategic budgeting decisions.

For each observation we have data on both inputs and outputs to the research process. Our primary measure of input is research spending on discovery, and our measures of output include patents, INDs, NDAs, new drug introductions, sales and market share. After carefully cleaning and matching these data, we were left with an unbalanced panel of
5320 observations, indexed by firm, research program, and year.[2] The internal firm data are complemented by a variety of measures of scientific opportunity and pharmaceutical demand derived from public sources. Since our measure of scientific opportunity is only available after 1975, after matching to the research data the number of usable observations is reduced to 2707. Table (1) presents descriptive statistics for this working sample drawn from our database. Full details of variable construction are given in Appendix (2).

4. A Qualitative Analysis: Racing in Pharmaceutical Research?

As a first step in the analysis, we exploit the qualitative data to explore the nature of competition in ethical drug discovery. At first glance, competition in the pharmaceutical industry seems to be a text book example of "racing" behavior. Consider, for example, the case of captopril

and the discovery of the ACE inhibitors.

In 1977 Cushman and Ondetti, two scientists working at the privately funded Squibb institute, announced that they had synthesized an orally active inhibitor of the angiotensin-converting enzyme (Ondetti, Rubin, and Cushman, 1977). The compound, subsequently named captopril, proved to be extraordinarily potent in the treatment of hypertension and triggered an explosion of interest in the medical and scientific communities (Laragh 1984, Gilman et al., 1985).[3] By 1992, at least twelve other ACE inhibitors had been patented, all of them chemically related to the original molecule, and ACE inhibitors accounted for nearly 30% of antihypertensive drugs sales.[4] Figure (1) outlines this history.

Insert Figure (1) about here

At first glance this would seem to be a clear case of "racing" -- head to head competition between firms racing to be first using mere "molecular manipulation," -- although the assumption that there is only one "prize" to the race is clearly violated. The identifiable winners in the race, Squibb and Merck, currently market compounds which together comprise over 80% of the market for ACE inhibitors, and the other ten patented compounds could be seen as evidence of socially wasteful over-investment by the losers. However a deeper exploration of the steps that led up to captopril's discovery calls into question some of the fundamental assumptions of many stochastic racing models.

Cushman and Ondetti's synthesis of captopril drew on many years of prior research in both the public and the private sectors. ACE inhibitors lower blood pressure by blocking a critical path in the renin angiotensive system (see Figure (2), derived from Julian, 1988). They are, literally, Angiotensin II converting enzyme inhibitors.

The idea that blocking the renin system might reduce high blood pressure originated with the work of Goldblatt and his colleagues (Goldblatt, Lynch and Hanzal, 1934). However serious interest in anti-renin system therapy as a potential treatment for hypertension only began with the publicly funded work of Laragh (1972), Gross (1968) and Erdos (1970), who first clarified the structure of the renin angiotensive system and its role in the control of blood pressure.

Insert Figure (2) about here

Although this research laid the groundwork for the subsequent discovery of the ACE

Figure (1) Case study: ACE Inhibitors and hypertension

1934-70: public sector researchers identify role of renin angiotensive system in controlling blood pressure

1965: pit-viper venom found to contain large numbers of compounds affecting heart muscle, vascular dilation, blood clotting etc

1971: Squibb publishes description of compound inhibiting production of Angiotensin Converting Enzyme, reduces blood pressure in rats, but research community skeptical

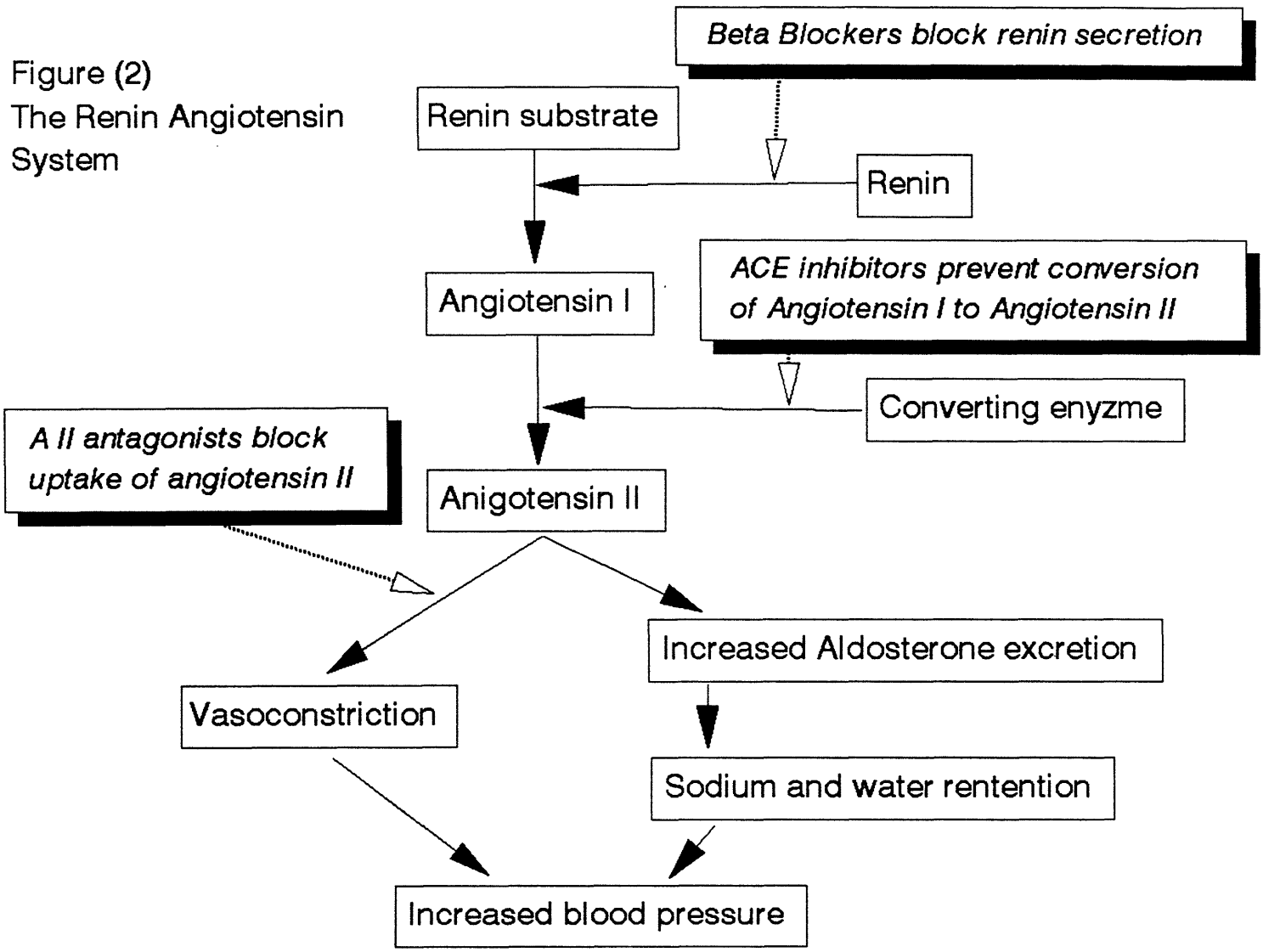
1977: Squibb patents captopril: orally active ACE inhibitor

Flurry of work on related compounds, results in

Generic Name	Firm	Date of first Patent	Date of first U.S. Patent
Captopril	Squibb	1977	1977
Enalapril	Merck	1980	1980
Lisinopril	Merck	1980	1980
Alacepril	Dainippon	1980	1980
Perindopril	French, public sector	1982	1982
Quinapril	Warner Lambert	1982	1982
Fosinopril	Squibb	1982	1982
Moveltipril	Chugai	1982	1982
Delapril	Takeda	1982	1983
Ramipril	Hoechst	1983	1986
Cilazapril	Hoffman La Roche	1983	1985
Benazepril	Ciba Geigy	?	?

