Racing or Spilling?
The Determinants of Research Productivity in Ethical Drug Discovery

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WP # 3642-93 December 1993

This paper was prepared for the A.E.I. Conference
"Competitive Strategies in the Pharmaceutical Industry"
and is forthcoming in the Conference volume.

This research was funded by four pharmaceutical companies and by the Sloan Foundation. 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 for his outstanding work as our research assistant. The conclusions and opinions expressed in this paper are our own, and any errors or omissions remain entirely our responsibility.

Introduction

In 1971 the members of the Pharmaceutical Manufacturer's association spent about three hundred and sixty million dollars on research and development.[1] In 1991 they spent 8.9 *billion*, an increase of over two thousand three hundred percent. But while industry sales have grown in line with research expenditures, there has been no significant increase in the number of new drugs introduced. Why have costs increased so dramatically? Breakthroughs in pharmaceutical research can lay the groundwork for qualitative improvements in the quality of life and for significant reductions in the cost of health care, but escalating health care costs have focused attention on every aspect of health care expenditure and have led several observers to question this apparent decline in pharmaceutical research productivity. This paper hopes to contribute to this debate by exploring the issue in the context of a broader study of the determinants of research productivity in ethical drug discovery.

We draw upon a detailed data set compiled from the internal records of ten major pharmaceutical firms. The data set allows us to distinguish between research (or "discovery") and development expenditures at a highly disaggregated level. For example within the general class of "cardiovascular therapies" we can observe the distinctions between fields such as hypertension, cardiotonics and blood related conditions. Section I presents some descriptive statistics from the sample. Our sample firms display the long term decline in productivity characteristic of the industry as a whole. Both research and development expenditures have increased dramatically in real terms, while the output of "important" patents has fallen, and the number of drugs discovered has remained approximately constant.

Section II explores the degree to which the escalation in real research costs may reflect a change in the mix of research projects that are being pursued. Real research costs may have increased, for example, if resources have shifted away from "easy" fields towards "more difficult" fields such as oncology (cancer) and gerontology (the study of aging). However the disaggregate data suggest that this effect is probably not very important as a driver of falling productivity. While on average there has been a shift of resources across fields, there is no evidence that this shift has been to fields in which it has been on average more difficult to obtain results.

Sections III and IV explore the degree to which rising real research costs reflect increased competition in the industry. Some economic theory suggests, for example, that an increase in the expected returns to an industry will encourage firms to increase their investment in research in the

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[1] Here and throughout the paper, all amounts are denominated in deflated 1991$.

hope of capturing these returns from their rivals. In the extreme, these theories suggest that private returns in the industry will be driven to nothing as competing firms dissipate all of the available returns by "overinvesting" in research.

This is an important issue for public policy since it highlights the dangers of relying on the "research cost per drug" as a useful measure of research costs. On the one hand, if there is significant over investment in research, so that competing firms are "racing" each other to market by investing in substantially identical research, average research costs per drug per firm substantially *overstate* the actual expenditure required to discover a new drug. On the other hand, if there are significant spillovers between firms and between research projects within the same firm, and if firms do not immediately dissipate anticipated returns through excess investment, then mean research costs substantially *understate* the resources required to discover a new drug.

Unfortunately it is difficult to test these ideas systematically since the theoretical models very quickly become fundamentally indeterminate. As a first step towards a richer understanding of the issue, we focus here on the exploration of the assumptions on which the theoretical literature rests. The rather extreme conclusion that free entry unambiguously leads to over investment in research is crucially dependent upon at least five key assumptions: that entry will occur until marginal private returns have been driven to zero, that there is no spillover of knowledge between firms, that there is total appropriability of consumer surplus, that competing projects are perfect substitutes for each other and that there are no efficiency gains to multi firm competition.

The validity of the last three assumptions are beyond the scope of this paper, but in section III we explore the first through an examination of the dynamics of investment behavior. Following methodology pioneered by Scherer (1992) and Meron and Caves (1991), we distinguish between a "leader," "core followers" and "fringe" firms. We find some weak evidence that core followers invest in response to investment by the leading firm, while fringe firms reduce the investments in research as follower firms increase their research expenditures. However these effects are only marginally significant, and of very small magnitude. Our results suggest that by far the most important determinant of this year's research spending is last year's spending: a finding consistent with a world in which investment decisions are driven much more by heterogeneous firm capabilities, adjustment costs and scientific opportunity than by strategic interactions. We interpret this as suggesting that while firms may respond strategically to each other, these reactions are probably not sufficiently important to drive marginal private returns to zero. In section IV we investigate the nature of spillovers in the industry through a study of the determinants of the output of important patents. Our

results are consistent with the presence of substantial spillovers, both within and across firms, suggesting that the entry of additional firms into the R&D "race" is not unequivocally welfare destroying.

Section V presents our conclusions and explores their implication for the formulation of public policy. Our results suggest that the apparent decline in industry's long term productivity is probably a function of escalating real research costs. There is no evidence of a shift from "easier" to more "difficult" classes, or of an increase in racing behavior across firms. However our research highlights the complexity of pharmaceutical research. In the absence of good measures of the returns to innovation in the industry we cannot know whether there is, on average, "too much" spent on R&D, but our results suggest that while the pharmaceutical industry is sometimes held up as a textbook example of dissipative racing behavior in research and development competition, the reality is probably considerably more involved. On the one hand we find some evidence consistent with the kinds of correlated patterns of investment at the research program level which we would expect to see if R&D spending decisions were dominated by strategic interaction of the kind captured by game-theoretic models. On the other, we find evidence consistent with significant R&D project complementarities and other spillover benefits across firms, suggesting that correlated investment strategies may create significant externalities. While our results must be interpreted with care, they suggest that the simple characterization of the costs of R&D by an average "dollars per drug" figure is almost certainly incorrect.

I. Long Term Trends in Industry Productivity

Figure (1) plots average spending on research and development by the firms in our sample from 1965 to 1990. (Appendix (1) describes the construction of the data set in detail.) While research spending has increased in real terms, the lion's share of the increase in pharmaceutical research costs is a function of the accelerating cost of clinical development. Figure (2) plots research and development spending as share of sales: while research expenditures are increasing roughly in line with sales, development expenditures have far outstripped them.

Figure (3) plots average outputs per dollar from 1965 to 1990. The number of "important" patents granted to the mean firm in our sample has fallen dramatically.[2] This mirrors trends observed

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[2] We define "important" patents as those granted in two of the three major world markets: the U.S., Japan and the European community.

