

# THE TRUTH ABOUT DRUG INNOVATION: Thirty-Five Summary Case Histories On Private Sector Contributions To Pharmaceutical Science

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The increasingly important role of prescription medicines as both complements to and substitutes for other medical procedures, as well as rising costs for newer and more effective medicines, has precipitated an array of proposals for reducing private and public spending on drugs. Some prominent observers have questioned whether the current system of research and development is as cost-effective as alternatives might be, and, in particular, whether the central role of private pharmaceutical firms in drug research and development produces commensurate social benefits.

One contention that recently has attracted considerable attention can be summarized as follows: most of the scientific advances that yield new and improved medicines are the fruit of research financed or conducted by public agencies, the National Institutes of Health (NIH) foremost among them, rather than the pharmaceutical companies that produce and market them.

The goal of this study is to test the accuracy of this proposition. To do so, we compiled summary case histories of thirty-five drugs and drug classes (a group of drugs used to treat a given medical condition in similar ways) identified in the scholarly literature as important and/or that were among the most prescribed in 2007. Our conclusions can be described as follows: the literature on the histories of drugs makes it clear that the scientific contributions of the private sector were crucial for the discovery and/or development of virtually all of the thirty-five drugs and drug classes examined in this study. Such scientific advances can be classified as the basic science of biology and disease processes relevant for given medical conditions; the applied science of discovering compounds that treat particular conditions; and the development of compounds with improved clinical (medical) effects, of large-scale manufacturing processes, and the like.

Three examples of advances yielded by private-sector research are, respectively, the discoveries in basic science that led to the development of the modern drugs used to treat serious bacterial infections; the discoveries in applied science yielding drugs used to treat hypertension; and the advances in recombinant genetic science that allowed large-scale production of such drugs as Epogen (used in treatment of anemia).

More generally, among our thirty-five drugs and drug classes, private-sector research was responsible for central advances in basic science for seven, in applied science for thirty-four, and in the development of drugs yielding improved clinical performance or manufacturing processes for twenty-eight. In short, all or almost all of the drugs and drug classes examined in this study would not have been developed—or their development would have been delayed significantly—in the absence of the scientific or technical contributions of the pharmaceutical firms.

Table S1 summarizes these findings, derived from the thirty-five summary case histories presented in this study.

Central Private-Sector Scientific Contributions to Thirty-Five Drugs/Classes	
Scientific Category	Number
Basic Science: Biologic Processes, etc.	7
Applied Science: Compounds Exploiting Targets, etc.	34
Clinical Improvement, Manufacturing Protocols, etc.	28

Scientific research efforts funded, respectively, by the NIH and by pharmaceutical firms occupy very different—but complementary—niches in the process of drug development. Research conducted at government or university laboratories (often funded by the NIH or other agencies) tends to be concentrated in the basic science of disease biology, biochemistry, and disease processes. A major goal of that work is the identification of biologic targets that could

prove susceptible to future drug candidates. Basic research often yields advances that cannot be patented and that often are made long before the subsequent scientific and clinical work that leads to viable new therapies.

The scientific contributions of the private sector have been weighted heavily, though not exclusively, toward the applied science of discovering ways to exploit the findings of basic science. This scientific work can be characterized as the discovery, synthesis, testing, and (often complex) manufacturing of candidate compounds intended to exploit biologic targets for the purpose of curing medical conditions or mitigating their adverse effects.

In short, although basic research occurs in both the public and private sectors, the applied science of drug development and clinical refinement of compounds occurs almost exclusively in the private sector. It is those efforts that ultimately allow new scientific discoveries to be translated into new medicines.

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# CONTENTS

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1	<b>I. Introduction and Central Findings</b>
2	Table 1. Central Private-Sector Scientific Contributions for Thirty-Five Drugs/Classes
5	<b>II. The Process and Cost of Drug Development</b>
7	<b>III. Summary Case Histories for Thirty-Two Drug Classes</b>
9	Table 2. Merged Drug List
23	Table 3. Summary Findings for Thirty-Two Drug Classes
24	<b>IV. Summary Case Histories for Taxol, Epogen, and Gleevec</b>
29	<b>V. Conclusions and Policy Implications</b>
31	<b>References</b>





# THE TRUTH ABOUT DRUG INNOVATION: THIRTY-FIVE SUMMARY CASE HISTORIES ON PRIVATE SECTOR CONTRIBUTIONS TO PHARMACEUTICAL SCIENCE

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## I. INTRODUCTION AND CENTRAL FINDINGS

Rising health-care spending on pharmaceuticals developed and marketed by pharmaceutical companies has drawn increased scrutiny to industry's role in the drug innovation process. Critics allege that companies "free-ride" on public investments in scientific research, without making major scientific contributions themselves.

Specifically, a recent argument that has grown in prominence can be summarized as follows: most of the important scientific advances that yield new and improved medicines do not result from private-sector research, but instead are the fruits of research efforts financed or conducted by public agencies, the National Institutes of Health (NIH) foremost among them.

The central focus of this study is an examination of that argument. We apply the scholarly literature on drugs and drug classes deemed important clinically, combined with data on the most prescribed

medicines in 2007, to construct a list of thirty-seven important drug classes (a group of drugs used to treat a given medical condition in similar ways), among which thirty-two are discussed in the scientific literature in sufficient detail to allow us to develop summary case histories. We explore also the development histories of three specific drugs that have figured prominently in the public discussion of the role of the private sector in drug development. In short, this study examines thirty-five drugs and drug classes in the context of private-sector contributions to the advance of pharmaceutical science.

We find that, for the discovery and/or development of all or virtually all of the thirty-two drug classes discussed in Section III, the scientific contributions of the private sector were crucial; and the same is true for three drugs—Taxol, Epogen, and Gleevec—that have received widespread attention, as discussed in Section IV. All or almost all the drugs discussed below would not have been developed—or, at best, would have been delayed significantly—in the absence of private-sector scientific discoveries.

We can separate the pharmaceutical research and development process, crudely, into three categories: the basic science of discovering biologic targets; the applied science of discovering compounds useful for exploiting those biologic targets; and the science of

discovering compounds with improved characteristics in terms of clinical practice, manufacturing protocols, and the like. Table 1 presents summary data derived from our thirty-five case histories in terms of the respective private research efforts and each of the three categories; the numbers are for the drugs and drug classes in our overall sample of thirty-five for which private-sector research was responsible for some substantial contribution in the respective categories, as indicated in the published literature.

Among our thirty-five summary case histories for drugs and drug classes, the private sector contributed at least seven significant scientific advances in basic science, at least thirty-four in applied science, and at least twenty-eight in terms of improved clinical performance of compounds, manufacturing processes, and the like.<sup>1</sup>

This study does not dispute the importance of publicly funded research. Both NIH-sponsored and private-sector research are crucial for the advance of pharmaceutical science and the development of new and improved medicines. Research conducted at universities and government laboratories, often funded by the NIH or other government agencies, has been an indispensable component of the advance of pharmaceutical science and the development of new medicines. In general, the research conducted or sponsored by the NIH is concentrated in the basic science of disease biology, biochemistry, and disease processes, a major goal of which is the identification of biologic targets that in theory might prove vulnerable to “attack” by drugs yet to be developed.

Often, such work takes decades, cannot be patented, and yields discoveries long in advance of the subsequent scientific and clinical work leading to development of drugs; indeed, it is often difficult to trace the development of a given drug back to a specific set of NIH research grants.<sup>2</sup>

**Table 1. Central Private-Sector Scientific Contributions for Thirty-Five Drugs/Classes**

Scientific Category	Number
Basic Science: Biologic Processes, etc.	7
Applied Science: Compounds Exploiting Targets, etc.	34
Clinical Improvement, Manufacturing Protocols, etc.	28
Source: Derived from analysis presented in Sections III and IV Note: Private research may contribute to more than one category for a given drug/class.	

<sup>1</sup> For basic science, this estimate may understate the private-sector contribution in that the available literature often provides little or no information on the respective historical discoveries of the biologic disease processes and the like. With respect to applied science, we exclude the PDE5 blockers in that the medical action of sildenafil was discovered somewhat by accident, even though accidental discovery is a dominant theme in the history of most scientific inquiry. See the discussion in Section III.

<sup>2</sup> Toole estimates that a 10 percent increase in public investment in basic research ultimately leads to a 6.4 percent increase in the number of new drugs on the market. See Toole, “The Impact of Public Basic Research on Industrial Innovation.”

At the same time, the scientific contributions of the private sector have not been negligible, or limited to a mechanical sorting process through thousands of chemical compounds to find the ones useful for exploiting the research findings funded by the NIH, combined with the implementation of subsequent clinical trials.<sup>3</sup> Instead, the scientific contributions of the private sector also have been crucial, but have been weighted heavily toward the applied science of discovering ways to exploit the findings of basic science in pursuit of treatments and cures for adverse medical conditions.

This scientific work can be characterized as the discovery, synthesis, testing, and (often complex) manufacturing of candidate compounds intended to exploit the targets in order to cure or mitigate the adverse effects of medical conditions. Accordingly, NIH and private research efforts are concentrated in distinct but highly complementary dimensions of the overall research and development process for pharmaceuticals.

Given the interdependence of public and private research efforts, why has this question—the allocation of the credit for the advance of pharmaceutical science—increased in prominence? Pharmaceuticals are

costly to develop and often are expensive for buyers. U.S. spending on prescription medicines has been increasing, as a result of some combination of rising prices, increasing use (in part due to an aging population), and perhaps a shift toward more costly (and effective) medicines.<sup>4</sup> In 2007, over 20 percent of that total spending on drugs was paid out-of-pocket by consumers, while the role of government programs as purchasers of drugs has grown to almost 35 percent of the total.<sup>5</sup>

The visibility of prices and total costs for pharmaceuticals has yielded political pressures and criticism, as the private and public purchasers of drugs have focused more attention upon public policies affecting the cost and availability of prescription drugs.<sup>6</sup> These political pressures are reflected as well in changing perceptions of the pharmaceutical industry both by the public and by observers and commentators; among the latter there has developed a view on the part of some that, to summarize crudely, the prices demanded by drug producers often are greater than the (medical) value of the drugs, or are greater than the contribution by those producers to that value. Part of this argument is the “me-too” premise, to wit, that drug producers invest (or waste) substantial

<sup>3</sup> Marcia Angell characterizes the private-sector scientific contribution as “finding promising drug candidates and then studying their properties in animals and cell cultures ... to see if they will target the Achilles’ heel found by the basic research.” See Angell, *The Truth about the Drug Companies*, 23. Note that her description of the research and development process is correct in broad outline; but our findings reported in this paper are inconsistent with her implicit (but clear) argument about the relative values of the NIH and private-sector contributions. In an interview, Angell argued:

[T]he pharmaceutical industry is what’s parasitic on publicly funded research. The pharmaceutical industry likes to depict itself as a research-based industry, as the source of innovative drugs. Nothing could be further from the truth. This is their incredible PR and their nerve. In fact, if you look at where the original research comes from on which new drugs are based, it tends to be from the NIH, from the academic medical centers, and from foreign academic medical centers. Studies of this, looking at the seminal research on which drug patents are based, have found that about 15 percent of the basic research papers, reporting the basic research, came from industry. That’s just 15 percent. The other 85 percent came from NIH-supported work carried out in American academic medical centers. In one study, 30 percent came from foreign academic medical centers. So what we know about the numbers indicates that the foreign academic medical centers are responsible for more new drug discoveries than the industry itself.

Note that this quotation from Angell fails to distinguish research in basic science from that in applied science and other related areas. See <http://www.pbs.org/wgbh/pages/frontline/shows/other/interviews/angell.html>.

<sup>4</sup> Spending on drugs should be evaluated in the context of overall health-care costs, in that pharmaceuticals are a substitute for other medical procedures in many cases and thus are likely to conserve resources on net. See Lichtenberg, “The Impact of New Drugs on U.S. Longevity and Medical Expenditure, 1990–2003.”

<sup>5</sup> See Centers for Medicare and Medicaid Services, “National Health Expenditures Projections 2007–2017, Forecast Summary and Selected Tables,” at [http://www.cms.hhs.gov/NationalHealthExpendData/03\\_NationalHealthAccountsProjected.asp#TopOfPage](http://www.cms.hhs.gov/NationalHealthExpendData/03_NationalHealthAccountsProjected.asp#TopOfPage), Table 11.