1990 Captopril and Enalapril hold 82% of the U.S. market.

Figure (2)
The Renin Angiotensin System



inhibitors, a great deal of further work was required to translate the fundamental scientific insight into therapeutically useful compounds. There was, initially, considerable skepticism that interference with the renin angiotensive system would reduce blood pressure, since the physiological and biochemical mechanisms that underlie hypertension are extraordinarily complex and interdependent. Many in the medical and scientific community believed that any reduction in blood pressure achieved by blocking the action of the renin angiotensin system would be automatically compensated by increased activity in other blood pressure regulating mechanisms. Even amongst those focusing on the system, there was disagreement about the most appropriate place in which to disrupt the chain. Some researchers explored the activity of propranolol and the other beta blockers, which inhibit renin secretion (Buhler, et al., 1972), while others investigated the properties of Saralasin, a compound that interferes with the uptake of angiotensin II (Burner et. al., 1974). This work was undertaken by researchers working in both the public sector and in commercial firms (Pals et al., 1971).

Interest in inhibitors of the angiotensin II converting enzyme was aroused by the 1967 publication of results showing that a peptide isolated from the venom of a Brazilian snake blocked conversion of angiotensin I to angiotensin II ((Hodge et al., 1967). Although this peptide was synthesized by Ondetti and his colleagues (Ordetti et al., 1971), there continued to be widespread doubt as to its therapeutic potential, and despite a sequence of papers exploring its role in the treatment of hypertension (Gavras et al., 1974; Case et al., 1976, 1977), there was little general interest in exploiting the discovery commercially. It was not until Cushman and Ondetti published their achievement in synthesizing an orally active enzyme inhibitor that research in the field took on something of the characteristics of the race, with several pharmaceutical companies attempting to synthesize compounds with similar properties (Cushman et. al., 1977). Even at this late stage, research in the field continued to be characterized by high publication rates and the relatively free flow of information.

Thus the discovery of the ACE inhibitors rested on over twenty years of wide ranging and often apparently unproductive effort characterized by the extensive exchange of knowledge across firms and between the private and public sectors. It was only in the last stage of the work that the competitive dynamics took on the characteristics of a "race," and even then the description is misleading. On the one hand, it does not recognize that the proliferation of ACE inhibitors may have significant therapeutic benefits (Laragh, 1984). Enalapril, for example, appears to have a lower incidence of side effects such as rash and disturbance of taste in some patient groups (Goodman et al., 1985). Unlike captopril, enalapril is a "prodrug" which is not itself highly active, but must be

converted in the body to the active principle, enalaprilate. The resulting differences in the rate at which enalapril is metabolized and excreted compared to captopril imply different dosing regimes, and significant benefits to some patients.

On the other hand, a characterization of this research as a "race" neglects the fact that many of the companies that invested in ACE inhibitor research continued to engage in the same kind of fundamental research and open exchange of information that characterized Squibb's program (Patchett et. al., 1980). For example, Merck, the firm that introduced enalapril, continued to explore alternative hypertensive therapies, and in 1991 formed a joint venture with Du Pont to exploit the latter's discovery of losartan, an angiotensin II receptor antagonist. Similarly all of the firms in our sample continue to publish actively in the field at rates exceeding those which accompanied the initial burst of scientific interest.

This pattern, which we believe to be relatively typical of the industry,[5] is confirmed by the accounts of those responsible for setting research strategy. In general, the managers whom we interviewed claimed that in planning their investment programs they focused on three criteria: the size of the unmet medical need, the scientific potential of a field, and the idiosyncratic capabilities of their researchers. Some also mentioned the views of their marketing departments and the need to service an existing franchise as critical factors in their decisions. But when pressed on the role of competitive investment in their criteria, the managers that we interviewed claimed that they tried to avoid head to head competition, or "racing" as inherently unproductive.

While the qualitative evidence is suggestive, ultimately the degree to which competition in ethical drug discovery is well characterized as a rent-dissipating race is an empirical question, and we thus turn to the quantitative analysis.

Specification of the Econometric Model

Ideally, we would like to proceed by constructing a full structural model of research investment. However although our data set is significantly more comprehensive and disaggregated than has been available to previous researchers, it is still neither sufficiently detailed nor complete enough to allow us to do this with any confidence. We would need to assume a structure for the payoff function, and to model accurately the relative position of firms over time, the magnitude of spillovers and the nature of firm asymmetries, as well as the evolution of the information structure of the game and the beliefs of each player. Quite apart from the usual concerns about functional form, whether or not we have the "true" model and so on, this places very serious demands on the data.

Some of these variables are intrinsically difficult to measure, and in other cases we are limited by the availability of data. One of the most serious problems facing us is modelling payoffs: in the pharmaceutical industry, potential sales of a newly discovered compound are very difficult to assess *ex ante*, and are only realized after long delays (five years or more) and the resolution of great uncertainty about regulatory approvals and the efficacy of the drug in clinical use. Interesting research is under way modelling demand and competition in the final product market (Suslow, 1992; Berndt, 1993), but we still know relatively little about the fundamental factors which determine the sales of new drugs or the dynamics of how new products displace existing drugs. The problem is particularly acute in the case of markets such as drug therapies for Alzheimer's disease where there is clearly great unmet medical need, but there are very few existing products and thus very limited information about potential demand, price elasticities etc. We attempted to capture some aspects of demand at the level of therapeutic classes by using data on firm and industry sales revenues, numbers of physicians practicing in relevant specialties etc, but these variables are not very satisfactory. A further difficulty is that a test of a complete structural model would require a data set that included information about every player in each "race", and since we were only able to obtain data from a subsample of the industry, our analysis would be subject to serious problems of selection bias. As a first step, therefore, we rely on reduced form analysis to explore some of the issues discussed above.

5.1 Investment Equation

We begin by looking for correlations in the level of research investments across competitors among the firms in our sample, using the research program as our primary unit of analysis and controlling for other exogenous factors which we think are driving investment decisions.

Our "base case" model is a reduced form regression of each firm's own investment in discovery in each period in each program on internal, firm-specific variables such as lagged own investment and prior success in the program, as well as a number of measures of demand and technical opportunity intended to capture the dynamics that our qualitative research suggests are important to the determination of investment. In order to test for positively correlated investment across competitors we then introduce suitably lagged measures of competitive investment in the area. Thus we use the specification:

$$R_{it} = \alpha + \beta_1 R_{i,t-1} + \beta_2 T_t + \beta_3 D_t + \beta_4 C_t + \epsilon_{it} \qquad (3)$$

where T is a vector of variables capturing shocks to technological opportunity, D is a vector of

variables capturing demand and perceived medical need, and C is a vector of measures of competitors' investment. A test of the hypothesis that investments are correlated across firms is then simply whether $\beta_4 > 0$. Since we only have data for a sample of firms, and not for the industry, our competitor variables are not entirely satisfactory. But we believe that our sample is not markedly unrepresentative of the industry as a whole so that they are probably a reasonable proportionate approximation to industry investment. Timing issues are clearly important here, and we addressed this empirically by trying a variety of models in which we include contemporaneous competitors' investment, the first and second lags, and a stock variable which can be thought of a geometric distributed lag on subsequent lags. In the event our results are not significantly affected. Inclusion of both contemporaneous investment and the first or second lags reduces the significance of all three, but introduced alone neither is significantly more significant than the other.

Our proxies for demand do not work very well, and are essentially collinear with therapeutic class dummies, so in the results reported here we attempt to capture demand as well as other unmeasured effects by including firm and therapeutic class dummies and a time trend. We measure scientific opportunity using counts of "important" scientific papers in the field, where importance is defined by the fact that they were included in ISI's list of the 100 most highly cited scientific papers in a given year. In most of the regressions we also include the stock of own discovery spending (calculated using the perpetual inventory formula with an assumed depreciation rate of 20%) to proxy for accumulated knowledge capital, and own sales in the program to try to capture some aspects of demand.[6]

There are a number of important econometric issues. Firstly, since our dependent variable is truncated at zero -- many firms choose to invest nothing in many areas, and might indeed prefer to be disinvesting faster than the depreciation rate of knowledge capital -- there is a potential for bias in the OLS estimates, and we therefore also estimate the equations where appropriate using Tobit analysis with appropriate corrections for heteroskedasticity in the error terms.[7] Secondly, this is a panel data set, and to the extent that there are significant unobserved program effects in the data, using a lagged dependent variable will induce bias in the parameter estimates (Anderson and Hsiao, 1982). This is not a serious problem here, since the bias is inversely proportional to the number of observations per program, which is fairly large here -- on average we observe each program for just over 17 years -- and indeed the tell-tale changes in parameter estimates moving from fixed effects to random effects models were not found in exploratory calculations.