FIGURE (1)

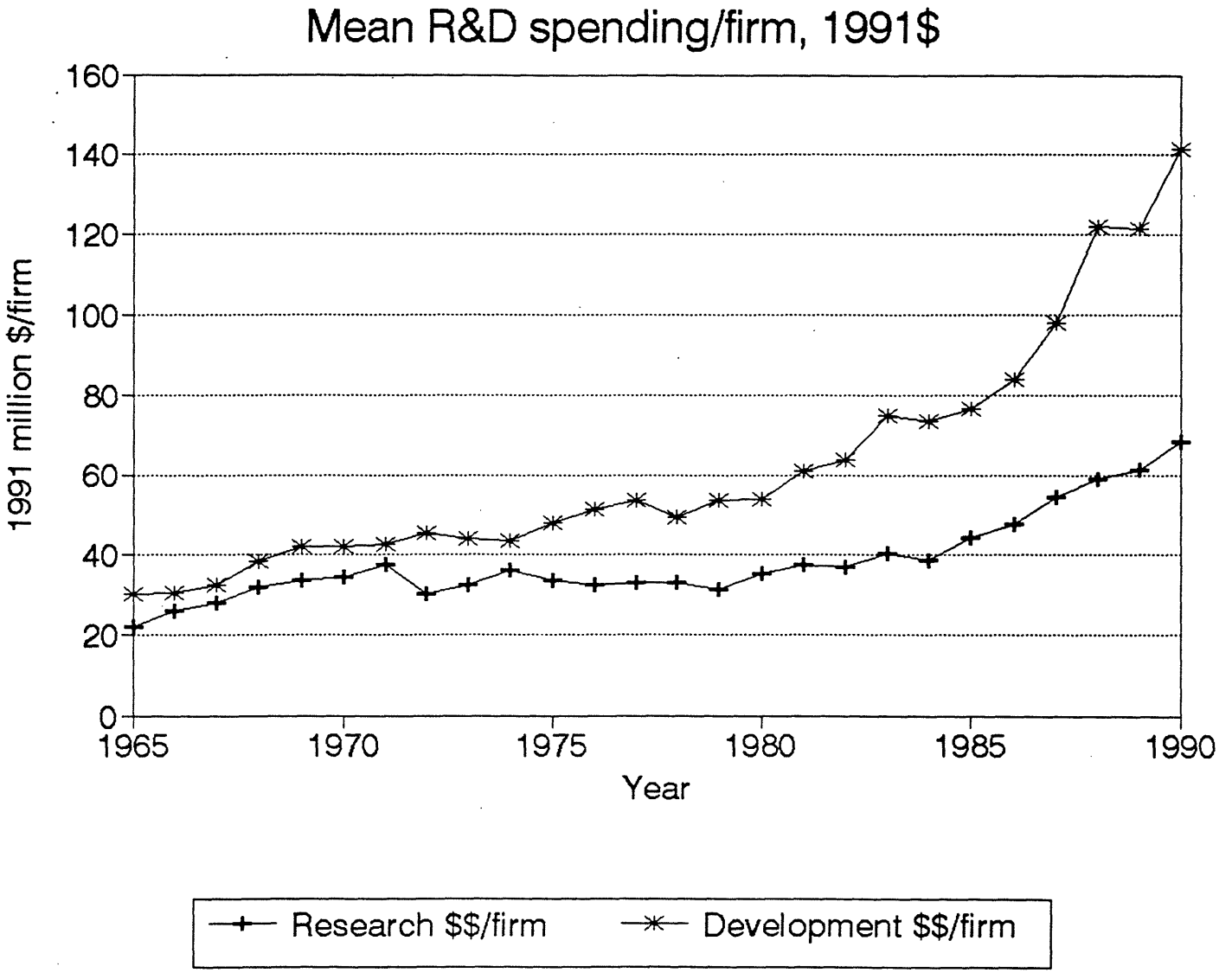

Mean R&D spending/firm, 1991$
1991 million $/firm
160
140
120
100
80
60
40
20
0
1965
1970
1975
1980
1985
1990
Year
Research $$/firm
Development $$/firm

FIGURE (2)