<sup>6</sup> See, e.g., Mathews and Johnson, “Drug Companies Face Political, Scientific Attacks.”

resources in the development of drugs that are little better than ones already on the market.<sup>7</sup>

The focus of this study, as noted above, is on the second part of the argument: that the private sector is responsible for few (if any) important pharmaceutical innovations. Instead, all or most of the important scientific “breakthroughs” leading to the development of new and improved medicines are purported to result from research sponsored or conducted by government agencies, the National Institutes of Health foremost among them; the private-sector pharmaceutical industry supposedly adds little scientifically. Marcia Angell, a physician and former acting editor in chief of the *New England Journal of Medicine*, argues that “learning about the disease or condition is usually the beginning of the ‘research’ part of R&D, and it can take a very long time—sometimes decades. There is no question that this is the most creative, and the least certain, part of the R&D process. Contrary to industry propaganda, it is almost always carried out at universities or government research labs, either in this country or abroad. In the United States, most of it is supported by the National Institutes of Health.”<sup>8</sup>

Angell goes on to argue that once the given disease is understood, along with the biological paths available to treat it, the private sector then begins its work by synthesizing a molecule that will exploit the disease process in useful ways, and then by conducting expensive clinical trials, which Angell characterizes as “the least creative part of the process.”<sup>9</sup>

Why is the record of private-sector scientific contributions to the development of new medicines important? If the centrality of pharmaceutical research funded by the NIH is the reality—if private-sector research and development investments do not yield important scientific advances—then policy questions surrounding drug prices (federal negotiation of prices for Medicare Part D; importation of price-controlled medicines from abroad; FDA regulation of the industry) might be easier to resolve.

After all, if certain public policies can be predicted to yield less pharmaceutical research and development investment by the private sector but not a significant adverse effect in the development of new and improved medicines, the case against such policies might be weakened considerably.<sup>10</sup> At the same time,

<sup>7</sup> For a prominent presentation of the “me-too” argument, see Angell, *The Truth about Drug Companies*, 74–93. That argument is not the focus of this paper, although it is useful to note that it displays a profound misunderstanding of the process of drug development, particularly in the context of the FDA approval process. See Section II below. It misunderstands as well the central nature of follow-on drugs as improvements over earlier market entrants in given chemical classes in terms of patient convenience, absorption characteristics, maintenance of preferred drug levels in blood, and a number of other clinical parameters. And even if one concedes simply for discussion purposes the argument that follow-on drugs are little better than the original ones in a class, such “me-tooism” in the rest of the economy usually is applauded as “competition,” with the usual array of economic benefits assumed to result from it. See DiMasi and Paquette, “The Economics of Follow-on Drug Research and Development.” See also Grabowski, “Competition between Generic and Branded Drugs”; and Roden and George, “The Genetic Basis of Variability in Drug Responses”; and Comanor, “Research and Competitive Product Differentiation in the Pharmaceutical Industry in the United States.”

<sup>8</sup> Angell, *The Truth about Drug Companies*, 22. As an aside, the “creativity” assertion is inconsistent with the evidence offered in a few previous analyses of this question. Kneller finds that of the 171 drugs approved by the FDA from 1998 to 2003, 85 percent originated (were discovered) in the private sector. DiMasi et al. find that of the 284 new drugs approved in the U.S. from 1990 to 1999, 93.3 percent originated from industrial sources. Kaitin et al. find that the pharmaceutical industry was the source of 92.4 percent of the new drugs approved during 1981 through 1990. See below, n. 9. See Kneller, “The Origins of New Drugs”; DiMasi, Hansen, and Grabowski, “The Price of Innovation”; and Kaitin, Bryant, and Lasagna, “The Role of the Research-Based Pharmaceutical Industry In Medical Progress in the United States.”

<sup>9</sup> Angell, *The Truth about Drug Companies*, 23. Angell’s discussion does not make clear how she measures differences in “creativity.” Another prominent critique of the role of the private sector in the development of new drugs is presented by Merrill Goozner, formerly chief economics correspondent at the *Chicago Tribune*. See Goozner, *The \$800 Million Pill*. A central issue addressed in the Goozner book is the source (or genesis) of drugs; he does not answer that question in a systematic fashion but instead provides case histories of several drugs with significant public-sector input. Some of these drugs are discussed below in Section IV.

<sup>10</sup> For a recent set of estimates of the relationship between such policies and the development of new drugs, see Zycher, “The Human Cost of Federal Price Negotiations.”

a shift of a major component of the overall research and development process for drugs to the NIH from the private sector might engender a new set of problems and shortcomings, a topic beyond the scope of this study.<sup>11</sup>

A substantial literature exists on the contributions of government-funded (NIH) research to drug development.<sup>12</sup> Accordingly, we strive here to examine the general argument that the private sector contributes little to the advance of pharmaceutical science, with the few, if any, important “breakthroughs” instead contributed largely or solely by conducting (or funding) clinical trials.

Before turning to the case studies used to examine that issue, we offer in Section II a summary of the process and cost of drug development as useful background information. Section III presents thirty-two summary case histories as a systematic examination of the scientific role of the private sector in drug development. Section IV offers more detail on the past scientific processes yielding Taxol, Epogen, and Gleevec, three drugs that have received considerable attention in the literature and that have led some to conclude that private-sector scientific contributions to drug development have been relatively unimportant. Section V presents some conclusions and policy implications.

## II. THE PROCESS AND COST OF DRUG DEVELOPMENT

For new drugs, the process of discovery, development, and regulatory approval from the Food and Drug Administration for commercial distribution is lengthy, risky, and very costly.<sup>13</sup> For a pharmaceutical company to be able to repeat this process, it must be reasonably confident that the revenues that its drugs generate during their commercial life can exceed the cost of marketing and developing them. Below, we describe the process by which new drugs are developed and indicate the amount of resources that must be devoted to it.

### The Drug Discovery and Development Process

New drug development is usually a sequential process. Basic biomedical research can yield scientific knowledge of the biochemistry of a disease process, which can then be used to identify biological targets that molecules might affect in such a way as to modify the disease or condition being studied. Following the vision articulated by Vannevar Bush in the 1940s<sup>14</sup> for an efficient division of resources between basic research and applied research and development, much basic biomedical research is conducted in academic

<sup>11</sup> However, see DiMasi and Grabowski, “Should the Patent System for New Medicines Be Abolished?”; and idem, “Patents and R&D Incentives.”

<sup>12</sup> Several examples are: Gelijns, Rosenberg, and Moskowitz, “Capturing the Unexpected Benefits of Medical Research”; Cockburn and Henderson, “Absorptive Capacity, Coauthoring Behavior, and the Organization of Research in Drug Discovery”; Joint Economic Committee (U.S. Senate), *The Benefits of Medical Research and the Role of the NIH*; Baker, *The Benefits and Savings from Publicly Funded Clinical Trials of Prescription Drugs*; Zinner, “Medical R&D at the Turn of the Millennium”; Garber and Romer, “Evaluating the Federal Role in Financing Health-Related Research”; National Institutes of Health, “A Plan to Ensure Taxpayers’ Interests Are Protected”; U.S. General Accounting Office, *Agencies’ Rights to Federally Sponsored Biomedical Inventions*, GAO-03-536; Reichert and Milne, *Public and Private Sector Contributions to the Discovery and Development of “Impact” Drugs*; Toole, “Does Public Scientific Research Complement Private Investment in Research and Development in the Pharmaceutical Industry?”; Lichtenberg and Sampat, “NIH Research and Pharmaceutical Innovation”; Gluck, “Federal Policies Affecting the Cost and Availability of New Pharmaceuticals”; Schacht, “Federal R&D, Drug Discovery, and Pricing”; Smith, “The National Institutes of Health (NIH)”; and Schacht, “The Bayh-Dole Act.”

<sup>13</sup> See DiMasi, “New Drug Development in the United States, 1963–1999”; Kaitin and Cairns, “The New Drug Approvals of 1999, 2000, and 2001”; DiMasi, “Risks in New Drug Development”; DiMasi, Hansen, and Grabowski, “The Price of Innovation,” 157; and DiMasi and Grabowski, “The Cost of Biopharmaceutical R&D.”

<sup>14</sup> Vannevar Bush, *Science, the Endless Frontier*.

institutions and nonprofit institutes and is funded to a substantial degree by the public sector, while the bulk of applied research and development is funded by the private sector. The complementary nature of this division of labor and support has proved to be highly effective.<sup>15</sup> Knowledge and resource feedback loops connecting the public and private sectors have been found to enhance the productivity of the system as a whole.<sup>16</sup>

Once basic research has identified targets for which drugs might be effective, compounds are isolated, synthesized, or bioengineered and then screened to identify the most promising or “lead” drug candidates. These are designated for further investigation. The process by which lead compounds are identified is predominantly conducted in the private sector and involves an extensive and complex set of scientific activities such as combinatorial chemistry, structure-activity relationship analysis, and bioinformatics. Often, lead compounds are then modified in a process called “lead optimization” to enhance activity or reduce toxicity.

After a drug candidate has been marked for development, it undergoes testing *in vitro* and/or in animals to test for activity against the targeted disease or condition as well as for serious side effects. This process may take several years. Additional research and testing will be conducted to assess the drug’s purity, stability, and shelf life and to ensure that the compound can be produced on a commercial scale. These activities are generally conducted by or funded by industry.

If the compound remains a viable candidate after pre-clinical testing, a manufacturer interested in pursuing clinical (human) testing will detail data and findings on the drug in an application, called an Investigational New Drug (IND) application, which it submits

to the FDA. For drugs developed in the United States, initial human testing may have been conducted anywhere in the world.

For drugs that proceed to regulatory marketing approval, clinical testing is generally conducted in three successive phases. Although Phase I studies may be conducted with patients who have the targeted disease or condition, usually they are conducted with healthy volunteers. Information on pharmacokinetics (how the body absorbs, distributes, metabolizes, and excretes the drug) and a safe dosing range is obtained from Phase I studies. A limited number of patients with the targeted disease or condition are tested in Phase II studies, which provide the initial (“proof of concept”) evidence of efficacy, information on side effects, and data to help determine optimal dosing. Phase III studies are large-scale trials designed to establish firmly the efficacy of the compound and to provide further data on side effects, including those that occur infrequently. If a drug proceeds successfully through all three phases of development, the drug’s sponsor will compile all the information that it has gathered on the drug in a very lengthy application for regulatory marketing approval. The regulatory authority will decide whether the drug product has a sufficiently high benefit/risk ratio and chemistry and manufacturing standards to justify marketing approval.

## Trends in Drug-Development Metrics

The drug-development and regulatory-approval process outlined above is both lengthy (on average, 10 to 15 years)<sup>17</sup> and costly (hundreds of millions of dollars in direct costs, including the costs of failures, and at least as much in indirect costs).<sup>18</sup> For every compound that is approved for marketing, many thousands may be screened and hundreds may

<sup>15</sup> See, for example, Toole, “Does Public Scientific Research Complement Private Investment in Research and Development in the Pharmaceutical Industry?”

<sup>16</sup> See Cockburn and Henderson, “Absorptive Capacity, Coauthoring Behavior, and the Organization of Research in Drug Discovery.”

<sup>17</sup> See DiMasi, “New Drug Development in the United States, 1963–1999”; and Kaitin and Cairns, “The New Drug Approvals of 1999, 2000, and 2001.”

<sup>18</sup> See DiMasi, Hansen, and Grabowski, “The Price of Innovation”; and DiMasi and Grabowski, “The Cost of Biopharmaceutical R&D.”



enter preclinical development; of those that make it to clinical testing, only approximately one in five will ever get approved.<sup>19</sup>

The trend in pharmaceutical research and development costs has been relentlessly upward for decades. The total costs of pre-approval industrial research and development per approved new drug, including both the costs of researching drugs that failed to make it to approval and the time (“opportunity”) costs of drug development (expenditures must be made years before any returns can be earned), have shown a fairly consistent compound annual growth rate of over 7 percent above general price inflation for nearly forty years.<sup>20</sup> Of particular note is the high growth rate of clinical period costs in the last decade or so (a compound annual growth rate of over 11 percent above general price inflation).<sup>21</sup> These results are consistent with other data on the growth in drug-development, particularly clinical, costs.<sup>22</sup>

To help ensure that these increases do not stifle innovation in this crucial area, technological advances in drug-discovery methods are needed, as well as improved preclinical identification of promising compounds, clinical trial designs that yield better information, faster development of the most promising drugs, earlier termination of research and trials of drugs that are unlikely to succeed, and the regulatory adjustments necessary to support these initiatives. Collaborative efforts among industry scientists, academics, government regulators, and government scientists, such as those envisioned by the FDA’s Critical Path Initiative,<sup>23</sup>

have the potential to bridge gaps in the translation of upstream research into downstream development. If realized, the result should be an increase in the number of useful new therapies and an increase in the speed with which they reach patients.<sup>24</sup>

### III. SUMMARY CASE HISTORIES FOR THIRTY-TWO DRUG CLASSES

The existing literature suggests that the general assertion of NIH/government centrality in pharmaceutical innovation—and the near-irrelevance of the private sector in terms of important contributions to pharmaceutical science—is problematic at a minimum.<sup>25</sup> In this section, we summarize the available case-history literature for thirty-two drug classes to see if a dominant pattern can be discerned in terms of a consistent presence or an absence of private-sector contributions to pharmaceutical science. Again, the importance of government-funded research in terms of pharmaceutical development generally, and the science of disease processes and the like in particular, is not in dispute; instead, our goal is an examination of the premise that all or most of the “big breakthroughs” come from NIH, that is, that the private sector contributes little more than funding for clinical trials rather than important scientific advances.