Note also that it is unclear that investment *levels* will necessarily show a strong correlation

across firms even if racing behavior is an important factor. Recall that at equilibrium, investment levels should only be correlated across firms in the event of common responses to unobserved shocks in demand or in scientific opportunity. To the extent that realized investment levels reflect these equilibrium responses and rational beliefs about competitors, including competitive investment in the regression does not introduce any additional information. Furthermore, our qualitative work suggests that adjustment costs are very significant, and that in the short term firms are largely constrained to adjust spending at the margin. Building research capability requires sustained investments over time in both people and equipment, and organizational issues also limit the speed with which research resources can be reallocated within the firm. We therefore turn to an examination of the extent to which own investment reacts to changes in competitors' investment.

Firstly, following previous research, we explore correlations in first differences across firms. Secondly we use two different methods to decompose changes in investment into "anticipated" and "unanticipated" components. In the first place we construct "news" variables, defined as the difference between this period's flow of investment, and the amount necessary to maintain the beginning of year stock given our assumed depreciation rate, or:

$$News_t = R_t - 0.2 * K_t \qquad (4)$$

where K_t is stock of investment in research.

In the second place, we calculate a residual measure of unanticipated investment by taking residuals from a simple investment equation, summing them over competitors for each therapeutic class-year observation, and then including this measure in subsequent regressions.

5.2 Output Equation

Our qualitative analysis has already put the usefulness of one of the assumptions fundamental to much of the theoretical work in this area into doubt. The ACE inhibitor "race" led to the introduction of several compounds, some of them with significantly different therapeutic profiles from the first entrant, suggesting that, in this case at least, it may be inappropriate to characterize research competition as a single "winner take all" race.

We extend and generalize this analysis through a quantitative exploration of the correlation in research outputs across rivals. Recall that our discussion of the literature suggested that the entry of an additional firm into the research "race" is unambiguously welfare destroying only under a number of quite strong assumptions, including the belief that competing projects are substitutes rather than

complements and that there are no substantial spillovers of knowledge across firms. Our goal in this analysis is to explore the usefulness of these assumptions in the context of pharmaceutical research.

In previous work (Henderson and Cockburn, 1993) we estimated a number of research output equations in which competitors' research outcomes (as captured by "important" patents) were modelled as a measure of the spillover of knowledge across firms, entering the research production function with a strong positive coefficient. We interpreted this as evidence that competing research programs are complements rather than substitutes, and that on the whole competitors' success in a particular field does not represent a net "mining out" of opportunities. We reproduce some of these results here, with the addition of our measures of scientific opportunity to control for the possibility that the positive correlation of outputs obtained in previous work reflects common trends in research productivity induced by common shocks to opportunity. Since the dependent variable is a discrete count of important patents, we use Poisson regression.[8]

6. Results

6.1 Are inputs correlated?

Tables (2) to (5) present our results. As a basis for comparison, and to illustrate the pitfalls inherent in using aggregate data, we begin by exploring the correlation between own and competitive investment using data aggregated to the firm level. These results are shown in Table (2). We regress own investment on investment in the previous period, stock of investment, firm sales, and "news" in patents obtained in the area. These regressions are dominated by the lagged dependent variable, which is highly significant, with a coefficient very close to unity. Firm dummies are jointly significant, but add little to the explanatory power of the regression.

Models (4) and (5) and (6) include competitors' investment in the equation. Competitors' investment in the current period is negatively and significantly correlated with own investment, while competitors' investment in the previous period is insignificant. Model (6) regresses the first difference in own investment on first differences in the explanatory variables, and again competitors' investment is negative and significant. Thus at first blush our data appear to suggest that there are strong strategic effects operating between firms. However given that the theory only tells us about competition at the level of research projects, and that we cannot control for technological opportunity in the aggregate analysis it is not clear that this interpretation is warranted.

Tables (3a), (3b), (4), and (5) report results using our disaggregated program level data. Table (3a) presents OLS estimates of simple investment equations, but these are badly misspecified

because of the censoring of the dependent variable at zero. Table (3b) presents more satisfactory results from Tobit analysis. As in the firm level data, investment at the level of the research program is overwhelmingly driven by investment in the previous period. Firm and therapeutic class dummies are jointly and individually significant. In Model (4) we control for technological opportunity, measured as shocks to the underlying science base, as captured by "news" in the publication rate of papers in any given area appearing on ISI's annual list of the 100 most significant papers published in the life sciences. This variable is only marginally significant -- to a large extent the impact of variation in technological opportunity conditions is also being captured by therapeutic class dummies. In Table (4) we again include competitors' investment in the equation. Regressing own investment onto competitors' investment alone, as in Model (1), suggests strong correlation between the two across firms, but once we control for own investment in the last period, this variable becomes insignificant. Neither controlling for technological opportunity (Model 3), nor using contemporaneous versus lagged values of competitors' investment (Model 4), has any significant effect on the estimated coefficients. The difference between these program level results and those obtained using data aggregated to the firm level dramatically illustrates the danger of using aggregate, firm level data to explore the validity of models derived from project level interactions.

Tables (3) and (4) test for the presence of reactions across firms using data in levels. As argued above, however, expectations about competitive behavior should already be incorporated into investment strategy where they are reflected in the highly significant and positive coefficient on own investment in the previous period. In Table (5) we therefore explore the hypothesis that firms react strategically to (unanticipated) changes in competitive investment. As discussed above, we measure the unanticipated component of competitors' investment in three different ways -- models (1) and (2) estimate the investment equation in first differences, models (3) and (4) use "news" versions of the key variables (the extent to which the current flow exceeds the amount necessary to maintain the previous period's stock unchanged) while model (5) uses residuals from a "first stage" regression of own investment on to lagged investment, sales, technological opportunity and the usual firm and class dummies. In the first differences and "news" models we find a weak correlation between changes in own and competitors' investment, but this result is not robust to the inclusion of firm and therapeutic class dummies. The residuals model also shows no evidence of correlated strategies once exogenous and predetermined variables have been partialled out. We interpret these results as rejecting simple reaction-function or tit-for-tat models -- they provide little evidence of strategic co-movements in inputs to the research process across firms above and beyond that induced by common exogenous

shocks.

6.2 Are outputs correlated?

If firms are "racing" each other in the sense implicit in much of the theoretical literature, then outputs will be negatively correlated across firms -- since if firms are racing for a single, well defined goal, the odds that any firm will obtain it necessarily falls as others reach it successfully. Our qualitative discussion threw doubt on the assumption that pharmaceutical firms compete for a single goal. Here we explore this issue quantitatively.

In previous work (Henderson and Cockburn, 1993), we showed that at the program level research outputs, as captured by "important" patents, were positively correlated across firms. However in this analysis we failed to control for changes in technological opportunity, raising the possibility that the observed correlations across firms merely reflected exogenous shifts in opportunity that made it easier to obtain patents in any given class.

Table (6) presents Poisson regression results that include controls for shifts in technological opportunity. The dependent variable is a count of important patents applied for (and subsequently granted) in the program area, where we define "important" by the observation that the patent was granted in two or more major jurisdictions. Model (1) replicates results from our previous work, using a somewhat larger sample, and illustrates the strongly significant and positive correlation between own output and the success of rival firm's efforts.[9] Models (2) and (3) are estimated from the smaller 1975-88 sample used in the investment equation. Controlling for shocks to scientific opportunity (Model (3)) does <u>not</u> attenuate the positive correlation between own and rivals' research success[10]. Models (4) and (5) repeat the analysis for a much more limited subset of the data that covers cardiovascular drugs where we were able to use our knowledge of the scientific history of the field and consultation with experts to identify "Key Events" -- those papers that had a seminal influence on the field and that represented order of magnitude changes in scientific opportunity. Again, the inclusion of these measures does not effect the estimated coefficient on competitors' research output. Far from being a "mining out" of opportunities, competitors' research appears to be a complementary activity to own R&D.