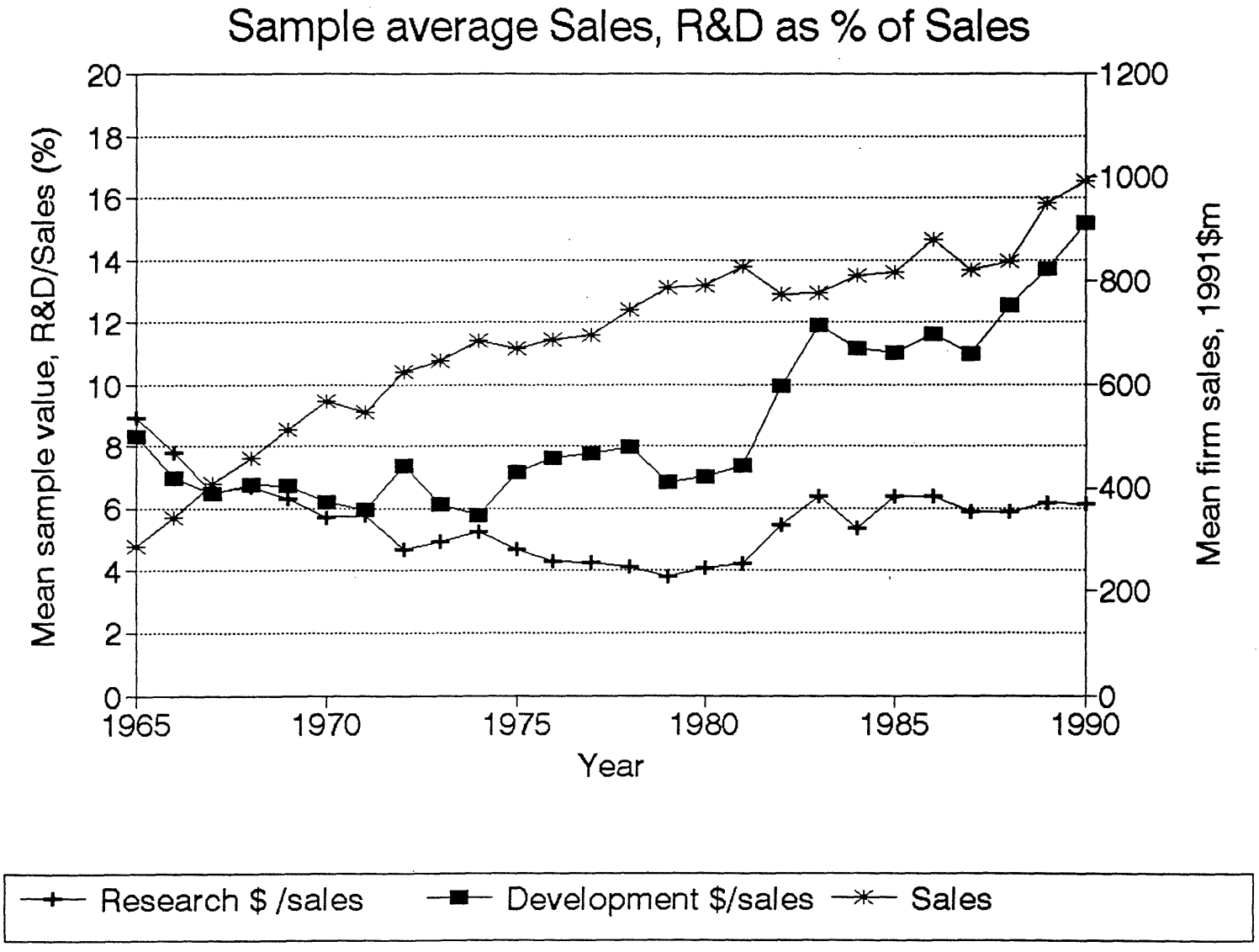
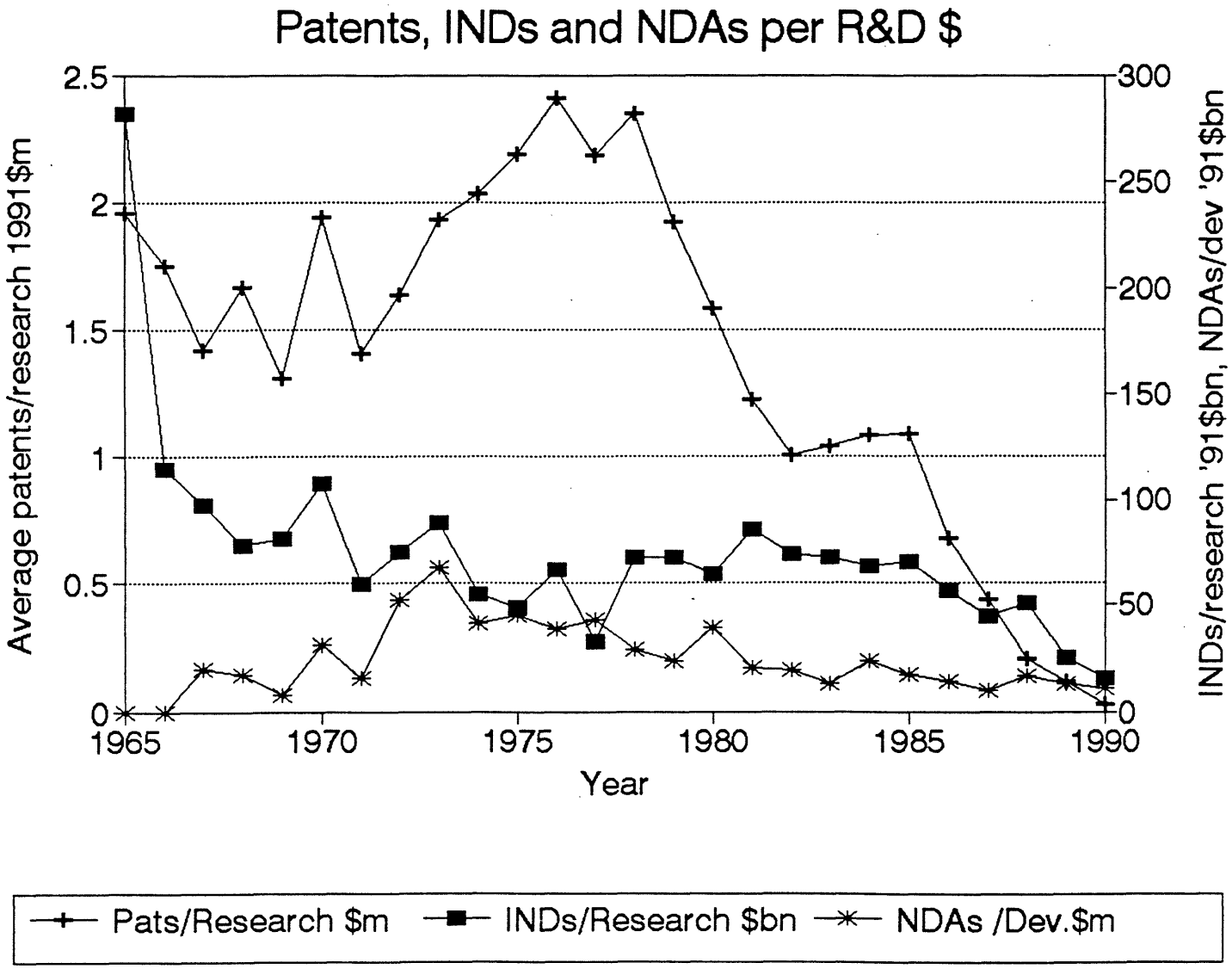

Sample average Sales, R&D as % of Sales
Mean sample value, R&D/Sales (%)
Mean firm sales, 1991$m
Year
0
2
4
6
8
10
12
14
16
18
20
0
200
400
600
800
1000
1200
1965
1970
1975
1980
1985
1990
Research $ /sales
Development $/sales
Sales

FIGURE (3)


Patents, INDs and NDAs per R&D $
Average patents/research 1991$m
INDs/research '91$bn, NDAs/dev '91$bn
2.5
2
1.5
1
0.5
0
300
250
200
150
100
50
0
1965
1970
1975
1980
1985
1990
Year
Pats/Research $m
INDs/Research $bn
NDAs /Dev.$m

for the economy as a whole, but while the number of patents granted by the U.S. patenting office to U.S. firms fell in every industry in the seventies, a number of the firms in our sample are European, and the decline in patenting rates by our sample firms is significantly greater than this more general trend (Griliches, 1990).[3]

On average, the number of INDs (Investigational new Drug Applications) and NDAs (New Drug Applications) obtained for each dollar invested in research and development by the firms in our sample has steadily declined.[4] This trend must be interpreted with caution since it can take more than ten years to file an NDA once an IND has been granted, and thus it is possible that the acceleration in development spending that we observe in the late 1980s will be followed by an outpouring of NDAs over the next decade. In general, however, our data are in line with the aggregate statistics in suggesting that increases in spending on R&D have not been accompanied by a proportionate increase in the easily tracked measures of output: patents, INDs and NDAs.