We adopt here a summary case-history approach, using lists of important drugs and drug classes offered by the literature. Fuchs and Sox created a list of

<sup>19</sup> See DiMasi, “Risks in New Drug Development.”

<sup>20</sup> See DiMasi, Hansen, and Grabowski, “The Price of Innovation.”

<sup>21</sup> Ibid.

<sup>22</sup> Ibid.; and Kaitin, ed., *Growing Protocol Design Complexity Stresses Investigators, Volunteers*.

<sup>23</sup> U.S. Department of Health and Human Services, *Critical Path Opportunities Report*.

<sup>24</sup> The processes we describe here and the recommendations we make may not apply to the emerging field of individualized pharmacology, made possible by breakthroughs in the study of human genetics. See, e.g., Trusheim, Berndt, and Douglas, “Stratified Medicine”; and Roden and George, “The Genetic Basis of Variability in Drug Responses.” See also Calfee and DuPre, “The Emerging Market Dynamics of Targeted Therapeutics.”

<sup>25</sup> See the works cited above in nn. 8 and 12.

thirty major medical innovations by searching through twenty-five years of the *Journal of the American Medical Association* and the *New England Journal of Medicine*.<sup>26</sup> Of those thirty innovations, fifteen were drugs or drug classes.<sup>27</sup> Cockburn and Henderson constructed a list of twenty-one drugs “identified by two leading experts as ‘having had the most impact upon therapeutic practice’ between 1965 and 1992.”<sup>28</sup> Another list of “drugs that were ‘blockbusters’ in 1993 (in terms of sales)” is provided by Gelijns et al., but it largely duplicates the Fuchs-Sox and Cockburn-Henderson lists.<sup>29</sup> Those lists are useful for the work reported here because they were constructed independently; but they are a bit dated. In order to capture the relevant histories of newer drugs, we include in the construction of Table 2 the twenty-five brand-name drugs most prescribed in the U.S. in 2007, as reported by Verispan VONA.<sup>30</sup> Table 2 presents a list of thirty-seven drug classes and respective drugs merged from the Fuchs-Sox, Cockburn-Henderson, and Ver-

ispan VONA compilations.<sup>31</sup> The discussion that follows offers a summary of the respective case histories available in the literature for the drug classes.<sup>32</sup>

### **1. Angiotensin Converting Enzyme (ACE) Inhibitors.**<sup>33</sup>

Captopril was the first ACE inhibitor proven effective when taken orally. It was approved by the FDA in 1981 for use in patients responding poorly to other therapies, with severe hypertension, and for patients on multidrug regimens. Additional clinical experience showed that use of the drug at lower doses yielded continued effectiveness with minimal side effects, particularly for patients suffering from congestive heart failure, coronary insufficiency, diabetes, and asthma. Scientific study conducted by John Vane at the Royal College of Surgeons of England in the 1960s showed that an extract of the venom of the Brazilian arrowhead viper acted as an ACE inhibitor. Miguel Ondetti and others at Squibb then isolated several peptides from the venom in the early 1970s; one was teprotide

<sup>26</sup> Fuchs and Sox, “Physicians’ Views of the Relative Importance of Thirty Medical Innovations.” Fuchs and Sox then conducted a survey of internists to rank the innovations in terms of relative importance to patients.

<sup>27</sup> Note that Fuchs and Sox combine ACE inhibitors with angiotensin antagonists; proton pump inhibitors with H2 blockers; SSRIs with non-SSRIs (SNRIs and MAOIs); and NSAIDs with Cox-2 inhibitors. We separate those subclasses in the construction of Table 2 below.

<sup>28</sup> Cockburn and Henderson, “Absorptive Capacity, Coauthoring Behavior, and the Organization of Research in Drug Discovery.” The Joint Economic Committee paper, *The Benefits of Medical Research and the Role of the NIH*, examines the role of public funding in the development of “the 21 drugs introduced between 1965 and 1992 that were considered by experts to have had the highest therapeutic impact on society.” Only fifteen of the twenty-one drugs actually are listed in the study, and of those fifteen, five are duplicates, leaving a net list of ten. Those ten are included in the Cockburn-Henderson list, so the JEC study is not used here as an independent source of candidates for the summary case studies.

<sup>29</sup> Gelijns et al., “Capturing the Unexpected Benefits of Medical Research,” 696.

<sup>30</sup> See <http://drugtopics.modernmedicine.com/drugtopics/data/articlestandard/drugtopics/072008/491207/article.pdf>. Alternatively, the twenty-five highest-selling brand-name drugs by retail dollars in 2007 could be used as a measure of economic value; but the important role of third-party payment may make that characterization problematic. The two lists, as might be expected, do not differ greatly, as eighteen of the top sellers by revenue appear among the twenty-five most prescribed; four are among the fifty most prescribed, and the remaining three are ranked 51, 79, and 84 in terms of the number of prescriptions.

<sup>31</sup> See above, nn. 26–30. See also information on individual drugs at [www.webmd.com](http://www.webmd.com), [www.drugs.com](http://www.drugs.com), [www.accessdata.fda.gov](http://www.accessdata.fda.gov), [www.freepatentsonline.com](http://www.freepatentsonline.com), [www.mayoclinic.com](http://www.mayoclinic.com), and [www.medlibrary.org](http://www.medlibrary.org). The list of thirty-seven drug classes and drugs comprises all drugs on the Fuchs-Sox and Cockburn-Henderson lists, plus the fifty most prescribed drugs from the Verispan VONA compilation, and then with duplicates eliminated.

<sup>32</sup> Of the thirty-seven drug classes listed in Table 2, we find sufficient literature on the respective development histories for thirty-two. The five not discussed below are: monoamine oxidase inhibitors, leukotriene receptor antagonists, cytomegalovirus (CMV) antivirals, thyroid-stimulating hormones, and bisphosphonates.

<sup>33</sup> See Maxwell and Eckhardt, *Drug Discovery: A Casebook and Analysis*, 19–34; Sneader, *Drug Discovery: A History*, 280–82; Scriabine, “Discovery and Development of Major Drugs Currently in Use,” 187; Patchett, “Enalapril and Lisinopril,” 3:129–37; and Lednicer, *New Drug Discovery and Development*, 50–51. See also Turk, “Targeting Proteases.”



Table 2. Merged Drug List		
Class	Generic Examples	Brand Examples
Angiotensin converting enzyme inhibitors	Captopril/Benazepril	Capoten/Lotensin
Angiotensin II antagonists	Losartan/Valsartan	Cozaar/Diovan
Calcium channel blockers	Nifedipine/Amlodipine/Nisoldipine	Procardia/Norvasc/Sular
Beta blockers	Propranolol/Metoprolol	Inderal/Toprol-Lopressor
Platelet aggregation inhibitors	Dipyridamole/Ticlopidine/Clopidogrel	Persantine/Ticlid/Plavix
Statins	Lovastatin/Simvastatin/Atorvastatin	Mevacor/Zocor/Lipitor
Fibrates	Gemfibrozil/Fenofibrate	Lopid/Tricor
Cholesterol absorption inhibitors	Ezetimibe	Zetia
H2 blockers	Cimetidine/Ranitidine	Tagamet/Zantac
Proton pump inhibitors	Omeprazole/Lansoprazole/Pantoprazole	Prilosec/Prevacid/Protonix
Selective serotonin reuptake inhibitors	Fluoxetine/Paroxetine/Sertraline	Prozac/Paxil/Zoloft
Serotonin norepinephrine reuptake inhib.	Venlafaxine/Duloxetine	Effexor/Cymbalta
Monoamine oxidase inhibitors	Phenelzine/Tranylcypromine	Nardil/Parnate
Bronchodilators	Albuterol (Salbutamol)	Proventil/Ventolin
Inhaled corticosteroids	Flunisolide/Beclomethasone	Aerobid/Qvar
Leukotriene receptor antagonists	Montelukast	Singulair
Nonsteroidal anti-inflammatory drugs	Aspirin/Ibuprofen	Bayer/Advil
Cox-2 inhibitors	Celecoxib/Rofecoxib	Celebrex/Vioxx
Long-acting opioids	Oxycodone	Oxycontin/Percolone
Fluoroquinolone antibiotics	Ciprofloxacin/Levofloxacin	Cipro/Levaquin
Third-generation cephalosporins	Cefotaxime/Ceftriaxone	Claforan/Rocephin
Imidazole and triazole antifungals	Ketoconazole/Fluconazole	Nizoral/Diflucan
Antivirals (herpes simplex/zoster)	Acyclovir	Zovirax
HIV antiretrovirals/NRTIs	Enfuvirtide/Zidovudine (AZT)	Fuzeon/Retrovir
Cytomegalovirus (CMV) antivirals	Foscarnet	Foscavir
Hypoglycemic agents/Thiazolidinediones	Metformin/Pioglitazone/Rosiglitazone	Glucophage/Actos/Avandia
Selective estrogen receptor modulators	Tamoxifen/Raloxifene	Nolvadex/Soltamox/Evista
Chemotherapy agents	Cisplatin	Platinol
5-HT3 blockers	Ondansetron/Granisetron	Zofran/Kytril
PDE5 blockers	Sildenafil/Tadalafil/Vardenafil	Viagra/Cialis/Levitra
Nonsedating antihistamines	Loratadine/Cetirizine/Fexofenadine	Claritin/Zyrtec/Allegra
Immunosuppressants	Cyclosporine/Tacrolimus/Daclizumab	Sandimmune/Prograf/Zenapax
5-alpha reductase inhibitors	Finasteride	Proscar
Triptans (selective 5-HT1 agonists)	Sumatriptan/Frovatriptan	Imitrex/Frova
Interferons	Interferon alfa-N3/beta-1A	Alferon N/Avonex
Thyroid-stimulating hormones	Levothyroxine	Synthroid/Levoxyl
Bisphosphonates	Alendronate	Fosamax
Sources: Fuchs and Sox, "Physicians' Views of the Relative Importance of Thirty Medical Innovations"; Cockburn and Henderson, "Absorptive Capacity, Coauthoring Behavior, and the Organization of Research in Drug Discovery"; and Verispan VONA, n. 30, above. See also n. 31, above.		

(already isolated by Vane), which then was synthesized and tested extensively in animals by the Squibb scientists. It proved to be an effective hypertensive agent when administered intravenously but ineffective when administered orally. The Squibb researchers then tested about 2,000 nonpeptides without success in the search for an ACE inhibitor effective with oral administration. A paper by Byers and Wolfenden of the University of North Carolina, supported by NIH research grants, yielded scientific findings that led the Squibb researchers to synthesize additional binding compounds for ACE.<sup>34</sup> Sneader notes: “The resulting compound ... was still not potent enough to be considered as a candidate compound for clinical investigations and it required considerable effort and ingenuity to enhance its potency.”<sup>35</sup>

The Squibb researchers then experimented with a number of molecular approaches until discovering that replacement of the carboxyl molecule group with a thiol group, yielding “a one-thousand-fold increase in inhibitory activity for captopril. This was the first nonpeptide ACE inhibitor suitable for introduction into the clinic.”<sup>36</sup> In sum, private-sector research at a minimum yielded a chemical compound with sufficient potency to make it an effective candidate for clinical use.