These results have several possible interpretations depending on the degree to which firms are engaged in closely related research projects. At one end of the spectrum, suppose firms investing in the same area are pursuing very different approaches. In this world positive correlation across outputs would reflect solely the spillover of knowledge across firms, and it might still be possible to model a

particular race as having only a single reward. At the other end of the spectrum, suppose that firms are engaged in almost identical research. Then the finding that outputs are positively correlated would suggest both that there are significant spillovers of knowledge across programs and that any single "race" has several "rewards."

Our qualitative work suggests that the reality lies somewhere in between these two extremes: some firms pursue different goals within the same general therapeutic area while others compete more directly. In either case publication and the norms of professional disclosure appear to ensure the rapid exchange of knowledge across the industry. Thus there are some grounds for believing that the entry of additional firms into the pharmaceutical research "race" is not unambiguously welfare destroying. Competing projects are probably better described as complements rather than substitutes, and there may well be significant spillovers of knowledge across firms.

7. Conclusions

Recent advances in the theoretical literature have greatly expanded our understanding of the forces that shape the competitive dynamics of research and development, but a paucity of sufficiently detailed empirical data has left these insights relatively untested. In this paper we draw on unusually detailed qualitative and quantitative internal data provided at the research program level by ten major pharmaceutical firms to explore the usefulness of the modern literature as a source of insight into the dynamics of competition in ethical drug discovery.

Our analysis focusses on one particularly compelling aspect of the literature: the suggestion that in winner take all situations, competition in R&D becomes a Prisoner's Dilemma, leading to over-investment in research. Without adequate measures of the social return to innovation, we can say nothing about whether there is "too much" or "too little" research undertaken by the industry, but our results do not support the suggestion that investment in drug discovery is driven by the "tit-for-tat" or simple reaction function models hinted at by the institutional literature.

Two key results were obtained from estimating simple reduced form models of research investment and output from program level data. Firstly, research investment is only weakly correlated across firms once common responses to exogenous shocks are accounted for. Secondly, rivals' results are positively correlated with own research productivity, which we interpret as evidence for extensive spillovers rather than the depletion externality implied by winner take all models.

These results are not, of themselves, sufficient to reject the hypothesis that investment behavior in the industry is driven by strategic considerations. There is, after all, theoretical support

for a very wide variety of observable behavior as equilibrium outcomes of strategic interaction. Nonetheless, knowledgeable critics of the industry have charged that "racing" is a useful characterization of industry dynamics, and our results provide little support for the most obvious form which we expect to this to take. If "me too" or responsive investment occurs -- and there is certainly qualitative evidence that it occurs occasionally -- it appears not to be characteristic of the bulk of research investment. A better characterization, and one that is consistent with our qualitative research, is that investment decisions are driven by the heterogeneous capabilities of the firm, by adjustment costs, and by the evolution of technological opportunity.

Clearly, much additional work needs to be done to determine the nature of R&D competition in pharmaceuticals. Our results illustrate the potentially fruitful ways in which the modern game theoretic literature can frame the examination of complex strategic issues. However they also point to the need to model R&D as a race with multiple prizes, and to develop theories that by incorporating richer models of adjustment costs and of firm heterogeneity can give insight into the complexity of competition in particular industries.

Endnotes

1. Cardiovascular drugs were chosen as the focus of the study for several reasons. Cardiovasculars are one of the largest and most rapidly growing classes of drugs. Moreover the class includes both extraordinarily powerful agents whose mechanism of action - the precise biochemical means whereby the drug has a physiological effect - is well understood (such as the ACE inhibitors) and less effective agents that have been used for many years and whose precise mechanism of action has not been fully elucidated. (Drugs such as digitalis and some of the antiarrhythmic agents fall into this category.)

2. With a complete, rectangular, panel we would have 11,400 observations, made up of ten firms, 38 detailed research areas, and up to 30 years of data. In practice not all of these observations are available: the average time period for which we have complete data is on average just under 20 years per firm, and not all firms are active in all research areas. Our working sample is drawn from a data base which currently has 5320 observations, which after lagging variables leaves us with 4930 observations covering the period 1961-1990.

3. Hypertension is a condition in which the patient's blood pressure is consistently greater than the normal level. Although in its early stages it has few symptoms, persistent high blood pressure severely damages the cardiovascular system, and hypertension, "the silent killer," is probably directly or indirectly responsible for 10-20% of all deaths (Julian, 1988).

4. Data from *IMS America*

5. Research in conditions that are less well understood, such as Alzheimer's or oncology (cancer), is probably even closer to a collaborative, diverse model, while research in the better understood areas such as the development of new anti-infective drugs is probably closer to a pure stochastic race.

6. Own sales is also intended to proxy for the firm's investment in complementary assets such as specialized marketing capabilities. In interviews, some managers identified "the need to maintain a franchise" as an important factor in their investment decisions.

7. Assuming that heteroskedasticity is a result of variation in program size, the variance of the residual was modelled as a function of lagged investment: $\theta_i = \sigma \exp(\alpha R_i)$. Including other variables in this ancillary model had little effect on the results.

8. See Henderson and Cockburn (1993) for a more detailed discussion of the specification and estimation of this equation, where similar results were obtained using Negative Binomial and Quasi-likelihood estimation.

9. Using competitors' discovery spending in place of their patents gives very similar results: competitors' investment has a positive and significant impact on own research productivity.

10. An alternative measure of opportunity "cites to key papers" performed very similarly.

Bibliography

Anderson, T.W. and C. Hsiao, 1982, "Formulation and Estimation of Dynamic Models Using Panel Data", *Journal of Econometrics*, v. 18, 47-88.

Arrow, K., 1962, "Economic Welfare and the Allocation of Resources for Invention." in R. Nelson, ed. *The Rate and Direction of Inventive Activity*, Princeton: Princeton University Press, 609-619.

Baldwin, W.L and J.T. Scott, 1987, *Market Structure and Technological Change*, Chur, Switzerland: Harwood Academic Publishers.

Berndt, Ernst, 1993, "Price Indexes for Antihypertensive Drugs that Incorporate Quality Change; A Progress Report on a Feasibility Study." MIT Program on the Pharmaceutical Industry, Working Paper Number 6-92.

Dasgupta, P. and E. Maskin, 1987, "The Simple Economics of Research Portfolios", *Economic Journal*, v. 97, 581-595.

Dasgupta, P. and J. Stiglitz, 1980a, "Industrial Structure and the Nature of Innovative Activity", *Economic Journal*, v. 90, 266-293.

Dasgupta, P. and Stiglitz, J., 1980b, "Uncertainty, industry structure and the speed of R&D," *Bell Journal*, v. 11, 1-28.

DiMasi, J., et al., 1991, "The Cost of Innovation in the Pharmaceutical Industry", *Journal of Health Economics*, v. 10, 107-142.

Dixit, Avinash, 1988, "A General Model of R&D Competition and Policy", *Rand Journal of Economics*, v. 19, No. 3, 317-326.

D'Aspremont, C. and A. Jacquemin, 1988, "Cooperative and Noncooperative R&D in Duopoly with Spillovers", *American Economic Review*, v. 78, No. 5. 1133-1137.

D'Aspremont, C. and A. Jacquemin, 1990, "Cooperative and Noncooperative R&D in Duopoly with Spillovers: Erratum", *American Economic Review*, v. 80. 641-642.

DiMasi, J., et al., 1991, "The Cost of Innovation in the Pharmaceutical Industry", *Journal of Health Economics*, v. 10, 107-142.

Fraja, Giovanni, 1993, "Strategic Spillovers in Patent Races", *International Journal of Industrial Organization*, v. 11, 139-146.