II. Heterogeneity Across Therapeutic Classes

Wiggins (1979) first demonstrated the importance of distinguishing between therapeutic classes in modeling the determinants of productivity in the industry, and Table (1) begins the process of pulling apart the aggregate numbers to reveal the heterogeneity of pharmaceutical research. It shows the ratio of cumulative outputs to cumulative inputs by therapeutic class for the years 1975-1990. These numbers must be approached with caution, since they are subject to both left and right censoring.[5] However they illustrate the variety that is hidden by aggregating the data. The number of important patents obtained per million dollars invested in research, for example, varies from a high of 2.6 in dermatology to a low of .2 in anti-infectives. Similarly the ratio of INDs obtained per billion

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[3] The very low patenting rates for 1988-1990 may reflect two complicating factors. These data were obtained from Derwent publications in 1991. On average patents are granted two years after they are applied for. We graph number of patents granted by year of application, so there may well be patent applications still outstanding for these years. Once granted, each patent must be classified by Derwent. This process is not instantaneous, and may lead to further under counting in recent years.

[4] In order to test a drug in humans in the United States, firms must fail an "IND" - an "Investigational New Drug Application." If clinical trials are completed successfully, the firm then files an "NDA" - a "New Drug Application." We count only INDs for original indications.

[5] It is certainly the case, for example, that some of the discovery and development spent over this period has yet to yield fruit, and that some of the output results from investment made before 1975.

dollars varies from 25 for anti-infectives to 81 for dermatology, and the ratio of NDAs to cumulative R&D spending varies from a low of 6 per billion in musculo-skeletal research to a high of 34 per billion in dermatology.

These variations translate into significant differences in the average "cost per drug" in each class. Making the very crude assumption, for example, that investment in each program is constant across the sixteen year period, and that the time value of money is 9%, these differences translate into an approximate "cost per NDA" of over three hundred and seventy million dollars for a musculo-skeletal NDA, of around two hundred million dollars for a cardiovascular NDA and of around sixty six million for an NDA in dermatology.[6]

Thus differences in costs across therapeutic classes are one possible explanation for the apparent decline in industry research productivity. If firms have shifted resources away from "easy" fields such as dermatology towards "hard" fields such as anti infectives, then research costs would rise and output would fall solely as a result of a change in portfolio composition. Figures (4) and (5) explore this issue. Figure (4) graphs mean share of the research portfolio by therapeutic class over time, while figure (5) graphs mean share of the development portfolio. Both graphs suggest that it is very unlikely that increases in research costs are driven by shifts in portfolio composition. In general, investment in research has been characterized by a switch away from anti-infectives towards cardiovascular drugs. From the results of table (1) this shift should have *increased* research productivity, all other things equal! In development the firms in our sample have been shifting out of central nervous system research towards work in cardiovasculars while the share of resources devoted to anti-infective work has remained more or less constant. Again, the summary statistics of table (1) suggest that this shift should have left research productivity approximately unchanged, all other things equal.

Thus although research productivity differs systematically across therapeutic classes, there is little evidence to suggest that shifts between classes is at the root of the long term "decline" in the productivity of pharmaceutical research and development. We thus turn next to an exploration of the dynamics of investment behavior and of differences in firm productivity as a source of insight into changes in industry productivity.

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[6] These numbers are reassuringly in line with those calculated by Di Masi et. al (1991). Note, however, that they are very approximate and indicate no more than an "order of magnitude". The Di Masi study uses a much more sophisticated methodology and more detailed project data to calculate the "cost per drug."

FIGURE (4)