**2. Angiotensin II Antagonists.**<sup>37</sup> Losartan, approved originally by the FDA in 1995, has been shown in extensive clinical trials to be as effective as the ACE inhibitors as antihypertensives but without the dry cough caused by the latter. In 1982, Yoshiyasu Fu-

rukawa, Shoji Kishimoto, and Kohei Nishikawa of Takeda Chemical Industries reported that they had developed a chemical derivative of imidazole-5-acetic acid that inhibited the hypertensive effect of angiotensin II.<sup>38</sup> Building upon that scientific advance, DuPont Merck began a research program that yielded its own imidazole derivative, which was called losartan. Merck scientists synthesized losartan in 1991, after which extensive clinical studies were conducted, followed by FDA approval in 1995. Scientists at Ciba-Geigy subsequently developed valsartan, which is not metabolized in the liver and therefore less likely to interact with certain other drugs, and it is not contraindicated in the case of patients with liver disease. Accordingly, private-sector research at a minimum yielded compounds reducing the adverse side effects of existing therapies.

**3. Calcium Channel Blockers.**<sup>39</sup> Nifedipine was first approved by the FDA in 1981. There is some dispute between German and Belgian researchers over the sources of the initial discoveries that drugs could induce calcium withdrawal from cells, thus relaxing smooth muscle cells in the walls of blood vessels; but it is clear that a substantial part of that work was conducted by Albrecht Fleckenstein at the University of Freiburg.<sup>40</sup> In any event, scientists at Bayer reported in 1970 on the antihypertensive effects of a group of compounds called dihydropyridines;<sup>41</sup> Bayer then proceeded to synthesize and screen more than 2,000 variations of the compounds. Nifedipine was chosen as the compound for further investigation—in tests on animals, it was shown to be particularly

<sup>34</sup> Byers and Wolfenden, “Binding of the By-Product Analog Benzylsuccinic Acid by Carboxypeptidase A.”

<sup>35</sup> Sneader, *Drug Discovery: A History*, 281.

<sup>36</sup> Ibid.

<sup>37</sup> See Sneader, *Drug Discovery: A History*, 425–26; Scriabine, “Discovery and Development of Major Drugs Currently in Use,” 188–89; and Lednicer, *New Drug Discovery and Development*, 51–52.

<sup>38</sup> Their U.S. patent 4355040 can be found at [www.delphion.com/details?pn10=US04355040](http://www.delphion.com/details?pn10=US04355040). They report in the abstract that their derivatives of imidazole-5-acetic acid have hypotensive activity.

<sup>39</sup> See Lednicer, *New Drug Discovery and Development*, 48–50; Sneader, *Drug Discovery: A History*, 421–22; Scriabine, “Discovery and Development of Major Drugs Currently in Use,” 190–95; Maxwell and Eckhardt, *Drug Discovery: A Casebook and Analysis*, 35–51; and Hara, *Innovation in the Pharmaceutical Industry*, 51–61.

<sup>40</sup> Some of this early history is reported in Fleckenstein, *Calcium Antagonism in Heart and Smooth Muscle*.

<sup>41</sup> See Bossert and Vater, “Dihydropyridine, eine neue Gruppe stark wirksamer Coronartherapeutika,” 578.

effective—and clinical work confirmed both its anti-hypertensive effects and the fact that the drug acted as a calcium channel blocker. Maxwell and Eckhardt report that the development of all first-generation calcium channel blockers resulted from research in the private sector.<sup>42</sup> This research led to the discovery of a compound that exploited the advance in basic science identifying a useful biological target.

**4. Beta Blockers.**<sup>43</sup> Propranolol, approved by the FDA in 1967, was the first beta blocker to be marketed successfully; the more technical term for beta blockers is “beta-adrenoceptor antagonists.” Pathbreaking scientific work on adrenoceptors was conducted by Raymond P. Ahlquist of the University of Georgia in the late 1940s, when he determined that they could be separated into alpha and beta families.<sup>44</sup> The first beta-adrenoceptor antagonist (or beta blocker) was discovered by scientists at Lilly Laboratories in 1957; those findings were confirmed subsequently by other researchers at Emory University. Several years of work then followed at Imperial Chemical Industries (ICI, subsequently part of AstraZeneca), led by James W. Black, who in 1988 was one of three awarded the Nobel Prize in Physiology or Medicine. Black presented the initial pharmacological findings for the first beta blocker, pronethalol, in 1962, which proved to have some adverse toxicity effects. Other scientists at ICI then synthesized propranolol and demonstrated its antihypertensive effect in 1964.<sup>45</sup> Indications for propranolol have increased—for angina pectoris, arrhythmias, myocardial infarction, glaucoma, and migraine—and the pharmaceutical sector over time

has developed a series of improved beta blockers offering various therapeutic advantages over propranolol.<sup>46</sup> This history of the development of beta blockers is consistent with the dominant development path for drugs: a basic scientific advance was followed by private research that discovered compounds that exploit the basic scientific knowledge and that yield improved drugs with broader applications and the like.

**5. Platelet Aggregation Inhibitors.**<sup>47</sup> Dipyridamole received FDA approval in 1961, and earlier was a component of a group of homopurine compounds for which the Karl Thomae Company was granted a British patent in 1959. It was initially used as a coronary dilator; publicly funded research at the Medical Research Council discovered that it had a significant effect in inhibiting the formation of platelet clumps (thrombi). Further advances in the development of platelet aggregation inhibitors have focused on specific conditions: ticlopidine (Roche Pharmaceuticals) for prevention of thrombotic stroke; dipyridamole (Boehringer Ingelheim) for prevention of thrombosis after cardiac valve replacement; clopidogrel (Sanofi-Aventis) as a substitute for ticlopidine with fewer side effects; and abciximab (Centocor/Eli Lilly) for use after angioplasty. At a minimum, therefore, private work improved the degree to which clinical practice was able to exploit the initial scientific discovery in terms of specific medical conditions; that is, it developed compounds able to attack more specialized biological targets associated with specific medical conditions or needs.

<sup>42</sup> See Maxwell and Eckhardt, *Drug Discovery: A Casebook and Analysis*, 44 (Table 1).

<sup>43</sup> See Hara, *Innovation in the Pharmaceutical Industry*, 38–51; Scriabine, “Discovery and Development of Major Drugs Currently in Use,” 182–86; Lednicer, *New Drug Discovery and Development*, 42–43; Maxwell and Eckhardt, *Drug Discovery: A Casebook and Analysis*, 3–18; and Sneader, *Drug Discovery: A History*, 193–94.

<sup>44</sup> Ahlquist, “A Study of the Adrenotropic Receptors.”

<sup>45</sup> Black, Duncan, and Shanks, “Comparison of Some Properties of Pronethalol and Propranolol.”

<sup>46</sup> See Scriabine, “Discovery and Development of Major Drugs Currently in Use,” 183–85; and Sneader, *Drug Discovery: A History*, 193–94, for discussions of these advances.

<sup>47</sup> See Bhatt and Topol, “Scientific and Therapeutic Advances in Antiplatelet Therapy”; Jackson and Schoenwaelder, “Antiplatelet Therapy”; Scriabine, “Discovery and Development of Major Drugs Currently in Use,” 202–5; and Sneader, *Drug Discovery: A History*, 134–35.

**6. Statins.**<sup>48</sup> Beginning with the ongoing Framingham Heart Study, which has been conducted by the National Heart, Lung, and Blood Institute of the NIH since 1948, the causal relationship between elevated cholesterol levels and cardiovascular disease has become widely recognized. In 1976, Akira Endo and other researchers at the Sankyo Company and at Beecham Research Laboratories independently isolated mevastatin from fungi, after having screened more than 8,000 microbial extracts. Further research by Endo and colleagues showed that mevastatin reduced cholesterol levels in the liver;<sup>49</sup> subsequently, Endo and researchers at Merck separately isolated lovastatin from a different fungus. Lovastatin was shown to be more potent than mevastatin and was the first HMG-CoA reductase inhibitor approved by the FDA, in 1987, for the reduction of plasma cholesterol. Further research by private-sector laboratories has yielded additional statin drugs more potent and/or with fewer side effects than lovastatin: pravastatin, simvastatin, atorvastatin, and others, the newer of which have been synthesized in laboratories rather than isolated from natural materials. Private-sector research, in short, developed compounds exploiting new knowledge of a specific disease process, and developed improvements in terms of potency and side effects.

**7. Fibrates.**<sup>50</sup> Thorp and Waring, researchers at ICI, reported in 1962 that clofibrate reduced cholesterol levels in laboratory animals.<sup>51</sup> A subsequent large clinical study (of 5,000 patients) funded by the World Health Organization showed that mortality

from noncardiovascular diseases was higher in the group given clofibrate than the group given a placebo; at the same time, clofibrate reduced the incidence of nonfatal coronaries in patients with no previous history of heart disease. Accordingly, use of the drug was restricted by the FDA to patients for whom hyperlipidemia did not respond to changes in diet and to patients with very high triglyceride levels. In response, Parke-Davis screened more than 8,000 related compounds for lipid-lowering effects in laboratory animals; gemfibrozil was found effective in that research. It was synthesized in 1968 and approved by the FDA (brand name Lopid) in 1981. In a five-year clinical study, gemfibrozil reduced the rate of serious coronary events but not the total mortality rate, compared with a placebo group.<sup>52</sup> In sum, private research discovered a compound that exploited existing knowledge about a disease process, and synthesized numerous follow-on compounds in an effort to improve the clinical usefulness of the drugs.

**8. Cholesterol Absorption Inhibitors.**<sup>53</sup> The absorption of cholesterol from the intestine requires an enzyme; scientists at Schering-Plough initiated a research program in the early 1990s to identify compounds that would block the enzyme and thus inhibit absorption of cholesterol.<sup>54</sup> This effort led to the development of ezetimibe, which received FDA approval in 2002, and was subsequently marketed as Zetia. Although the Schering-Plough research was directed at ACAT inhibitors, “the actual mechanism by which this compound inhibits absorption of

<sup>48</sup> See Tobert, “Lovastatin and Beyond”; Lednicer, *New Drug Discovery and Development*, 64–68; Scriabine, “Discovery and Development of Major Drugs Currently in Use,” 208–9; and Sneader, *Drug Discovery: A History*, 343–44, 353.

<sup>49</sup> Mevastatin inhibits an enzyme called 3-hydroxy-methylglutaryl-coenzyme A (HMG-CoA) reductase.

<sup>50</sup> See Scriabine, “Discovery and Development of Major Drugs Currently in Use,” 206–7; Lednicer, *New Drug Discovery and Development*, 62–64; and Sneader, *Drug Discovery: A History*, 274–76.

<sup>51</sup> Thorp and Waring, “Modification of Metabolism and Distribution of Lipids by Ethyl Chlorophenxyisobutyrate.”

<sup>52</sup> Frick et al., “Helsinki Heart Study.” The study appears to have been administered at the University of Helsinki.

<sup>53</sup> See Linsel-Nitschke and Tall, “HDL as a Target in the Treatment of Atherosclerotic Cardiovascular Disease”; Earl and Kirkpatrick, “Ezetimibe”; and Lednicer, *New Drug Discovery and Development*, 68–70.

<sup>54</sup> The enzyme is called ACAT, or acyl-CoA: cholesterol O-acyltransferase. This brief description of the research is taken from Lednicer, *New Drug Discovery and Development*, 68.

cholesterol is not yet fully understood.”<sup>55</sup> The development of ezetimibe reflects the common pattern of pharmaceutical science: private research developed a compound designed to exploit a target identified by earlier basic science.

**9. H<sub>2</sub> Blockers.**<sup>56</sup> Before the development of H<sub>2</sub> blockers, treatment of peptic ulcers was limited to the intensive use of antacids, various drugs (anticholinergics) with unpleasant side effects, or surgery. Pharmaceutical scientists recognized that histamine induces the secretion of gastric acids, but none of the available antihistamines blocked that effect. In 1964, James W. Black, Robin Gannellin, and colleagues at Smith Kline & French hypothesized that more than one histamine receptor existed; this led to the synthesis of more than 700 compounds over eight years. Burimamide was the first of them found to be a blocker specific for gastric acids. However, it was not absorbed well orally; in 1973, Black discovered metiamide, which was proven active orally but which had serious side effects in some patients. Further work enabled Black and his associates in 1975 to discover cimetidine, which received FDA approval in 1977, and was marketed as Tagamet by Smith Kline & French (which, through a series of mergers, became GlaxoSmithKline in 2000). The clinical and financial success of cimetidine led to the development of a number of other H<sub>2</sub> blockers, among them ranitidine, developed by GlaxoSmithKline and approved by the FDA in 1984. Marketed as Zantac, it is more specific than cimetidine as an antagonist for H<sub>2</sub> receptors and has fewer side effects. Private-sector research developed a compound that exploited the basic science of histamines, with further research

aimed at the discovery of follow-on compounds with improved clinical properties.