Grabowski, Henry and Nevine Baxter, 1973, "Rivalry in Industrial Research and Development." *Journal of Industrial Economics*, v 21, 209-35.

Harris, C. and J. Vickers, 1987, "Racing with Uncertainty," *Review of Economic Studies*, v. LIV, No. 177, 1-22.

Henderson, Rebecca, and Iain Cockburn, 1993, "Scale, Scope, and Spillovers: Determinants of Research Productivity in Ethical Drug Discovery", NBER Working Paper #4476.

Khanna, Tarun., 1993, "Racing Behavior: Technological Evolution in the High-End Computer Industry," Mimeo, Harvard Business School.

Lee, T.K., and L.L. Wilde, 1980, "Market Structure and Innovation: A Reformulation," *Quarterly Journal of Economics*, v. 94, 429-436.

Lerner, Joshua., 1991, "The Empirical Exploration of a Technology Race: The Winchester Disk Drive Industry, 1972-1988." Mimeo, Harvard Business School.

Loury, Glenn, 1979, "Market Structure and Innovation", *Quarterly Journal of Economics*, v. 93 395-410.

Meron, Amos, and Richard E. Caves, 1991, "Rivalry among Firms in Research and Development Outlays", Paper presented at the 1991 UBC Summer IO Conference.

Reinganum, J.F., 1982, "A dynamic game of R and D: Patent Protection and Competitive Behavior", *Econometrica*, v. 50, 671-688.

Reinganum, J.F., 1989, "The Timing of Innovation: Research, Development and Diffusion", in Schmalensee, R. and R. Willig, eds., *Handbook of Industrial Organization, Volume 1*, Amsterdam: North Holland.

Reiss, Peter C. and Richard C. Levin "Cost-reducing and demand-creating R&D with spillovers", *Rand Journal of Economics*, v. 19, No. 4, 538-556.

Scherer, F. M., 1967, "Research and Development Resource Allocation Under Rivalry," *Quarterly Journal of Economics*, v. 81, 359-394

Scherer, F.M., 1992, *International High Technology Competition*. Harvard University Press, Cambridge Mass.

Schumpeter, J. A., 1934, *The Theory of Economic Development*, Cambridge, Massachusetts: Harvard University Press.

Schumpeter, J. A., 1950, *Capitalism, Socialism and Democracy*, Cambridge, Massachusetts: Harvard University Press.

Spence, Michael, 1984, "Cost Reduction, Competition and Industry Performance." *Econometrica*, v. 52., No. 1. 101-121.

Suslow, Valerie, 1992, "Are There Better Ways to Spell Relief: A Hedonic Pricing Analysis of Ulcer Drugs" University of Michigan, Working Paper #696.

Suzumura, K., 1992, "Cooperative and Noncooperative R&D in an Oligopoly with Spillovers", *American Economic Review*, v. 82, No.5. 1307-1320.

Scientific References

Buhler et al., 1972, "Propranolol inhibition of renin secretion. A specific approach to diagnosis and treatment of renin-dependent hypertensive diseases", *New England Journal of Medicine*, v 287, 1209-1214.

Brunner et al., 1974, "Hypertension in man. Exposure of the renin and sodium components using angiotensin II blockade", *Circulation Research* (Suppl. 1) 34-43.

Case, D.B et al., 1976, "Estimating renin participation in hypertension. Superiority of converting enzyme inhibitor over saralasin. *American Journal of Medicine*, v 61, 790-796.

Case D.B. et al., 1977, "Possible role of renin in hypertension as suggested by renin-sodium profiling and inhibition of converting enzyme", *New England Journal of Medicine*, v 296, 641-646.

Cushman, D. W., Cheung, H.S., Sabo, E.F., and Ondetti, M.A., 1977, "Design of potent competitive inhibitors of angiotensin-converting enzyme. Carboxyalkanoyl and mercaptoalkanoyl amino acids. *Biochemistry*, v 16, 5484-5491.

Erdos, E.G. (ed.), 1970, "Bradykinin, Kallidin, and Kallikrein," *Handbuch der Experimentellen Pharmakologie*, v. 25., Berlin: Springer-Verlag.

Goldblatt H.J., Lynch R.F. Hanzal R.F. et al., 1934, "Studies on experimental hypertension. Production of persistent elevation of systolic blood pressure by means of renal ischemia", *Journal of Experimental Medicine*, v 49, 347-379.

Gavras et al., 1974, "An angiotensin converting enzyme inhibitor to identify and treat vasoconstrictor and volume factors in hypertensive patients", *New England Journal of Medicine*, v 291, 817-821.

Goodman, A., L. S. Goodman, T. W. Rall and F. Murad, 1985, *The Pharmacological Basis of Therapeutics*, New York: Macmillan.

Gross, F., 1968, "The regulation of aldosterone secretion by the renin-angiotensin system under various conditions. *Acta Endocrinol.* (Kbh.) Suppl. v 124, 41-64.

Hodge, R.L., R.D. Lowe, J.R.Vane, 1967, "Concurrent Measurement of Renin and Angiotensin in the Circulation of the Dog", *Nature,* v 215, 853.

Julian, Desmond G., 1988, *Cardiology,* London: Bailliere Tindall.

Laragh, J.H., et al., 1972, "Renin, angiotensin and aldosterone system in pathogenesis and management of hypertensive vascular disease", *American Journal of Medicine,* v 52, 644-652.

Laragh, John H., 1984, "Concept of Anti-Renin System Therapy: Historic Perspective", *American Journal of Medicine*, v. 77 (2A).

Ordetti M.S. et al., 1971, "Angiotensin-converting enzyme inhibitors from the venom of Bothrops jararca: isolation, elucidation of structure and synthesis", *Biochemistry,* v 10, 4033-4039.

Ondetti M.A., Rubin B., and Cushman D.W., 1977, "Design of specific inhibitors of angiotensin-converting enzyme. New class of orally effective antihypertensive agents", *Science*, v 196, 441-444.

Pals et al., 1971, "A specific competitive antagonist of the vascular action of angiotensin II. *Circulation Research,* v 29, 664.

Patchett A.A., Harris, E., Tristram E.W. et al., 1980, "A new class of angiotensin-converting enzyme inhibitors", *Nature*, v 288, 280-282.

Appendix One: Qualitative Research Strategy

- Detailed study of secondary sources
- Field interviews, 10 large pharmaceutical firms. Interviews were semi structured in that each respondent had been provided with a list of key questions before the interview, and each interview lasted from one to three hours. These data were supplemented with interviews with a number of industry experts, including senior academics in the field. In all over one hundred individuals were interviewed.

Company	1	2	3	4	5	6	7	8	9	10
General overview	X	X	X	X	X	X	X	X	X	X
Senior cardiovascular managers	X	X	X	X	X	X		X	X	X
Comprehensive interviews	X		X	X		X			X	

Appendix Two: Sources and Construction of Quantitative Data

The data set used in this study is based on detailed data on R&D inputs and outputs at the research program (narrow therapeutic class) level for ten ethical pharmaceutical manufacturers.

Inputs

Our data on inputs to the drug discovery process is taken from the internal records of participating companies, and consists primarily of annual expenditures on exploratory research and development by research program. Several issues arise in dealing with these data.

(a) Discovery vs. Development

The distinction between discovery and development is important. We define resources devoted to discovery as all pre-clinical expenditures within a therapeutic class, and development as all expenses incurred after a compound has been identified as a development candidate. Where exploratory research was attributable to a particular research program, this is included in the discovery category. Non-program exploratory research was included in the overhead allocation for each research program. Clinical grants are included in the figures for development, and grants to external researchers for exploratory research are included in the total for discovery.

In some cases, the companies supplied us with data already broken down by discovery vs development by research program. In others, we had to classify budget line items for projects/programs into the appropriate category. This was done based on the description of each item in the original sources, and the location of items within the structure of the company's reporting procedure.

(b) Overhead

In order to maintain as much consistency in the data collection process as possible, we tried to ensure that these figures include appropriate overhead charges directly related to discovery activities, such as computing, R&D administration and finance etc., but exclude charges relating to allocation of central office overhead etc. The overhead also includes some expenditures on discipline-based exploratory research such as "molecular biology" which appeared not to be oriented towards specific therapies. Overhead was allocated across therapeutic classes according to their fraction of total spending.