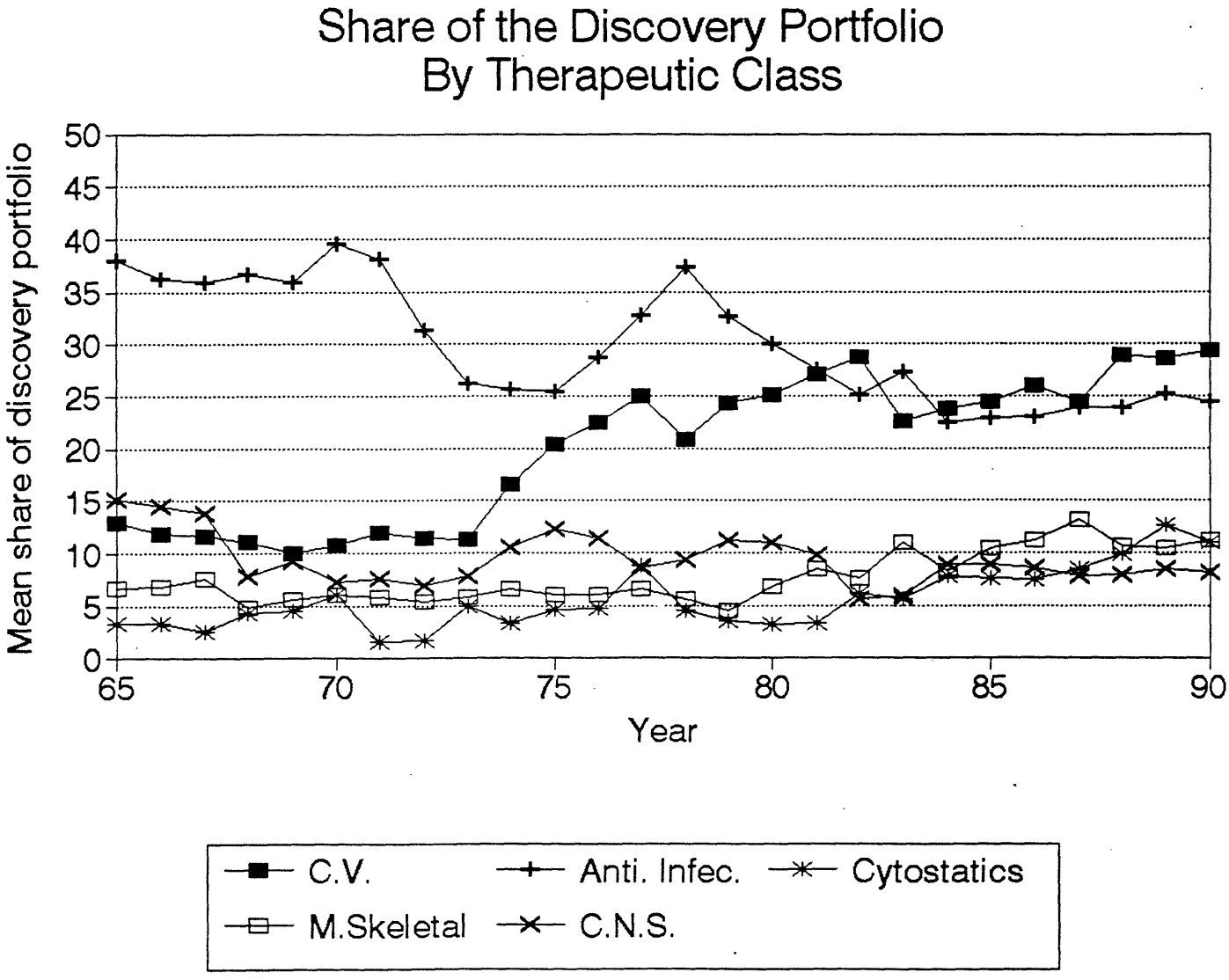
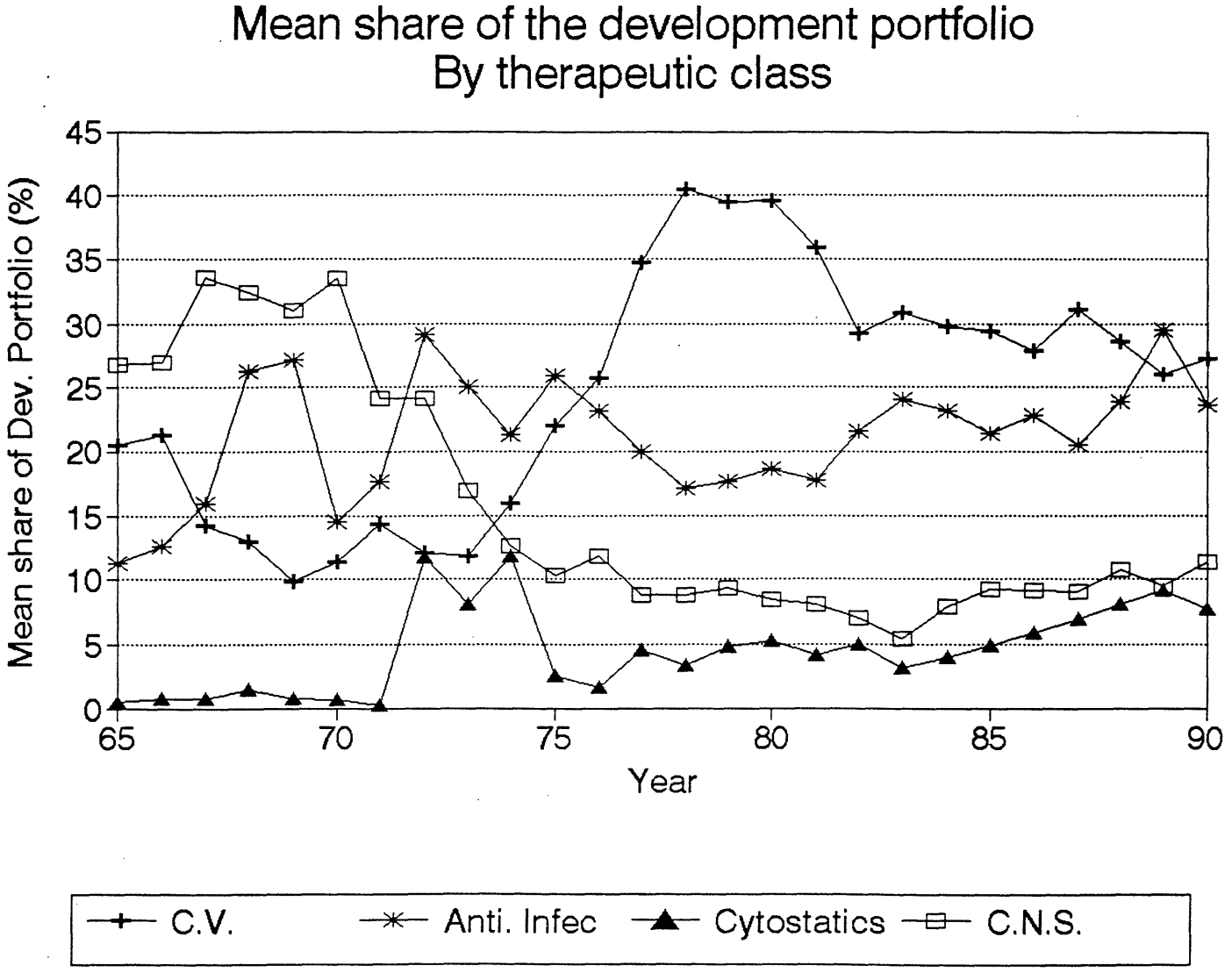

Share of the Discovery Portfolio
By Therapeutic Class
Mean share of discovery portfolio
50
45
40
35
30
25
20
15
10
5
0
65
70
75
80
85
90
Year
C.V.
Anti. Infec.
Cytostatics
M.Skeletal
C.N.S.

FIGURE (5)


Mean share of the development portfolio
By therapeutic class
Mean share of Dev. Portfolio (%)
45
40
35
30
25
20
15
10
5
0
65
70
75
80
85
90
Year
C.V.
Anti. Infec
Cytostatics
C.N.S.

III. Overinvestment in Research? The Dynamics of Investment Behavior.

Escalating real industry research costs may reflect increasing competition and "overinvestment" in research. The theoretical literature exploring the relationship between competitive dynamics and investment strategy is both voluminous and inconclusive, but many of the models raise the concern that free entry into R&D competition will result in over-investment relative to both the private and social optima. Intuitively, these results are driven by the assumption that in deciding to invest in research, firms consider only their own marginal returns, 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, 1980, Loury, 1979, and Reinganum 1982,1989.)

Unfortunately it is difficult to test these ideas. Models that attempt to incorporate all of the relevant variables quickly become dauntingly complex, and we have, as yet, no general results about the relationship between market structure, scientific or technological regime and the relationship between realized and optimal levels of research investment (Baldwin and Scott (1987), Harris and Vickers, 1987; Reinganum (1989)).