**10. Proton Pump Inhibitors.**<sup>57</sup> The discovery of the histamine H<sub>2</sub> blockers induced a search for alternative drugs that might inhibit the secretion of gastric acids without blocking the histamine receptor. Cimetidine required multiple doses per day and yielded undesirable fluctuations in gastric acid levels; in addition, it did not treat gastro-esophageal reflux disease (GERD) or some other related conditions well. In 1968, George Sachs and colleagues at Smith Kline & French began work that discovered the proton pump that forces acid across the protective gastric mucosa. Collaboration at scientific conferences and the like yielded a search begun in the 1970s at Astra Pharmaceuticals (formerly AB Hässle) for drugs that might improve upon the performance of the H<sub>2</sub> blockers. Earlier compounds<sup>58</sup> proved overly toxic or afflicted with other problems, but continued work resulted in the discovery of omeprazole in 1978. It was approved by the FDA in 1989, marketed as Prilosec. Omeprazole displayed significant variability across patients in terms of acid secretion and other effects, and a significant proportion of patients require higher or multiple doses. Accordingly, in 1987, Astra began a research program intended to find a proton pump inhibitor that increased bioavailability by reducing liver involvement. Several hundred compounds were synthesized and screened over five years, after which esomeprazole was demonstrated in clinical trials to be superior to omeprazole for some patients.<sup>59</sup> It was approved by the FDA in 2001 and marketed as Nexium. Private-sector research in this case discovered a central disease process previously unknown,

<sup>55</sup> Ibid.

<sup>56</sup> See Leurs, Bakker, Timmerman, and de Esch, “The Histamine H<sub>3</sub> Receptor”; Maxwell and Eckhardt, *Drug Discovery: A Casebook and Analysis*, 365–76; Lednicer, *New Drug Discovery and Development*, 116, 151–54, and 232–33; and Sneader, *Drug Discovery: A History*, 212–15.

<sup>57</sup> See Berkowitz and Sachs, “Life Cycle of a Blockbuster Drug”; Olbe, Carlsson, and Lindberg, “A Proton-Pump Inhibitor Expedition”; Sneader, *Drug Discovery: A History*, 397–99; Lednicer, *New Drug Discovery and Development*, 154–55; and Scriabine, “Discovery and Development of Major Drugs Currently in Use,” 232–33.

<sup>58</sup> See Berkowitz and Sachs, “Life Cycle of a Blockbuster Drug”; Olbe, Carlsson, and Lindberg, “A Proton-Pump Inhibitor Expedition”; Sneader, *Drug Discovery: A History*, 397–99; Lednicer, *New Drug Discovery and Development*, 154–55; and Scriabine, “Discovery and Development of Major Drugs Currently in Use,” 232–33.

<sup>59</sup> Some individuals are “slow metabolizers,” i.e., they lack a liver enzyme important for the metabolism of a number of drugs including omeprazole. See Olbe et al., “A Proton-Pump Inhibitor Expedition,” 136–37.

and developed compounds designed to exploit that target and to improve clinical performance.

### **11. Selective Serotonin Reuptake Inhibitors.**<sup>60</sup>

The search for drugs with which to treat depression began in the late 1950s, leading to the investigation and development of early monoamine oxidase inhibitors, particularly iproniazid, a drug that had been developed earlier by Hoffmann–La Roche for the treatment of tuberculosis. It and several successor drugs exhibited nontrivial degrees of liver toxicity and other adverse side effects, inducing a search for improved alternatives. Scientists at J. R. Geigy Ltd. began to conduct clinical trials with several of its potential antipsychotic drugs, leading to further research on the effects of imipramine, an uptake inhibitor for norepinephrine and serotonin. The discovery of imipramine, combined with earlier work at the NIH by Julius Axelrod on the identification of neurotransmitters (for which Axelrod won the Nobel Prize in Physiology or Medicine in 1970), led to the development of a class of drugs called the tricyclic antidepressants; some were specific inhibitors of norepinephrine, and others for serotonin, while others blocked the uptake of dopamine. These drugs had several common side effects, among them cardiac toxicity and dry mouth. The continued search for safer and more effective antidepressants led in 1972 to the discovery of flu-

oxetine by researchers at Lilly Laboratories; it is a drug much more selective for serotonin than for norepinephrine.<sup>61</sup> Marketed as Prozac, it received FDA approval late in 1987. This private research effort, building upon earlier breakthroughs in basic science, developed compounds designed to exploit targets suggested by brain chemistry, and then developed newer drugs with improved effectiveness and reduced side effects.

### **12. Serotonin Norepinephrine Reuptake Inhibitors.**<sup>62</sup>

Duloxetine was synthesized in 1988 by part of the Lilly research team that had discovered fluoxetine. Unlike the latter, highly selective for serotonin, the researchers reported that “LY227942 has the pharmacological profile of an antidepressant drug and is useful to study the pharmacological responses of concerted enhancement of serotonergic and norepinephrine neurotransmission.”<sup>63</sup> This development of duloxetine advanced the search for drugs effective at exploiting biologic targets in the brain.

**13. Bronchodilators.**<sup>64</sup> Isoproterenol was discovered in 1940 at Boehringer Ingelheim, and for years was the treatment of choice for acute asthma attacks because it induced a strong bronchodilator effect without the hypertensive effects of earlier drugs. Its effects are of short duration, however, and it acts as

<sup>60</sup> See Wong et al., “A Selective Inhibitor of Serotonin Uptake: Lilly 110140”; Wong, Perry, and Bymaster, “The Discovery of Fluoxetine Hydrochloride (Prozac)”; Lednicer, *New Drug Discovery and Development*, 150–51; Scriabine, “Discovery and Development of Major Drugs Currently in Use,” 218–20; and Sneader, *Drug Discovery: A History*, 415–17.

<sup>61</sup> Wong, Perry, and Bymaster, “The Discovery of Fluoxetine Hydrochloride (Prozac),” 765, note that the Lilly research team “presented the pharmacological evidence that led to the search for inhibitors that are targeted selectively to the uptake of 5-HT.” See Fuller, Perry, and Molloy, “Effect of an Uptake Inhibitor on Serotonin Metabolism in Rat Brain.” Wong, Perry, and Bymaster, 765–68, note as well the crucial contributions of university researchers to the scientific understanding of chemical processes in the brain.

<sup>62</sup> See Waitekus and Kirkpatrick, “Duloxetine Hydrochloride”; Wong et al., “LY227942, An Inhibitor of Serotonin and Norepinephrine Uptake”; *Encyclopedia of Chemistry*, “Duloxetine,” at [www.chemie.de/lexicon/e/Duloxetine](http://www.chemie.de/lexicon/e/Duloxetine); and Wong and Licinio, “From Monoamines to Genomic Targets.” Information on the development history of venlafaxine (Effexor), approved by the FDA in 1993, was not found during the course of this research. Duloxetine (Cymbalta) was approved in 2004; the published record offers only the limited information on the development history referenced here, but it is clear that duloxetine (Lilly LY227942 and LY248686) was created by researchers at Lilly.

<sup>63</sup> Wong et al., “LY227942, An Inhibitor of Serotonin and Norepinephrine Uptake,” 2053.

<sup>64</sup> See Maxwell and Eckhardt, *Drug Discovery: A Casebook and Analysis*, 333–48; Scriabine, “Discovery and Development of Major Drugs Currently in Use,” 226–27; Sneader, *Drug Discovery: A History*, 142, 189–92; and Barnes, “New Drugs for Asthma.”



a potent heart stimulant; accordingly, research proceeded to find a similar drug (beta2-adrenoceptor agonist) that would not stimulate the heart. Albuterol (also called salbutamol) was discovered in 1967 at Allen and Hanbury (now part of GlaxoSmithKline). Another such drug with greater selectivity for the beta2-adrenoceptor is terbutaline, developed at Astra Pharmaceuticals. Note that the crucial distinction of the different effects of alpha- and beta-adrenoceptors was discovered by Raymond Ahlquist of the School of Medicine at the University of Georgia, a breakthrough in the basic science that made the discovery of the newer drugs possible.<sup>65</sup> Maxwell and Eckhardt note that when inhaled, “the more selective [beta2] agonists are virtually devoid of the side effects related to vasoconstriction and/or cardiac stimulation that are evident with epinephrine and isoproterenol.” They note as well that of the four major scientific advances leading to the discovery of albuterol, one was made at a university, one by a government agency, and two by the private sector.<sup>66</sup> The advance in basic science achieved by Ahlquist led the private sector to search for compounds improving upon the clinical performance offered by existing therapies.

**14. Inhaled Corticosteroids.**<sup>67</sup> The usefulness of cortisone for the treatment of arthritis led in the late 1940s and early 1950s to the synthesis of several anti-inflammatory corticosteroids, which quickly were recognized as useful for the treatment of asthma. However, heavy use yielded a number of serious side effects; accordingly, interest grew in the development of inhaled versions of the drug class. Early efforts exhibited substantial variability in terms of effectiveness and difficulty in terms of preserving the useful local

(respiratory) effects while reducing the adverse systemic side effects. Further work led to the synthesis of beclomethasone by Glaxo, with a patent issued in 1966. A further patent was issued for the inhaled version of the drug in 1989.<sup>68</sup> Maxwell and Eckhardt attribute to the private sector two of the three major scientific advances crucial for the development of the drug, with the third attributed to a hospital study. Again, the private research yielded compounds with improved properties in terms of clinical practice.

**15. Nonsteroidal Anti-Inflammatory Drugs.**<sup>69</sup> Analgesics are drugs that reduce pain, while antipyretics reduce fever and anti-inflammatory drugs reduce the inflammation caused by arthritis or other conditions. Aspirin (acetylsalicylic acid) has all three properties; it was invented by a chemist at Bayer in the late 1890s. The most common side effects of aspirin are gastrointestinal irritation, often manifesting itself as bleeding in the intestinal tract, and a reduction of blood-clotting activity. Research continued at various centers, leading to the synthesis of paracetamol (or acetaminophen) at Bayer; it does not produce gastrointestinal bleeding but is less effective than aspirin in terms of its anti-inflammatory effect. Merck developed indomethacin (Indocin), effective in terms of the treatment of arthritis but, again, causing significant gastrointestinal side effects. Merck developed sulindac in the early 1960s, a drug with milder gastrointestinal effects. In addition to that central problem with aspirin and the earlier NSAIDs, it became clear during the 1950s that the long-term use of corticosteroids for treatment of arthritis causes serious medical problems. After synthesizing and testing about 600 compounds, researchers at Boots Pharmaceuticals developed ibuprofen in

<sup>65</sup> See Ahlquist, “A Study of the Adrenotropic Receptors.”

<sup>66</sup> See Maxwell and Eckhardt, *Drug Discovery: A Casebook and Analysis*, 333–34, 340.

<sup>67</sup> Ibid., 349–62; Sneader, *Drug Discovery: A History*, 210; and Scriabine, “Discovery and Development of Major Drugs Currently in Use,” 243–46. See also Patton and Byron, “Inhaling Medicines.” <sup>65</sup> See Ahlquist, “A Study of the Adrenotropic Receptors.”

<sup>66</sup> See Maxwell and Eckhardt, *Drug Discovery: A Casebook and Analysis*, 333–34, 340.

<sup>67</sup> Ibid., 349–62; Sneader, *Drug Discovery: A History*, 210; and Scriabine, “Discovery and Development of Major Drugs Currently in Use,” 243–46. See also Patton and Byron, “Inhaling Medicines.” <sup>68</sup> See [www.freepatentsonline.com/4866051.html](http://www.freepatentsonline.com/4866051.html).

<sup>69</sup> See Maxwell and Eckhardt, *Drug Discovery: A Casebook and Analysis*, 209–19; Scriabine, “Discovery and Development of Major Drugs Currently in Use,” 246–52; Sneader, *Drug Discovery: A History*, 359–60; and Lednicer, *New Drug Discovery and Development*, 91–109.

1964, with fewer gastrointestinal effects than aspirin and without the problems caused by the corticosteroids. Subsequently, other firms introduced such other NSAIDs as naproxen, ketoprofen, and fenoprofen, which generally are more potent than ibuprofen, have beneficial effects that are more long-lasting, and take effect more gradually. In sum, again, private research yielded a series of compounds with improved clinical properties and reduced side effects.