(c) Licensing

We treat up-front, lump-sum payments in respect of in-licensing of compounds, or participation in joint programs with other pharmaceutical companies, universities or research institutes, as expenditure on discovery. Royalty fees and contingent payments are excluded from the data.

Outputs

In this paper we focus on important patent grants as our measure of research output. We count patents by year of application. Our interest here is on determinants of technical success, defined in terms of producing new potentially important compounds, rather than on the ultimate commercial success or failure of new drugs. Since Patent Examiners award grants based on slowly changing objective criteria of novelty, non-obviousness, and potential industrial application, we believe that patent grants are an appropriate basis for measuring research output in this industry. Pharmaceutical companies patent prolifically, and patents are, of course, a rather noisy measure of research success, in part because the significance of individual patents varies widely. We partially control for this by counting only "important" patents, where we define "importance" by the fact that the patent was granted in two of the three major markets: the USA, Japan, and the European Community.

These data were provided by Derwent Publications Inc, who we asked to use their proprietary classification and search software to produce counts of "important" patents to us broken down by therapeutic class for 29 US, European, and Japanese pharmaceutical manufacturers for the 26 years preceding 1990. These firms were chosen to include the ten firms that have given us data together with 19 other firms chosen on the basis of their absolute R&D expenditures, R&D intensity, and national "home base" to try to get a representative, rather than exhaustive, assessment of world-wide patenting activity. These 19 firms have been consistently in the top 30 world wide pharmaceutical firms in terms of R&D dollars and sales.

Note that many of these patents will be "defensive" patents in that firms may patent compounds they do not intend to develop in the short term but that may have competitive value in the longer term. Alternative measures of "importance" include citation weighting and more detailed international filing data - "very" important patents are usually filed in nearly every major potential market. We hope to explore these alternative measures in later work.

Classification

Classification of inputs and outputs by therapeutic class is important because this drives our measure of spillovers. There are essentially two choices: to define programs by physiological mechanisms, e.g. "prostaglandin metabolism", or by "indications" or disease states, e.g. "arthritis". We have chosen to classify on the basis of indication, largely because this corresponds well to the internal divisions used by the companies in our sample (which is conceptually correct), but also because classification by mechanism is much more difficult (a practical concern). We classified both inputs and outputs according to a scheme which closely follows the IMS Worldwide classes. This scheme contains two tiers of aggregation: a detailed "research program" or "research area" level, and a more aggregated level which groups related programs into therapeutic classes. For example, the therapeutic class "CARDIOVASCULAR" includes the research programs "ANTI- HYPERTENSIVES", "CARDIOTONICS", "ANTITHROMBOLYTICS", "DIURETICS" etc.

There are some problems with this procedure. Firstly, some projects and compounds are simply very difficult to classify. A particular drug may be indicated for several quite distinct therapies: consider serotonin, which has quite different physiological actions on either side of the blood-brain barrier. As a neurotransmitter it is believed to play important roles in mediating motor functions. As a systemic hormone it has a variety of effects on smooth muscle, for example it functions as a vasoconstrictor. Some companies report expenditures in areas which are very difficult to assign to particular therapeutic classes: a company doing research using rDNA technology might charge expenditure to an accounting category listed as "Gene Therapy/Molecular Biology" which is actually specific research performed on e.g. cystic fibrosis, but we have no idea about which diseases the research is directed towards treating, and are forced to include these expenditures in "overhead". Secondly, our two-tier classification scheme may not catch all important relationships between different therapeutic areas. We believe that we are undercounting, rather than overcounting in this respect, so that the importance of spillovers will be underestimated rather than overestimated. Thirdly, where firms supplied us with "pre-digested" data, they may have used substantively different conventions in classifying projects. One firm may subsume antiviral research under a wider class of anti-infectives, while another may report antivirals separately. Not surprisingly there are major changes within companies in internal divisional structures, reporting formats, and so forth, which may also introduce classification errors. After working very carefully with these data, we recognize the potential for serious miss-assignment of outputs to inputs, but we believe that such errors that remain are not serious. The use of patents as the output measure should reduce vulnerability to this problem, since we observe relatively large numbers, and a few miss- classifications are unlikely to seriously affect our results. When we move to INDs and NDAs as our output measures, the much more sparsely distributed data are likely increase our vulnerability.

Matching

Data series on inputs and outputs for each firm were matched at the research program level. This procedure appears to successfully match outputs and inputs unambiguously for the great majority of programs. In a very few cases, however, we ended up with research programs where patents, INDs or NDAs were filed, but where there were no recorded expenditures. Of these the majority were obviously coding errors or reflected dilemmas previously encountered in the classification process, and appropriate corrections were made. In other cases, it was clear that these reflected "spillovers" -- research done ostensibly in, for example, hypertension, may generate knowledge about the autonomic nervous system which prompts patenting of compounds may be useful in treating secretory disorders (e.g. ulcers.) In such cases we set "own" inputs for the program equal to zero, and included these observations in the data base.

Deflation

Since our data sources span many years, it is important to base the analysis on constant dollar expenditures. We used the R&D price deflator constructed by Edwin Mansfield (1987) for his Oil and Chemicals industry grouping. This index is based on wage rates for R&D employees, and a price index for equipment and instrumentation purchases, and though its movement is quite different from the CPI or the GNP deflator, it varies much less across industries, leading us to believe that it may be a reasonable approximation to the "correct" index for pharmaceuticals. Mansfield's index exists only for 1969-1983, we extended it backwards to 1966 and forwards to 1990 using movement in the CPI. The periods 1966-1969 and 1983-1990 saw relatively little price inflation, so this approximation is unlikely to be serious problem. In a later paper we intend to exploit the

information that some companies were able to give us on R&D inputs in units of labor hours to construct an index specifically for research costs in the pharmaceutical industry.

Demand

We attempt to measure cross-sectional and time series variation in the state of demand for drug treatments for the different therapeutic classes using a variety of publicly available data. Firstly, we compiled statistics on disease incidence and mortality in the US population from a variety of sources, including the information provided by bodies such as the National Institutes of Health and the National Cancer Institute. Unfortunately, these data are not entirely comprehensive and consistent. Some diseases or conditions are under-reported because they are not sufficiently serious, or because of social stigma (e.g. depression). In many cases data only appear to have been gathered at five-year or longer intervals, and in others there were serious inconsistencies in series over time which presumably reflect differences in reporting requirements. There are also problems in comparing for example, diseases which have low incidence but high mortality rates with those with high incidence and low mortality (thyroid cancer vs common cold), or indeed in comparing diseases which are merely uncomfortable with those that are life-threatening.

Secondly, we complied data on the number of doctors in the US belonging to various specialties. These data are at best only available at a rather high level of aggregation (cardiology vs neurology) and their usefulness is also limited by the classification of many doctors into specialties such as Internal Medicine or Pediatrics which have no information about therapeutic classes.

These data are far from satisfactory measures of demand: they are neither as detailed as we would like, nor do they show much variation over time. Moreover they are not necessarily directly comparable in the cross section, nor do they capture the potential market size for e.g. drug therapies vs surgery. Our hope is that they pick up gross variation in levels of demand, or shocks to demand such as the appearance of AIDS. An alternative measure of demand is actual dollar sales of pharmaceuticals in the class. We compiled these data from the reports of IMS America (a market research firm) for each of the therapeutic classes in our data.

A final, and perhaps more fundamental, problem with these demand measures is that their usefulness as measures of incentives to do R&D may be rather limited. Ideally we would like some measure of the total consumer surplus available to be captured, based on market characteristics such as the price elasticity of demand, potential for drug therapies to enhance patients' quality of life or extend their life expectancy, the efficacy of currently available therapies etc. Our measures fall far short of this ideal, but may be the best that we can do with limited time and resources.