However the literature highlights several factors that determine whether the entry of an additional firm into the research "race" will raise or lower social welfare. For example, one can show that in markets characterized by perfectly competitive behavior, complete appropriability, and research projects that are perfect substitutes for each other, there will be considerable over investment in research (Dasgupta and Stiglitz, 1980b). Conversely, in industries characterized by weak appropriability, where investment in research is more cooperative than competitive and in which research projects are largely complements, there is likely to be under investment relative to the social optimum (D'Aspremont and Jacquemin, 1988, 1990; Dasgupta and Maskin, 1987; Fraja, 1993; Suzumura, 1992).

Since theoretical models that attempt to model the interaction between all of these factors simultaneously quickly become intractable, we instead explore the validity of two of the core assumptions on which the models of rent dissipation rely: firstly that under free entry firms will respond strategically to each other, and will invest in research until marginal returns to zero and secondly that there are no spillovers of knowledge either across projects within the firm or between firms. A more complete discussion of the theoretical issues involved and of the relationship between our research and the existing literature is given in our paper "Racing to Invest: The Dynamics of Competition in Ethical Drug Discovery."

In general the literature suggests that two plausible types of investment behavior are consistent with dissipating behavior. On the one hand Reinganum (1982) presents a model in which symmetric oliogopolistic firms "race" for a well defined prize. Under these conditions reaction functions are upward sloping, and marginal increases in spending by one firm are met by increased spending by its rivals. On the other hand Harris and Vickers (1987) develop a model of rivalry between asymmetric firms in which increased spending by the "leader" evokes a submissive response by "followers."

This distinction builds on earlier work by Scherer (1967), and is confirmed by previous empirical work. 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. Caves and Meron (1992) 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.

Tables (2) (3) and (4) present our analysis of the investment dynamics that characterize our sample. Table (2) shows results from regressing investment onto control variables suggested by the qualitative analysis. These include: the stock of research, which is intended to capture, among other things, unobserved differences in the "quality" of the program; firm and therapeutic class dummies; a time trend, and variables intended to capture shocks to scientific opportunity - "news" in own patents and in important papers. "News" is defined as the excess of the current year's flow over the amount necessary to maintain the stock, given a depreciation rate δ:

$$News_t = Flow_t - \delta Stock_t$$

This formulation is intended to capture activity in excess of "normal" levels.[7] Of all the control variables, only news in patents is significant.

We use three specifications for the dependent variable. In model (1) the dependent variable is just the level of research spending, and the explanatory variables include lagged research, included to capture the adjustment costs. This variable dominates the regression, and its coefficient is

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[7] Experimentation with various combinations of lags, depreciation rates etc. added little to our analysis.

indistinguishable from 1. In model (2) we constrain it to be 1 by using the first difference of R as the dependent variable. A lagged difference of R is included in this specification but is insignificant. Model (3) uses a "news" version of R, and lagged news on the right hand side. Lagged news is strongly significant, suggesting that changes in research strategy are correlated from year to year.

Table (3) introduces competitors' expenditures into the regression in order to test for the presence of strategic interactions.[8] Model (3) is reproduced from Table (2) for purposes of comparison. Model (4) tests the hypothesis that every firm responds to every other firm by including "news in competitors' research" as an independent variable. It is insignificant. Model (5) tests the hypotheses that the leading firm responds only to core followers, while core followers respond both to each other and to the leading firm, and fringe firms respond both to the leader and to the core followers.[9] All of the coefficients except that of the leader's response to the core followers have the expected sign, but only one is significant: fringe firms appear to react submissively to investment by core followers. Moreover the standard test for the significance of additional variables cannot reject the hypothesis that competitive spending adds no additional explanatory power to either model (4) or model (5). While interpretation of this result must be tempered by the fact that our firms together comprise only about twenty eight percent of the industry, it provides only very limited support for the presence of strategic interactions amongst firms.

Table (4) tests for the idea that "racing" behavior may have increased over time, even if it is not significantly present in the sample as a whole. Model (7) is run using the data for the period 1961 to 1974, while model (8) tests for the significance of competitive investment in the period 1975 to 1988.[10] Competitive investment is insignificant in both specifications and a Chow test cannot reject the hypothesis that the there is no difference in the dynamics of the two periods.

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[8] Obviously there is potential simultaneity between competitors' and own research investments. However plausible instruments are hard to find. Rather than use weak instruments, we simply present the ordinary least squared results here. We are actively pursuing this issue in our research.

[9] One firm in our sample consistently spent more on discovery research than all of the others. Following Caves and Meron (1992) we defined this firm as the "leader." Firms that consistently invested more than 30% of the leader's investment were defined as "core followers." Firms that spent less were defined as "fringe firms." There are three fringe firms and six core followers in the data set.

[10] The results of table (4) rely on a more limited set of explanatory variables than those of table (3) since we do not have data for "key papers" before 1975, and the fringe firms in our data set appear relatively late.

Thus we find only very limited evidence of strategic interaction in investment behavior. Moreover the magnitude of these reactions is very small: together, in the most successful specification they add only 0.1% to the explanatory power of the regression, and our results suggest that the overwhelmingly most important determinant of this period's investment is last period's investment.

These results are consistent with our qualitative findings. Highly trained personnel are expensive to hire and to let go, and dramatic increases in the size of a program are unlikely to lead to equally dramatic increases in its productivity.[11] Discovery research is a highly uncertain process, and our quantitative finding that investments are highly serially correlated is consistent with a world in which investment decisions are driven by heterogeneous firm capabilities, by adjustment costs, and by the evolution of scientific opportunity.

IV. Spillovers and Research Productivity.

In an industry characterized by straightforward duplicative "racing" behavior, one firm's success is another's loss since each firm invests in identical research programs and there are no spillovers of knowledge across firms. However if there are significant spillovers of knowledge across firms, research productivity may be correlated with competitive investment, and additional entry into the R&D "race" may be welfare enhancing.

We test for the presence of spillovers in our data by regressing important patents onto a variety of control variables and a set of measures designed to capture competitive activity in the field. These equations can be usefully thought of as a production function for "important patents" in which competitors' research successes enter as inputs to each other's R&D.

Table (5) presents our results. Models (9) and (10) use our full sample. Model (9) suggests that own output and the success of rival firm's efforts are positively and strongly significantly correlated. 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.[12] However this model fails to control for changes in scientific opportunity, raising the possibility that the observed correlations across firms merely reflect exogenous shifts in opportunity that make it easier to obtain patents in any given class. Model (10) includes "Key Papers" as a measure of

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[11] There is no evidence of increasing returns to scale in our data (Henderson and Cockburn, 1993).