**16. Cox-2 Inhibitors.**<sup>70</sup> It was not until the 1970s that the therapeutic action of aspirin and other NSAIDs was identified: it inhibits prostaglandin production by the cyclooxygenase (Cox) enzyme, an effect that yields both the therapeutic and adverse side effects of the NSAIDs. In the late 1980s, two scientific teams—one from Brigham Young University and Harvard University, the other from UCLA—identified a new gene that codes for a second form of the Cox enzyme. This discovery of that second form engendered a renewed search for anti-inflammatory drugs. The basic hypothesis was that inhibition of the (older) Cox-1 might be the cause of the familiar adverse side effects, while inhibition of the newly discovered Cox-2 might yield the desired anti-inflammatory effect. In 1990, researchers at the Dupont Company developed a drug called DuP697 and presented evidence that its benign gastric effects indeed were due to the different inhibition of the Cox enzymes. Researchers from Taisho Pharmaceutical reported the same effect with a different drug, called NS398. These findings induced rapid innovation: G. D. Searle developed celecoxib after screening more than 2,500 compounds, and Merck developed rofecoxib, which was withdrawn from the market in 2004.<sup>71</sup> This private research effort represents the classic pattern: a discovery of compounds exploiting the targets identified by more basic research conducted at the university level.

**17. Long-Acting Opioids.**<sup>72</sup> Oxycodone was synthesized in 1916 by scientists at the University of Frankfurt; an alternative method for synthesizing the drug subsequently was developed at Knoll Pharmaceuticals. More recently, research has been aimed at development of powerful analgesics less addictive than morphine and other available opioids. The FDA approved Oxycontin (Purdue Pharmaceuticals) in 1995; it is a controlled-release variant of oxycodone. Private research in this case produced a drug with improved characteristics for clinical practice.

**18. Fluoroquinolone Antibiotics.**<sup>73</sup> The development of fluoroquinolone antibiotics began in 1946 when scientists at the Sterling-Winthrop Research Institute synthesized a new form of chloroquine, a by-product of which was found to be effective against certain bacteria. Further work by scientists at Sterling in the early 1960s led to the discovery of nalidixic acid, which was followed by Warner-Lambert's oxolinic acid and by several discoveries in the 1970s and 1980s, particularly by private pharmaceutical firms in Japan. Ciprofloxacin was discovered by Bayer, and approved by the FDA in 1987; it is far more potent than nalidixic acid, and after testing against 20,000 different bacteria strains, it is shown to be effective (in varying degrees) against over 98 percent of them. Several additional such antibiotics were synthesized and approved over the following years, among them norfloxacin, levofloxacin, and gemifloxacin. This process of private-sector research, synthesis, testing, and approval has yielded a succession of antibiotics increasingly potent, with fewer side effects, more narrowly targeted, and effective against strains of bacteria developing resistance to older drugs.

**19. Third-Generation Cephalosporins.**<sup>74</sup> Cephalosporins first were discovered by Giuseppe Brotzu in

<sup>70</sup> See Flower, "The Development of Cox-2 Inhibitors"; Sneader, *Drug Discovery: A History*, 420; Lednicer, *New Drug Discovery and Development*, 106–8; and Scriabine, "Discovery and Development of Major Drugs Currently in Use," 251–52.

<sup>71</sup> See *FDA Consumer Magazine*, "Merck Withdraws Vioxx."

<sup>72</sup> See Sneader, *Drug Discovery: A History*, 119–20; and Lednicer, *New Drug Discovery and Development*, 80–82.

<sup>73</sup> See Payne et al., "Drugs for Bad Bugs"; Sneader, *Drug Discovery: A History*, 394–95; Lednicer, *New Drug Discovery and Development*, 15–17; and Scriabine, "Discovery and Development of Major Drugs Currently in Use," 172–73.

<sup>74</sup> See Hara, *Innovation in the Pharmaceutical Industry*, 144–58; Scriabine, "Discovery and Development of Major Drugs Currently in Use," 168–70; Sneader, *Drug Discovery: A History*, 324–28; and Lednicer, *New Drug Discovery and Development*, 12–14.



Sardinia and by researchers at Oxford in the late 1940s and early 1950s; but they proved not to be clinically useful. However, the Oxford researchers did develop cephalosporin C, and a research team at Ciba subsequently developed a process for producing it on a large scale. Cephalosporin C shared some characteristics with various penicillins, so a number of researchers sought methods with which to transform penicillins into cephalosporins in order to treat a broader range of conditions. The effort at Lilly was successful and led to the discovery in 1962 of cephalothin, the first clinically useful cephalosporin. Further work at Lilly and Bristol-Myers developed newer versions of these drugs with effectiveness against an even broader range of conditions, and with improved absorption properties.<sup>75</sup> Second-generation cephalosporins were developed in the 1970s and were effective against a wider spectrum of bacteria—in particular, against organisms resistant to penicillins. Among the first was cefoxitin, developed at Merck and patented in 1971; but it is not effective when taken orally. Lilly then developed cefaclor (Ceclor), effective orally, and approved by the FDA in 1979. Another advance was Glaxo's cefuroxime (Ceftin), which has improved absorption characteristics from the digestive tract. The first third-generation cephalosporin to be marketed in the U.S. was cefotaxime (Claforan), developed by Hoechst-Roussel and approved by the FDA in 1981. It offers a broader range of antibacterial activity with a longer therapeutic effect. Another is cefprozil (Cefzil), approved by the FDA in 1991; it is effective when administered orally. Another example is ceftriaxone (Rocephin), developed by Hoffmann-La Roche and approved by the FDA in 1984. It is effective for substantially longer periods of time, so that some conditions can be resolved with a single dose. As in the case of the fluoroquinolone antibiotics, private-sector research has led to the discovery, develop-

ment, and introduction of a succession of drugs with improved potency, improved clinical properties, and, again, effective against strains of bacteria developing resistance to older drugs

**20. Imidazole and Triazole Antifungals.**<sup>76</sup> The incidence (by population proportion) of fungal diseases has grown over the last several decades—perhaps in substantial part, as reported, in response to the expanding array of drugs useful in treating them—and fungal diseases are now recognized as common complications of cancer chemotherapy and AIDS. After some early successes with the use of imidazoles as anesthetics, researchers at Janssen developed miconazole and determined it to be an antifungal effective against a wide range of infections. However, it was not absorbed well from the digestive system and so could not be administered orally; further research at Janssen resulted in the development of ketoconazole in 1976, the first broad-spectrum imidazole suitable for oral administration. It was approved by the FDA in 1981. Further work at the drug companies was aimed at increasing the oral effectiveness and reducing the side effects of the antifungals; Pfizer researchers tested hundreds of analogues to ketoconazole, eventually synthesizing fluconazole (Diflucan), which received FDA approval in 1990. It is about 100 times as potent as ketoconazole, with better effectiveness when administered orally. It also can be administered once daily.

**21. Antivirals (Herpes Simplex/Zoster).**<sup>77</sup> The synthesis of acyclovir was a milestone in the development of antiviral drugs; it proved not to be toxic even at concentrations more than 100 times those required for antiviral effect, and it is effective against a range of herpes-like viruses.<sup>78</sup> It was approved by the FDA in 1985 and marketed as Zovirax by

<sup>75</sup> See Ryan et al., "Chemistry of Cephalosporin Antibiotics."

<sup>76</sup> See Scriabine, "Discovery and Development of Major Drugs Currently in Use," 176–78; and Sneader,

<sup>77</sup> See Brazil, "Herpes Simplex Achilles' Helicase"; De Clercq, "Three Decades of Antiviral Drugs"; idem, "Strategies in the Design of Antiviral Drugs"; Wastila and Lasagna, "The History of Zidovudine"; and Scriabine, "Discovery and Development of Major Drugs Currently in Use," 352–55.

<sup>78</sup> Examples noted by Scriabine, "Discovery and Development of Major Drugs Currently in Use," are HSV-1 (herpes simplex virus-1), HSV-2, and the varicella-zoster virus.

GlaxoSmithKline. Work in the late 1940s at Burroughs Wellcome, Sloan Kettering, and Indiana University demonstrated that certain purine compounds inhibited some viruses in the laboratory. Side effects in animal tests led Burroughs to abandon the search for antiviral compounds for many years. However, other researchers pursued the use of purines as antivirals, with some success; such new findings led Burroughs almost twenty years later to resume this work, which led to the synthesis in the mid-1970s of acyclovir, a drug that proved highly active against the herpes simplex virus (HSV) and others. The Burroughs team included Gertrude B. Elion and George H. Hitchings, both of whom shared the Nobel Prize in Physiology or Medicine (with James W. Black) in 1988, in part for the synthesis of acyclovir. In sum, private-sector research led to the discovery of a compound that exploited previous research findings and that displayed sharply lower toxicity in clinical practice.

**22. HIV Antiretrovirals/Nucleoside Reverse Transcriptase Inhibitors (NRTIs).**<sup>79</sup> Enfuvirtide was the first drug to inhibit the entry of HIV-1 virus into host (CD4) cells. It was approved by the FDA in 2003, and marketed by Roche as Fuzeon. Highly active antiretroviral therapy (HAART) has combined several classes of drugs in “cocktails” tailored for individual patients and their respective strains of HIV virus. Such therapy, however, eventually fails for the majority of patients, particularly because of increasing drug resistance. Accordingly, there is a continuing need for new antiretrovirals effective against HIV strains resistant to existing therapies. Enfuvirtide is such a drug, developed in a partnership between researchers at Duke University who formed a pharmaceutical company

called Trimeris, and scientists at Roche Laboratories. It inhibits HIV-1 but not (the less virulent) HIV-2. Matthews et al. note<sup>80</sup> that “it is by far the most complex antiretroviral ever manufactured at such a large scale.” The enfuvirtide molecule is large (in the context of small-molecule drugs), and thus the manufacturing process is highly complex, involving 106 steps.<sup>81</sup> (A typical manufacturing process for small-molecule drugs involves eight to twelve steps.) This highly complex large-scale manufacturing process itself can be viewed as a significant scientific achievement, as was the previous effort to develop drugs effective against strains of HIV exhibiting resistance to older therapies.

AZT (zidovudine) was first synthesized in 1964 at the Michigan Cancer Foundation (under an NIH grant) as a potential drug for leukemia. In the mid-1970s, German scientists reported that AZT inhibited a retrovirus, but little interest ensued because retroviruses were unknown in humans. But in 1983, scientists in France isolated HIV and determined that it is a retrovirus. Scientists at Burroughs Wellcome then began programs to search for drugs that would attack retroviruses; AZT was one of fourteen chosen for screening, and laboratory results obtained in late 1984 were highly encouraging. Samples of AZT were then sent to the National Cancer Institute for further testing; the scientists there concluded quickly that it was highly effective. The NCI findings were replicated at Duke University; subsequently, clinical trials were conducted, and AZT received FDA approval in 1987. It is marketed by GlaxoSmithKline as Retrovir. In the context of AZT, the historical record makes it clear that private research used prior scientific findings to find a compound effective against a particular retrovirus.<sup>82</sup>

<sup>79</sup> See Matthews et al., “Enfuvirtide”; Lednicer, *New Drug Discovery and Development*, 32–33; Scriabine, “Discovery and Development of Major Drugs Currently in Use,” 175–76; and Sneader, *Drug Discovery: A History*, 260–64.

<sup>80</sup> Matthews et al., “Enfuvirtide,” 224.

<sup>81</sup> See Ng, *Drugs: From Discovery to Approval*, 249.

<sup>82</sup> Angell, *The Truth about the Drug Companies*, 25–26, argues that Samuel Broder of the NCI in 1985 “found that AZT was effective against the AIDS virus in test tubes” after which “Burroughs Wellcome immediately patented the drug to treat AIDS and carried out later trials.” She does not note that it was previous research at Burroughs Wellcome by Marty St. Clair and Janet Rideout that demonstrated the powerful effectiveness of AZT against retroviruses; Burroughs Wellcome then collated all its information from previous studies of AZT and sent samples of AZT to the NCI “for further evaluation by Samuel Broder and Hiroaki Mitsuya.” See Sneader, *Drug Discovery: A History*, 261.

### **23. Hypoglycemic Agents and Thiazolidinediones.**<sup>83</sup>

In 1947, researchers at the U.S. Vitamin Corporation synthesized metformin, a drug introduced in Europe in 1957 to treat diabetes. Because of side effects, it was not marketed in the U.S. (as Glucophage, Bristol Myers Squibb) until its approval by the FDA in 1995. In 1975, researchers at Takeda Laboratories synthesized a number of compounds in the search for agents with hypoglycemic effects. A candidate compound (AL-321) was chosen, a large number of analogues were developed, and pioglitazone was discovered and approved by the FDA as Actos in 1999. Researchers at SmithKlineBeecham enhanced the potency of pioglitazone, and rosiglitazone was the result. It, too, received FDA approval in 1999, and is marketed as Avandia. Both drugs reduce blood-sugar levels by lowering resistance to insulin in patients with type-2 diabetes. In short: private-sector research efforts yielded the initial and improved compounds of a drug used widely.