Scientific Opportunity

We use two sources of data to measure "discrete" shocks to technological opportunity: bibliometric data based on the citation databases of ISI, and identification of key events in the evolution of the science base for particular therapeutic classes. The ISI publishes an annual list of the most significant papers published in the life sciences. For each year and each therapeutic class we noted the number of papers in that area which made the "Top 100" list, and also how many times that those papers were subsequently cited in the next two years. Problems with these measures of shocks to opportunity include: matching papers to therapeutic classes, which is often difficult if the paper refers to "generic" aspects of molecular biology or physiology rather than specific diseases or organ systems; failure of the scientific community to identify key advances until much time has passed; advances being of great importance to researchers in a narrowly defined field, but lacking sufficient general interest to attract enough citations to make the "Top 100" list etc. However these measures have the advantage that they are consistent and comparable over time, and reasonably well matched to specific therapeutic classes.

For cardiovascular therapies, we attempted to identify "key events". This process is more subjective, but is hopefully more comprehensive. We examined standard texts on pharmacology, such as Goodman and Gilman's "The Pharmacological Basis for Therapeutics" (1985), and accounts that focused particular on cardiovascular therapies, and attempted to identify significant steps forward in scientific understanding, such as the discovery of entirely classes of compounds showing desirable activity in vitro or in animal models, or the identification of important enzyme pathways.

Table (A1): Definition of Variables Used in the Regression Analysis

Observations are identified by (encoded) FIRM, CLASS, and YEAR.

Measures of scientific opportunity	
Papers	Total papers in the class listed in the ISI list of "Top 100 papers" in the biological sciences.
Key private papers (CV only)	Number of papers signalling major breakthroughs in the field published by authors employed by private firms.
Key public papers (CV only)	Number of papers signalling major breakthroughs in the field published by authors employed by the public sector.
Measures of demand	
Cases	Reported U.S. incidence of the disease.
Deaths	Reported U.S. mortality.
Doctors	Number of doctors identifying themselves as specialists in the area.
US sales in class	Wholesale U.S. sales of drugs in the class.
Measures of competitive activity	
Competitors' patents in this class	Important patents applied for by 28 major (worldwide) competitors.
Competitors' patents in related classes	Important patents applied for by 28 major (worldwide) competitors in related classes.
Competitors' investment in this class	Investment in discovery research by the other 9 firms in the core data base.
Competitors' investment in related classes	Investment in discovery research by the other 9 firms in the core data base in related classes.
Firm specific variables	
Investment	Expenditures by this firm in this research area, relating primarily to production of new compounds, by year, in millions of constant 1986 dollars.
Patents in this class	Important patents granted to this firm in this research area, by year, from the Derwent database. Note that throughout the analysis we count patents by year of *application*.

Patents in related classes	Important patents granted to this firm in the related therapeutic class, net of the patents granted in this research area.
Firm sales in class	Total US sales in the class
Scope	The number of research areas in which this firm has spent at least $0.5m dollars on discovery this year.
Total investment (size)	Total research expenditure by this firm in this year across all therapeutic classes.

Table (1): Descriptive statistics: Selected variables at the research program level

Variable	Full Sample				
	N	Minimum	Maximum	Mean	Std Dev
Discovery, 1986$M	2707	0.00	>20	1.29	2.68
Stock of discovery	2707	0.00	52.66	3.50	7.09
Own patents	2707	0.00	34.00	2.11	3.61
Stock of own patents	2707	0.00	96.18	8.08	12.63
Own patents in related programs	2707	0.00	38.00	3.37	5.25
News in own patents	2707	-11.41	23.97	0.49	2.32
Firm sales in program	2707	-0.06	>800	25.64	85.58
SCOPE: No. programs with disc>500K	2707	2.00	19.00	10.36	4.58
SIZE: Total discovery spending this year	2707	1.97	>4	3.40	0.68
Papers	2707	0.00	37.00	1.62	5.05
Sum of competitors' discovery spending	2707	0.00	63.78	8.72	12.33
News in competitors' discovery spending	2707	-3.30	31.38	3.65	5.71
Competitors' patents in the same program	2707	0.00	300.00	44.91	47.82
Competitors patents in related programs	2707	4.00	353.00	131.53	82.23

Table (2): Determinants of investment in discovery at the FIRM level.
OLS Regression. Dependent variable = Total firm investment in discovery, 171 observations.

	(1)	(2)	(3)	(4)	(5)
Intercept	2.599** (0.920)	0.453 2.221	0.775 (2.275)	3.230 (2.228)	1.713 (2.206)
Research Investment$_{(t-1)}$	1.043** (0.062)	0.986** (0.064)	0.971** (0.069)	0.963** (0.068)	0.966** (0.070)
Stock of own Investment$_{(t-1)}$	0.000 (0.020)	-0.017 (0.029)	-0.017 (0.031)	-0.027 (0.031)	-0.021 (0.031)
"News" in own patents$_{(t-1)}$			0.005 (0.024)	0.004 (0.023)	0.008 (0.023)
Firm Sales$_t$			0.002 (0.003)	0.001 (0.003)	0.001 (0.003)
Flow of Competitors' Investment$_{(t)}$				-0.046** (0.019	
Flow of Competitors' Investment$_{(t-1)}$					-0.024 (0.021)
Firm dummies		Sig.	Sig	Sig.	Sig.
Time	-0.357* (0.174)	-0.340* (0.201)	-0.449* (0.232)	-0.523** (0.227)	-0.444* (0.233)
Time * Time	0.0128* (0.006)	0.020** (0.006)	0.023** (0.007)	0.049** (0.012)	0.034** (0.011)
R-squared Standard error of regression	0.944 5.128	0.946 5.078	0.945 5.102	0.947 5.043	0.945 5.101

Dep. Variable: Δ Inv.$_t$	(6)
Intercept	4.688** (1.073)
Δ Own patents$_t$	-0.009 (0.026)
Δ Own sales$_t$	-0.004 (0.005)
Δ Competitors' Investment$_t$	-0.082** (0.030)
Time	-0.492 (0.184)
Time * Time	0.021** (0.007)
R-squared Standard error of regression	0.049 5.100

Heteroskedastic-consistent standard errors in parentheses. ** Significant at the 1% level. * Significant at the 5% level.

Table (3a): Determinants of investment in discovery at the PROGRAM level.
OLS Regression.
Dependent variable = Investment in discovery, 2707 observations.

	(1)	(2)	(3)	(4)
Intercept	-0.020 (0.815)	0.080 (0.828)	0.029 (0.835)	0.053 (0.832)
Flow of Investment in Discovery$_{(t-1)}$	0.987** (0.034)	0.980** (0.039)	0.976** (0.039)	0.976** (0.039)
Stock of Investment in Discovery$_{(t-1)}$	-0.002 (0.012)	-0.005 (0.013)	-0.008 (0.013)	-0.009 (0.013)
"News" in patents in this class$_{(t-1)}$			0.008 (0.011)	0.008 (0.010)
Own sales in this class$_{(t)}$			0.0008 (0.0005)	0.0007 (0.0006)
News in key papers in this class				0.002 (0.007)
Class dummies		Sig.	Sig.	Sig.
Firm dummies	Sig.	Insig.	Insig.	Insig.
Time	-0.012 (0.079)	-0.010 (0.078)	-0.008 (0.078)	-0.010 (0.079)
Time * Time	0.0007 (0.0019)	0.0007 (0.0018)	0.0007 (0.0019)	0.0007 (0.0019)
R-squared	0.870	0.871	0.871	0.871
Standard error of regression	0.971	0.969	0.969	0.968

Notes

Heteroskedastic-consistent standard errors in parentheses.
** Significant at the 1% level.
* Significant at the 5% level.

Table (3b): Determinants of investment in discovery at the PROGRAM level.
Heteroskedastic TOBIT Regression.
Dependent variable = Investment in discovery, 2707 observations.