[12] These results are not reported here.

scientific opportunity. There is no significant correlation between these measures and own output, and important competitive patents remain a significant predictor of own patents. (An alternative measure of opportunity, "cites to key papers" performed very similarly.) Models (11) and (12) repeat these analyses using cardiovascular data alone, where model (12) makes use of the more detailed measures of scientific opportunity.[13] Patent output is not significantly correlated with key papers in the public sector, suggesting that major shifts in the stock of public knowledge are not immediately translated into patents, but it is significantly correlated with the flow of key papers published by private sector individuals. Nonetheless, controlling for this effect strengthens the correlation between own research productivity and competitors' output.

Thus our results are consistent with the idea that there are significant spillovers of knowledge across firms. Important patents per discovery dollar are likely to be significantly higher if competitors have recently obtained a number of important patents in the area, and far from leading to a "mining out" of opportunities, competitors' research appears to be a complementary activity to own R&D. Thus the entry of additional firms into a therapeutic area may be welfare enhancing.

This result must be qualified by the observation that not all patents are equally important. If, for example, a major discovery in an area makes it easier to obtain patents in the area, and if this effect is not fully captured in our measures of scientific opportunity, then correlation in output across firms may reflect no more than the generation of "me too" patents for "me too" drugs. Two factors moderate this problem. The first is that so called "me too" drugs may offer important additional therapeutic benefits such as reductions in side effects or improved efficacy with different segments of the population. The second is our finding that output is positively associated with competitive *investment* as well as with competitive *output*, suggesting that we are capturing the effect of genuine spillovers of knowledge.

V. Conclusions

Over the last twenty years the pharmaceutical industry appears to have suffered a dramatic decline in productivity. This paper used disaggregated data at the research program level to explore

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[13] We used secondary sources and consultation with industry experts to identify those papers that had a seminal influence on the field and that represented an order of magnitude change in scientific opportunity. We divided these papers into two classes: those for which a majority of the authors were employed in the public sector: "Key Public papers" and those for which a majority of the authors were employed in the private sector: "Key Private papers."

this decline in the context of the drivers of productivity in drug discovery. Our results suggest that it is probably not a function of either a shift to research in "more difficult" areas or of an increase in "racing" behavior in the industry. Rather our results are consistent with the hypothesis that rising real research costs in the industry reflect decreasing returns. The switch to more science intensive methods of drug research appears to be a major contributor to increasing costs, but the most important driver of cost escalation appears to be the rocketing costs of clinical drug development. We speculate that this probably reflects both a shift to the treatment of conditions that require more complex clinical trials and increasing regulatory stringency, but we have no data about this issue.[14]

In general our results must be interpreted with caution. Our analysis of investment behavior and spillover effects applies only to competition in research, or drug discovery: we plan to explore the determinants of productivity in development in later work. Moreover the validity of our spillover analysis is crucially dependent on our use of important patents as a measure of output. We plan to extend our analysis through the use of alternate measures of output. We also hope to enrich our understanding of the ways in which the dynamics of the industry have evolved over time.

These results have potentially important implications for public policy. Most importantly, they suggest that the presence of several competitors in any given area may increase social welfare. While it may be tempting to think that one could "rationalize" the amount of research and development conducted by the industry, or to set prices on the basis of the research expenditures of a single firm, our analysis suggests that it may be dangerous to think of research costs in terms of some measure of "dollars per drug" deduced from the spending of any single firm. A reduction in the number of firms conducting research in any given area may have significant negative externalities, if R&D spending complements, rather than substitutes for rivals' investment. Intuitively the "true" cost of a drug may include the costs of those programs in rival firms that apparently "failed" but that contributed to the industry's common pool of knowledge by spilling information across the boundaries of the firm.

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[14] The decline in measured productivity may also reflect inadequate measures of output. The move to more "rational" drug design, for example, may have resulted in the introduction of drugs that were more expensive to discover but that have more valuable therapeutic effects.

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Table (1) Cumulative outputs over cumulative inputs, by class, 1975-1990

CLASS	Patents/ Research $m	Inds/ Research $bn	NDAs/ R&D $bn
Alimentary	1.7	34	13
Blood	0.8	32	8
Cardio.Vascular	1.0	41	11
Dermatology	2.6	81	34
Anti.infective	0.2	25	13
Hormones	1.9	96	16
Cytostatics	0.6	61	25
Musculo Skeletal	1.1	36	6
C.N.S.	1.6	49	14
Respiratory	1.7	43	9
Sensory Organs	1.1	38	32

Table (2): Determinants of investment in research at the program level. OLS Regression. Dependent variable = Investment in discovery. 4597 observations.

	(1)	(2)	(3)
Dependent variable	$Research_t$	Δ $Research_t$	"News" in $research_t$
Intercept	0.174** (0.072)	0.197** (0.075)	0.174** (0.072)
$Research_{(t-1)}$	0.984** (0.034)		
Δ $Research_{(t-1)}$		0.008 (0.049)	
"News" in $research_{(t-1)}$			0.824** (0.034)
Research $stock_{(t-1)}$	0.000 (0.012)	-0.004 (0.006)	0.005 (0.006)
"News" in $patents_{(t-1)}$	0.013* (0.008)	0.013* (0.008)	0.013* (0.008)
"News" in key $papers_{(t-1)}$	0.003 (0.007)	0.004 (0.007)	0.003 (0.007)
Class dummies	Sig.	Sig.	Sig.
Firm dummies	Partial Sig.	Partial Sig.	Partial Sig.
Time	-0.020** (0.007)	-0.021** (0.007)	-0.020** (0.006)
Time * Time	0.001** (0.000)	0.001** (0.000)	0.001** (0.000)
Adjusted R-squared	0.879	0.007	0.648

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

Table (3): Determinants of investment in research at the program level. O.L.S. Regression. Dependent variable = "News" in research