### **24. Selective Estrogen Receptor Modulators.**<sup>84</sup>

Approved by the FDA in 1977, tamoxifen for many years has been the frontline treatment for estrogen-positive receptor breast cancer. Professor Charles Huggins of the University of Chicago conducted the earliest studies on the use of sex hormones for cancer therapy. Further work was done in the 1940s at the University of Edinburgh and at ICI, which received a British patent in 1944 for an artificial estrogen. Tamoxifen was synthesized in 1962 by scientists at ICI, who discovered that one of its components acted as a blocker for estrogen receptors. It was patented in 1964, and shown to be efficacious in a large clinical trial in Manchester in 1971. Private-sector work ap-

pears to have been central throughout the process of discovering biologic targets and drugs designed to exploit them.

**25. Chemotherapy Agents.**<sup>85</sup> In 1964, scientists at Michigan State University discovered that electric current transmitted by platinum electrodes interfered with the division of bacteria cells. Alternative compounds containing platinum were tested, and a number were found to block cell division.<sup>86</sup> The findings were reported in 1969, and cisplatin, a chemical containing platinum, was subjected to successful clinical tests. Further work on alternative platinum compounds and on kidney toxicity attendant upon administration of cisplatin was conducted in England, at Bristol Myers, and at the National Cancer Institute. Cisplatin was approved by the FDA in 1978 and marketed by Bristol Myers as Platinol. Private research thus contributed to the discovery of a compound exploiting an earlier advance in basic biologic science.

**26. 5-HT<sub>3</sub> Blockers.**<sup>87</sup> Work by scientists at the University of Edinburgh in the 1950s centered on some nerve/serotonin interactions and distinguished between different serotonin receptors.<sup>88</sup> One of these later was renamed the 5-HT<sub>3</sub> receptor; one important problem caused by chemotherapy is nausea caused when cells in the gastrointestinal tract release 5-HT. Further work by scientists at Glaxo identified receptor blockers, and then synthesized a number for testing. One, named ondansetron, was found active when taken orally and was approved for antinausea therapy by the FDA in 1991. It is marketed as Zofran by GlaxoSmithKline. This is another example of the

<sup>83</sup> See Scriabine, "Discovery and Development of Major Drugs Currently in Use," 254–55; Sneader, *Drug Discovery: A History*, 274–76; Cohen and Goedert, "GSK3 Inhibitors"; and Ashiya and Smith, "Non-Insulin Therapies for Type-2 Diabetes."

<sup>84</sup> See Jordan, "Tamoxifen (ICI46474) as a Targeted Therapy to Treat and Prevent Breast Cancer"; idem, "Tamoxifen: A Most Unlikely Pioneering Medicine"; Bedford and Richardson, "Preparation and Identification of *cis* and *trans* Isomers of a Substituted Triarylethylene"; Sneader, *Drug Discovery: A History*, 198–99; Lednicer, *New Drug Discovery and Development*, 116–17; and Scriabine, "Discovery and Development of Major Drugs Currently in Use," 262.

<sup>85</sup> See Johnson, "Evolution of Cisplatin-Based Chemotherapy in Non-Small Cell Lung Cancer"; Kamb et al., "Why Is Cancer Drug Discovery So Difficult?"; Scriabine, "Discovery and Development of Major Drugs Currently in Use," 263–64; and Sneader, *Drug Discovery: A History*, 63–64. <sup>86</sup> See Rosenberg et al., "Platinum Compounds."

<sup>87</sup> See Sneader, *Drug Discovery: A History*, 216–18.

<sup>88</sup> Gaddum and Picarelli, "Two Kinds of Tryptamine Receptor."

recurrent theme: private research yielding compounds exploiting the targets identified by basic research.

**27. PDE5 Blockers.**<sup>89</sup> The search for asthma treatments led to a discovery in the early 1960s that a particular enzyme (a peptide) had the effect of relaxing involuntary muscles.<sup>90</sup> Further work discovered several variants of that enzyme, as well as the fact that PDE5 in kidney tissue inhibits the effect of the peptide. Accordingly, research at Pfizer in the mid-1980s focused on the development of an antagonist to PDE5, which might have the effect of using kidney function to reduce blood pressure by increasing the excretion of sodium and water. The Pfizer team focused on zaprinast, a compound that had been developed at Rhône Poulenc but that had gone unmarketed. They created a number of chemical variations of zaprinast, and after the synthesis of more than 1,600 compounds, sildenafil was discovered as an inhibitor of PDE5 with 100 times the potency of zaprinast. Clinical trials were discouraging when the drug was tested on patients with coronary heart disease, but “one of several side effects was only revealed when participants in a trial of sildenafil on 30 men in the Welsh town of Merthyr Tydfil in 1992 were questioned about their reluctance to return unused tablets when the trial was stopped.”<sup>91</sup> Sildenafil reverses erectile dysfunction and has advantages over earlier treatments in terms of safety and effectiveness when taken orally. It was approved by the FDA in 1998, and marketed by Pfizer as Viagra. In this case, private research efforts in the development of a compound for one purpose yielded beneficial effects in a very different clinical function.

**28. Nonsedating Antihistamines.**<sup>92</sup> Several synthetic antihistamines were developed in the late 1940s, but their major side effect was sedation. Researchers at American Schering in 1951 synthesized chlorpheniramine (Chlor-Trimeton), which caused less sedation than the antihistamines available earlier. Researchers at the Richardson-Merrell Company in 1973 developed terfenadine as a potential tranquilizer; it performed poorly in that function, but was then tested and found to be a nonsedating antihistamine. However, it had toxic cardiac effects when taken with some other medicines, and was withdrawn from the market. Subsequent efforts at Schering-Plough to develop antihistamines with anti-ulcer properties led to the discovery of loratadine, which received FDA approval in 1993, and was marketed by Schering-Plough as Claritin. Other successful compounds are cetirizine (Zyrtec), approved by the FDA in 1995, and fexofenadine (Allegra), approved by the FDA in 1996. In short, private research yielded a series of improved compounds.

**29. Immunosuppressants.**<sup>93</sup> The first drug acting as an immunosuppressant was mercaptopurine (Purinethol), discovered as an anti-leukemia drug by researchers at Wellcome in 1952. Several years later, scientists at Tufts University and the Harvard Medical School tested a number of existing drugs for immunosuppressive effect; mercaptopurine was found to be the most effective. The Wellcome researchers subsequently screened a number of compounds related to mercaptopurine, and chose azathioprine (Imuran) for further research. It received FDA approval in 1959. In 1972, researchers

<sup>89</sup> See Sneader, *Drug Discovery: A History*, 135–36; Lednicer, *New Drug Discovery and Development*, 53–54; and Scriabine, “Discovery and Development of Major Drugs Currently in Use,” 265–66.

<sup>90</sup> This is discussed in Terrett et al., “Sildenafil (VIAGRA™), A Potent and Selective Inhibitor of Type 5 cGMP Phosphodiesterase with Utility for the Treatment of Male Erectile Dysfunction.”

<sup>91</sup> Sneader, *Drug Discovery: A History*, 136.

<sup>92</sup> See Scriabine, “Discovery and Development of Major Drugs Currently in Use,” 230–31; Sneader, *Drug Discovery: A History*, 406–7; and Barnett and Green, “Loratadine.” Note that fexofenadine is the primary active derivative of terfenadine produced in the body when terfenadine is taken. See U.S. Food and Drug Administration, “FDA Approves Allegra-D, Manufacturer to Withdraw Seldane from Marketplace.”

<sup>93</sup> See Maxwell and Eckhardt, *Drug Discovery: A Casebook and Analysis*, 95–108; Scriabine, “Discovery and Development of Major Drugs Currently in Use,” 252–53; and Sneader, *Drug Discovery: A History*, 298–99.

at Sandoz discovered the immunosuppressive effect of cyclosporine; its effectiveness was demonstrated in 1978 in patients undergoing bone-marrow transplants, and it received FDA approval in 1983. Cyclosporine (Sandimmune) yielded a significant advance over the earlier immunosuppressants, in that it acts selectively against tissue rejection, with much less adverse effect on the immune response to infection. Scientists from Fujisawa Pharmaceutical Corporation in 1984 isolated a new immunosuppressant called tacrolimus, which proved effective for patients with liver transplants; it was approved by the FDA in 1994. In 1997, the FDA approved daclizumab (Zenapax) from Hoffmann-La Roche; it is the first drug that blocks only the immune cells attacking a transplanted organ. Accordingly, the early work was pursued by both private and public researchers, but the evolution of improved drugs with fewer side effects and more specific targeting was the result of private-sector research.

**30. 5-Alpha Reductase Inhibitors.**<sup>94</sup> 5-alpha reductase is an enzyme that converts testosterone into a more potent form called dihydrotestosterone. Individuals who have a 5-alpha reductase deficiency tend to display underdevelopment of the prostate gland. Accordingly, scientists at Merck hypothesized that inhibitors of 5-alpha reductase might yield benefits for men suffering not from prostate underdevelopment but from benign prostate enlargement. A screening program for such inhibitors led to the discovery of finasteride (Proscar) in 1985, approved by the FDA in 1992.<sup>95</sup> This is another case in which private research discovered a way to exploit a biologic target.

**31. Triptans (Selective 5-HT<sub>1</sub> Agonists).**<sup>96</sup> The first drug to treat migraine headaches was ergot-

amine, discovered by researchers at Sandoz in 1945. Sandoz researchers discovered methysergide as well in the 1950s; but it can have serious side effects with long-term use. However, its effectiveness in the treatment of migraines aroused interest in compounds with similar characteristics; this led to the discovery at Glaxo of sumatriptan, a drug highly selective as a vasoconstrictor of the carotid arteries (which are stretched by increased blood flow during a migraine attack) through a leveling effect on serotonin in the brain. Sumatriptan was approved by the FDA in 1992 and marketed as Imitrex by GlaxoSmithKline. Several other triptans have been developed and introduced, in efforts to find drugs faster-acting, longer-acting, with greater availability through oral administration, and with fewer side effects. Examples are zolmitriptan (Zomig), naratriptan (Amerge), and frovatriptan (Frova). Again, private research developed a series of compounds exploiting an adverse biologic process and exhibiting improved clinical performance.

**32. Interferons.**<sup>97</sup> Interferons are proteins produced by the immune system in response to the presence of tumors and such foreign agents as viruses. Three distinct interferons have been discovered, designated as alpha, beta, and gamma, with variations within each of the three types. Most pharmaceuticals are “small-molecule” chemicals; proteins are “large-molecule” compounds already produced by living organisms. Accordingly, while small-molecule drugs are produced with chemical processes, large-molecule proteins are produced by living cells. Interferons were discovered by researchers at the National Institute for Medical Research in London and found to increase resistance to a number of

<sup>94</sup> See Scriabine, “Discovery and Development of Major Drugs Currently in Use,” 246; and Sneader, *Drug Discovery: A History*, 206–7.

<sup>95</sup> See Rasmusson et al., “Azasteroids.”

<sup>96</sup> See Sneader, *Drug Discovery: A History*, 216–19; and Scriabine, “Discovery and Development of Major Drugs Currently in Use,” 234–36.

<sup>97</sup> See Ng, *Drugs: From Discovery to Approval*, 75–77, 93; Borden et al., “Interferons at Age 50”; Fitzgerald-Bocarsly, “The History of Interferon”; Scriabine, “Discovery and Development of Major Drugs Currently in Use,” 264; idem, “The Role of Biotechnology in Drug Development,” 284; Sneader, *Drug Discovery: A History*, 272–73; Pieters, *Interferon*, 147–87; and Hall, *A Commotion in the Blood*, 178–208.



viral infections.<sup>98</sup> A method of purifying interferon was developed by scientists at the NIH in the 1970s,<sup>99</sup> but production on a scale sufficient for clinical usefulness required genetic engineering (“cloning”), a process developed for the interferons by researchers at Biogen, Genentech, and Roche. The private researchers succeeded in recombining two different interferon genes into new, hybrid interferons, the “first time that proteins had been engineered in this way, resulting in a new kind of biosynthetic interferons with unique biological properties.”<sup>100</sup> There is no dispute that this private discovery represented a major scientific advance.