	(1)	(2)	(3)	(4)
Intercept	-2.162* (1.105)	-2.120 (1.147)	-2.153 (1.148)	-2.034 (1.170)
Flow of Investment in Discovery$_{(t-1)}$	1.190** (0.024)	1.172** (0.024)	1.175** (0.025)	1.175** (0.025)
Stock of Investment in Discovery$_{(t-1)}$	0.029** (0.006)	0.022** (0.006)	0.014* (0.007)	0.014* (0.007)
"News" in patents in this class$_{(t-1)}$			0.0004 (0.0109)	0.0008 (0.0109)
Own sales in this class$_{(t)}$			0.001** (0.0003)	0.001** (0.0002)
News in key papers in this class$_{(t-1)}$				0.012 (0.007)
Class dummies		Sig.	Sig.	Sig.
Firm dummies	Sig.	Sig.	Sig.	Sig.
Time	0.089 (0.100)	0.096 (0.106)	0.098 (0.106)	0.084 (0.108)
Time * Time	-0.002 (0.002)	-0.002 (0.002)	-0.002 (0.002)	-0.001 (0.002)
Coefficient on Lagged Discovery in variance model	0.151** (0.005)	0.152** (0.005)	0.153** (0.005)	0.152** (0.005)
Sigma	0.848** (0.011)	0.842** (0.011)	0.842** (0.011)	0.842** (0.012)
Log likelihood function	-2707.44	-2667.36	-2663.62	-2662.64

Notes

Heteroskedasticity modelled by $\theta_i = \sigma \exp(\alpha R_i)$
BHHH Standard errors in parentheses.
** Significant at the 1% level.
* Significant at the 5% level.

Table (4): Determinants of investment in discovery at the PROGRAM level.
Heteroskedastic TOBIT Regression.
Dependent variable = Investment in discovery, 2707 observations.

	(1)	(2)	(3)	(4)
Intercept	-1.263 (1.525)	-2.272* (1.168)	-2.162* (1.184)	-2.008 (1.182)
Flow of Investment in Discovery$_{(t-1)}$		1.175** (0.025)	1.175** (0.025)	1.175** (0.025)
Stock of Investment in Discovery$_{(t-1)}$		0.012 (0.007)	0.012 (0.007)	0.012 (0.007)
"News" in patents in this class$_{(t-1)}$		0.0004 (0.011)	-0.001 (0.011)	-0.001 (0.011)
Own sales in this class$_{(t)}$		0.001** (0.0003)	0.001** (0.0003)	0.001** (0.0003)
News in key papers in this class$_{(t-1)}$			0.012 (0.007)	0.012 (0.007)
Flow of Competitors' Investment in discovery in this class$_{(t)}$	0.028** (0.004)	0.0025 (0.0027)	0.0028 (0.0027)	
Flow of Competitors' Investment in discovery in this class$_{(t-1)}$				0.0012 (0.0029)
Class dummies	Sig.	Sig.	Sig.	Sig.
Firm dummies	Sig.	Sig.	Sig.	Sig.
Time	0.016 (0.140)	0.109 (0.107)	0.095 (0.109)	0.089 (0.109)
Time * Time	-0.003 (0.003)	-0.002 (0.003)	-0.002 (0.003)	-0.002 (0.003)
Coefficient on Lagged Discovery in variance model	0.279** (0.008)	0.151** (0.005)	0.151** (0.005)	0.151** (0.005)
Sigma	1.1363** (0.023)	0.843** (0.011)	0.843** (0.011)	0.843** (0.011)
Log likelihood function	-3574.47	-2663.20	-2662.10	-2662.56

Notes

Heteroskedasticity modelled by $\theta_i = \sigma \exp(\alpha R_i)$
BHHH Standard errors in parentheses.
** Significant at the 1% level,
* Significant at the 5% level.

Table (5): Determinants of investment in discovery at the PROGRAM level.
First differences, "News" and residuals.
OLS Regression. 2707 observations.

	(1)	(2)	(3)	(4)	(5)
Dependent Variable	$\Delta Invest_t$	$\Delta Invest_t$	"News" in $Invest_t$	"News" in $Invest_t$	Residual from $Invest_t = f\{..\}$
Intercept	-0.024 (0.805)	-0.013 (0.840)	-0.143 (0.827)	-0.090 (0.845)	-0.0001 (0.018)
Δ $Investment_{(t-1)}$	0.015 (0.057)	0.004 (0.057)			
"News" in own $investment_{(t-1)}$			0.832** (0.034)	0.815** (0.034)	
"News" in own $patents_{(t-1)}$	0.008 (0.011)	0.007 (0.011)	0.008 (0.011)	0.008 (0.011)	
"News" in $papers_{(t-1)}$	0.010 (0.008)	0.005 (0.008)	0.010 (0.008)	0.004 (0.008)	
Δ Competitors' $Investment_{(t-1)}$	0.024* (0.012)	0.020 (0.012)			
News in Competitors' $Investment_{(t-1)}$			0.011* (0.005)	0.007 (0.006)	
Competitors' Residual					-0.002 (0.010)
Firm dummies		Partial Sig.		Partial Sig.	
Class Dummies		Sig.		Sig.	
Time	-0.008 (0.077)	-0.006 (0.080)		0.001 (0.080)	
Time * Time	0.001 (0.001)	0.001 (0.002)		0.000 (0.002)	
R-squared	0.006	0.007	0.627	0.629	0.00002
Standard error of regression	0.986	0.986	0.975	0.973	0.962

Notes

Heteroskedastic-consistent standard errors in parentheses.
** Significant at the 1% level.
* Significant at the 5% level.

Table (6): Determinants of patent output at the PROGRAM level.
Poisson Regression. Dependent variable = PATENTS.

	(1) Full sample 1961-1988	(2) Full sample 1975-1988	(3) Full sample 1975-1988	(4) C.V. Only 1975-1988	(5) C.V. Only 1975-1988
N	4930	2707	2707	438	438
Intercept	-2.257** (0.134)	-0.380 (0.621)	-0.228 (0.625)	2.812* (1.309)	2.420 (1.329)
Ln(Investment)	0.024* (0.010)	-0.014 (0.012)	-0.013 (0.012)	-0.038 (0.026)	-0.044 (0.026)
Ln(Stock of Investment)	0.031** (0.010)	0.036** (0.010)	0.036** (0.011)	0.108** (0.036)	0.107** (0.036)
SCOPE: No. classes firm is active	0.104** (0.016)	-0.012 (0.034)	-0.013 (0.034)	0.037 (0.072)	-0.046 (0.072)
SCOPE * SCOPE	-0.006** (0.001)	-0.001 (0.002)	-0.001 (0.002)	-0.020 (0.003)	-0.016 (0.003)
Ln(SIZE): Total research spending by firm.	0.242** (0.042)	0.201** (0.066)	0.210** (0.067)	0.454** (0.139)	0.469** (0.140)
Stock own pats in this class	0.032** (0.001)	0.033** (0.001)	0.033** (0.001)	0.034** (0.002)	0.034** (0.002)
News in own patents in related classes$_t$	0.034** (0.003)	0.026** (0.005)	0.025** (0.005)	0.028** (0.009)	0.029** (0.009)
News in competitors' patents in this class$_t$	0.006** (0.001)	0.004** (0.001)	0.004** (0.001)	0.017** (0.002)	0.017** (0.002)
News in competitors' patents in related classes$_t$	0.002** (0.001)	0.003** (0.001)	0.003** (0.001)	-0.002 (0.001)	-0.002 (0.001)
News in Key papers$_{(t-1)}$			0.013** (0.005)		
Key private sector C.V. papers$_t$					0.464** (0.167)
Key private sector C.V. papers$_{t-1}$					-0.154 (0.419)
Firm dummies	Sig.	Sig.	Sig.	Sig.	Sig.
Class dummies	Sig.	Sig.	Sig.		
Time	0.071** (0.008)	-0.040 (0.060)	-0.060 (0.061)	-0.400** (0.128)	-0.364** (0.130)
Time * Time	-0.003** (0.000)	-0.002 (0.001)	-0.000 (0.001)	0.008 (0.003)	0.007 (0.003)
Log-likelihood	-8194.3	-4444.2	-4440.8	-755.7	-752.2

Notes

Standard errors from analytical second derivatives in parentheses.
** Significant at the 1% level.
* Significant at the 5% level.