	(3)	(4)	(5)
N	4597	4597	4115
Intercept	0.174** (0.072)	0.148* (0.072)	0.145* (0.084)
"News" in research$_{(t-1)}$	0.824** (0.034)	0.825** (0.034)	0.825** (0.036)
"News" in competitors' research$_{(t-1)}$		0.006 (0.006)	
Leader * News in core followers' research$_{(t-1)}$			-0.007 (0.016)
Follower * News in core leaders' research$_{(t-1)}$			0.026 (0.019)
Follower * News in core followers' research$_{(t-1)}$			0.004 (0.009)
Fringe firm * News in core leaders' research$_{(t-1)}$			-0.003 (0.017)
Fringe firm * News in core followers' research$_{(t-1)}$			-0.010* (0.006)
Research stock$_{(t-1)}$	0.005 (0.006)	0.004 (0.007)	0.005 (0.007)
"News" in patents$_{(t-1)}$	0.013* (0.008)	0.012 (0.007)	0.012 (0.008)
"News" in key papers$_{(t-1)}$	0.003 (0.007)	0.004 (0.007)	-0.006 (0.011)
Class dummies	Sig.	Sig.	Sig.
Firm dummies	Partial Sig.	Partial Sig.	Partial Sig.
Time	-0.020** (0.006)	-0.019** (0.007)	-0.018** (0.008)
Time * Time	0.001** (0.000)	0.001** (0.000)	0.001** (0.000)
Adjusted R-squared	0.648	0.649	0.645
Sum of Squared Residuals	3029.1	3026.8	2868.7

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

Table (4): Determinants of investment in research at the program level. Comparing competitive dynamics pre and post 1975. O.L.S. Regression. Dependent variable = "News" in research

	(6)	(7)	(8)
Sample	1961-1988	1961-1974	1975-1988
N	4170	1360	2810
Intercept	0.131* (0.071)	0.091 (0.086)	-0.220 (0.622)
"News" in research$_{(t-1)}$	0.825** (0.036)	0.744** (0.056)	0.827** (0.039)
Leader * News in core followers' research$_{(t-1)}$	-0.005 (0.016)	0.010 (0.035)	-0.012 (0.017)
Follower * News in core leaders' research$_{(t-1)}$	0.028 (0.019)	0.056 (0.040)	0.029 (0.021)
Follower * News in core followers' research$_{(t-1)}$	0.006 (0.016)	-0.016 (0.022)	0.007 (0.010)
Research stock$_{(t-1)}$	0.005 (0.007)	0.029** (0.013)	0.003 (0.008)
"News" in patents$_{(t-1)}$	0.012 (0.008)	0.018* (0.011)	0.007 (0.010)
Class dummies	Sig.	Sig.	Sig.
Firm dummies	Partial Sig.	Insig.	Partial Sig.
Time	-0.017* (0.008)	-0.010 (0.019)	0.011 (0.060)
Time * Time	0.001** (0.000)	0.001 (0.001)	0.000 (0.001)
Adjusted R-squared	0.646	0.701	0.639
Sum of Squared Residuals	2874.6	296.3	2554.1

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

Table (5): Determinants of patent output at the research program level. Poisson Regression. Dependent variable = PATENTS.

	Full Sample (9)	Full Sample (10)	C.V. only (11)	C.V. only (12)
N	4879	4879	491	491
Intercept	-2.807** (0.149)	-3.114** (0.158)	-1.651** (0.269)	-1.359** (0.344)
Ln(Discovery)	0.030** (0.010)	0.026** (0.010)	-0.026 (0.023)	-0.009 (0.030)
Ln(Stock of Discovery)	0.035** (0.009)	0.040** (0.009)	0.121** (0.029)	0.068 (0.035)
SCOPE: No. classes firm is active	0.105** (0.016)	0.123** (0.016)	0.107** (0.038)	0.112** (0.040)
SCOPE * SCOPE	-0.006** (0.001)	-0.007** (0.001)	-0.006** (0.001)	-0.005** (0.002)
Ln(SIZE): Total disc. spending by firm.	0.244** (0.042)	0.283** (0.043)	0.223* (0.093)	0.229* (0.104)
Stock own pats in this class	0.032** (0.001)	0.031** (0.001)	0.038** (0.002)	0.037** (0.002)
News in patents in related classes	0.033** (0.003)	0.032** (0.003)	0.053** (0.007)	0.061** (0.007)
News in competitors' patents in this class	0.007** (0.001)	0.006** (0.001)	0.018** (0.001)	0.010** (0.002)
News in competitors' patents in related classes	0.002** (0.000)	0.002** (0.001)	-0.003** (0.001)	0.002 (0.001)
Key papers$_t$		-0.002 (0.005)		
Key papers$_{t-1}$		0.011 (0.001)		
Key papers$_{t-2}$		-0.003 (0.005)		
Key public sector C.V. papers$_t$				-0.055 (0.164)
Key public sector C.V. papers$_{t-1}$				0.006 (0.161)

Key public sector C.V. papers$_{t-2}$				-0.145 (0.136)
Key private C.V. papers$_t$				0.286** (0.105)
Key private C.V. papers$_{t-1}$				0.074 (0.098)
Key private C.V. papers$_{t-2}$				0.135 (0.097)
Firm dummies	Sig.	Sig.		Sig.
Class dummies	Sig.	Sig.		Ommit.
Time	0.069** (0.010)	0.078** (0.009)		-0.017 (0.025)
Time * Time	-0.003** (0.001)	-0.003** (0.000)		-0.001 (0.001)
Log-likelihood	-8026.9	-7595.4	-1347	-977.1

Standard errors in parentheses. ln(variable) is set=0 when variable=0, and an appropriately coded dummy variable is included in the regression. The omitted therapeutic class dummy is class60, systemic anti-infectives.

** Significant at the 1% level.
* Significant at the 5% level.

Appendix One: Sources and Construction of Quantitative Data

This research relies on a data set obtained as part of a larger study of research productivity in the pharmaceutical industry. It draws upon data about spending and output at the *research program level* obtained from the internal records of ten pharmaceutical firms. We were able to obtain data about every program in which these firms invested for a period of up to thirty years - a total of more than one hundred and eighty programs. Although for reasons of confidentiality we cannot describe specifics of 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 28% of U.S. R&D and sales, and we believe that they are not markedly unrepresentative of the industry in terms of size, or of either technical or commercial performance.

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 discovery 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.

Outputs

In this paper we focus on 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.) In further work we intend to repeat the analysis using a "cut" by mechanism. 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, or chronic conditions with acute conditions.

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 (trend is driven by demographics), nor are they 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 scientific 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" (Gilman, A., Rall. W., Nies A.S and Taylor Palmer, 1990, MacMillan), or accounts that focused particular on cardiovascular therapies, including texts such as Hamer, (1986), Schneeweiss (1986) and Morganroth and Moore (1981), 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. We then cross checked our results with experts in the field.

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.
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.