Table 3 reorganizes the discussion of our thirty-two drug classes by decade of the respective initial research breakthroughs, and then lists the sources of the three kinds of scientific advances (if revealed by the literature), delineated as basic science, applied science, and improvements in clinical application, manufacturing, and the other later stages of preparing a drug for use.

Among our thirty-two summary case histories for drug classes, the private sector contributed at least seven significant scientific advances in basic science, at least thirty-one in applied science, and at least twenty-five in terms of improved clinical performance of compounds, manufacturing processes, and the other later stages of preparing a drug for use.<sup>101</sup>

These summary case histories suggest strongly that the purely scientific contributions of the private sec-

tor to drug development have not been negligible. Instead, we find that for all or virtually all thirty-five drugs (or drug classes) discussed in this study, the scientific contributions of the private sector were crucial to their discovery or development. The dominant pattern emerging from the case histories is the delineation of a biological target from basic research on disease processes and biological science, often—but not always—conducted at universities or other institutions likely to have received government funding.<sup>102</sup> That investigation of biological targets—enzymes, receptors, and so on—is followed by scientific advances in the discovery, development, synthesis, and screening of inhibitors and other compounds that might prove reactive with the biological targets. Those compounds then must be optimized in terms of their targeting properties, toxicities must be analyzed and research conducted to mitigate them, and large-scale production processes must be invented or adapted.

These findings are consistent with other surveys available in the literature. Maxwell and Eckhardt find that for the development of the thirty-two innovative drugs examined, 75 percent had crucial scientific contributions from the pharmaceutical industry; for government and universities, the respective figures are 9 percent and 53 percent. For 38 percent of the drugs, crucial scientific contributions came solely from the industry; for 22 percent, they came from nonindustrial sources.<sup>103</sup> Cockburn and Henderson found that of nineteen “key enabling discoveries” in their list of twenty-one drugs, publicly funded research was responsible for fourteen, while private

<sup>98</sup> Isaacs and Lindenmann, “Virus Interference. I. The Interferon.”

<sup>99</sup> See Anfinson et al., “Partial Purification of Human Interferon by Affinity Chromatography.”

<sup>100</sup> Pieters, *Interferon*, 159–60, referencing Charles Weissmann, one of the central Biogen researchers.

<sup>101</sup> For basic science, this estimate may understate the private-sector contribution in that the available literature often provides little or no information on the respective historical discoveries of the biologic disease processes and the like. With respect to applied science, we exclude the PDE5 blockers in that the medical action of sildenafil was discovered somewhat by accident even though accidental discovery is a dominant theme in the history of most scientific inquiry.

<sup>102</sup> Note that universities and other major nonprofit research centers sometimes collaborate with pharmaceutical firms. See, e.g., [www.answers.com/topic/the-scripps-research-institute?cat=biz-fin](http://www.answers.com/topic/the-scripps-research-institute?cat=biz-fin). See also Bremer, Innes, and McKinney, “Academic Technology Transfer,” 6–7.

<sup>103</sup> Maxwell and Eckhardt, *Drug Discovery: A Casebook and Analysis*, 422–23.

Table 3. Summary Findings for Thirty-Two Drug Classes				
Decade Initial Res. Finding	Drug Class	Basic Science	Applied Science	Clinical Improvement, Manufacturing, etc.
1890s	NSAIDs		Bayer, Merck	Boots Pharm., Merck
1910s	Long-Acting Opioids	U. Frankfurt	Knoll Pharm.	Purdue Pharm.
1940s	Beta Blockers	Emory U.	Lilly	ICI
1940s	Statins	NIH	Sankyo Co. Beecham Labs Merck	Pfizer, others
1940s	Bronchodilators	Boehringer Ing. U. Georgia	Boehringer Ing. Allen&Hanbury	Astra Pharm.
1940s	Inhaled Corticosteroids		Glaxo	Glaxo
1940s	Fluoroquinolones	Sterling-Winthrop	Sterling-Winthrop Warner-Lambert	Bayer, others
1940s	Third-Generation Cephalosporins	Oxford U.	Lilly, Bristol-Myers, others	Ciba, Lilly, others
1940s	Antivirals	Burroughs-Wellcome Indiana U., Sloan-K.	Burroughs-Wellcome	Burroughs-Wellcome
1940s	Hypoglycemic Agents/ Thiazolidinediones	U.S. Vitamin Corp.	SmithKlineFrench Takeda Labs	BristolMyersSquibb, SmithKlineBeecham
1940s	Selective Estrogen Rec. Modulators	U. Chicago	U. Edinburgh, ICI	
1940s	Nonsedating Histamines		American Schering Richardson-Merrell	Schering-Plough others
1940s	Triptans		Sandoz	Glaxo, others
1940s	Platelet Aggregation Inh.	Karl Thomae Co. Medical Res. Council		Roche, others
1950s	Fibrates		ICI, W.H.O.	Parke-Davis
1950s	SSRIs		Hoffmann-La Roche	J. R. Geigy, Lilly
1950s	5-HT3 Blockers	U. Edinburgh	Glaxo	
1950s	Immunosuppressants		Harvard U. Tufts U. Sandoz, Wellcome	Hoffmann-LaRoche, Fujisawa Pharm.
1950s	Interferons	National Inst. Medical Research (London)	NIH, Biogen, Genentech, Roche	Biogen, Roche, Genentech
1960s	ACE Inhibitors		Royal College of Surgeons, Squibb, U. North Carolina, NIH	Squibb
1960s	Calcium Channel Bl.	U. Freiburg	Bayer	
1960s	H2 Blockers	SmithKlineFrench	SmithKlineFrench	GlaxoSmithKline
1960s	Proton Pump Inh.	SmithKlineFrench	Astra Pharm.	Astra Pharm.
1960s	Chemotherapy Agents	Michigan St. U.	BristolMyersSquibb, National Cancer In.	BristolMyersSquibb, National Cancer In.
1960s	PDE5 Blockers		Pfizer, Rhone-Poulenc	
1970s	Imidazole/Triazole Antifungals		Janssen, Pfizer	Janssen, Pfizer
1970s	Cox-2 Inhibitors	Brigham Young U. Harvard U. UCLA	Dupont, Taisho Pharm. Merck, Searle	
1980s	Angiotensin II Ant.		Takeda Ind. Dupont-Merck	Ciba-Geigy
1980s	SNRIs		Lilly	
1980s	5-Alpha-Reductase Inh.		Merck	
1990s	HIV Antiretrovirals/NRTIs	Michigan Cancer Fndn.	Duke U., Roche GlaxoSmithKline NCI	Burroughs-Wellcome Roche
1990s	Cholesterol Absorption Inh.		Schering-Plough	
Source: Section III summary case histories				

research was responsible for the synthesis of the compound in sixteen of eighteen cases.<sup>104</sup> The Joint Economic Committee found that “public funding of research was instrumental in the development of 15 of the 21 drugs”; but, as noted above, only ten of the fifteen are not duplicated in their list.<sup>105</sup> The NIH study found that of all forty-seven FDA-approved drugs meeting a \$500 million annual sales threshold in 1999, “it was determined that NIH has Government use or ownership rights to *patented technologies* used in the development of four of those drugs.”<sup>106</sup> The GAO found that “in 2001 the government had licensing rights in only 6 brand name drugs associated with the top 100 pharmaceuticals that VA procured and in 4 brand name drugs associated with the top 100 pharmaceuticals that DoD dispensed.”<sup>107</sup>

#### IV. SUMMARY CASE HISTORIES FOR TAXOL, EPOGEN, AND GLEEVEC

Of the many criticisms directed at the pharmaceutical industry over the last few years, one of the most damning is that the industry produces few, if any, of the scientific breakthroughs responsible for the medicines it sells. Angell, for example, argues that “publicly funded medical research—not the industry itself—is by far the major source of innovative drugs.”<sup>108</sup>

Angell illustrates her argument by citing Taxol, Epogen, and Gleevec as examples “of the many impor-

tant drugs not discovered by big pharma” and by presenting brief case histories of their development.<sup>109</sup> As shown below, Angell’s discussion of these three drugs<sup>110</sup> is incomplete at best, yielding a narrative not supported by fuller accounts of how these compounds evolved from interesting ideas into breakthrough medicines.

#### Taxol

Angell’s account of the development of Taxol can be summarized as follows.<sup>111</sup> Paclitaxel (the active ingredient in Taxol) was derived from the bark of the Pacific yew tree in the 1960s. In 1991, Bristol-Myers Squibb (BMS) signed a cooperative research and development agreement (CRADA) with the National Cancer Institute (NCI), a part of the NIH. The main contribution of BMS was providing the NCI with seventeen kilograms of paclitaxel, which the firm obtained from a chemical company. The Pacific yew was in short supply, a problem for BMS solved in 1994 by NIH-funded scientists at Florida State University, who devised a method of synthesizing paclitaxel and who promptly licensed it to BMS. The company spent very little on research and development before getting initial approval to treat cancer of the ovary with the drug, but has undoubtedly spent substantial sums since then on testing it on other cancers. All the research on Taxol, which Angell calls “the bestselling cancer drug in history,”<sup>112</sup> was conducted at, or supported by, the NCI over thirty years, at a cost to

<sup>104</sup> See Cockburn and Henderson, “Absorptive Capacity, Coauthoring Behavior, and the Organization of Research in Drug Discovery,” Table 1.

<sup>105</sup> See Joint Economic Committee, *The Benefits of Medical Research and the Role of the NIH*, 27. See also n. 28, above.

<sup>106</sup> Emphasis added. See National Institutes of Health, “A Plan to Ensure Taxpayers’ Interests Are Protected,” 13–14. The four are Taxol, Epogen, Procrit, and Neupogen. As noted in Section I, research in basic science (funded by the NIH) often yields advances that are not patentable.

<sup>107</sup> See U.S. General Accounting Office, *Agencies’ Rights to Federally Sponsored Biomedical Inventions*, GAO-03-536, 1.

<sup>108</sup> Angell, *The Truth about the Drug Companies*, 59.

<sup>109</sup> *Ibid.*, 58; emphasis in the original. Angell makes the same claim for AZT, discussed above in Section III; see n. 82, above.

<sup>110</sup> See Angell, *The Truth about the Drug Companies*, 56–65.

<sup>111</sup> *Ibid.*, 58–59.

<sup>112</sup> *Ibid.*, 58. It is not clear whether by “bestselling” Angell means by revenues or by prescriptions.



taxpayers of \$183 million. Angell sums up her Taxol account by asserting that “it was virtually given as a gift to a large drug company for marketing, commercial exploitation, and further development. The public pays again when it buys Taxol at the exorbitant price Bristol-Myers Squibb charges for a drug it neither discovered nor developed.”<sup>113</sup>

That version of the extensive and complicated history of the discovery and development of Taxol omits a series of important events and thus minimizes and misrepresents the interdependence of and interplay between the public and for-profit sectors, which eventually made this drug one of the first breakthrough treatments for cancer.

A more complete history of Taxol begins in the mid-1950s, when the NCI, inspired by Eli Lilly’s discovery of the cancer drugs vinblastine and vincristine, which derived from tropical plants in Madagascar, began to screen natural extracts from around the world for anticancer activity. In the 1960s, the NCI entered into an agreement with the U.S. Department of Agriculture, under which the latter was to focus on plant-derived extracts. One of its successes was an extract from the bark of the Pacific yew tree, *taxus brevifolia*, from which paclitaxel was isolated by a biochemist at Research Triangle Park in North Carolina, who renamed it Taxol. Although Taxol looked very promising, major impediments to further research soon arose. First, although the NCI continued to commission the isolation of increasing quantities of the extract, by the late 1960s it had accumulated only a few grams of the pure material, not enough for more than initial testing. Second, Taxol was only mildly active against leukemia, the disease receiving the most attention at that time, and probably for this reason it languished in NCI labs for half a decade.<sup>114</sup>

However, in the wake of the declaration of the War on Cancer and the enactment of the National Cancer Act in 1971, the NIH reinvigorated its search for any promising cancer-fighting agents. Work at the Albert Einstein College of Medicine on microtubule formation demonstrated that Taxol had the potential to affect cell division and thus possibly to impede cancer growth. By 1978, Taxol showed promising in vitro activity, and over the next few years showed indications of activity in vivo as well. It took a number of years to transform the compound into a drug that could be administered and to resolve dosing issues sufficiently to proceed with testing beyond animals. In late 1982, the NCI applied for an Investigational New Drug permit for human trials.<sup>115</sup>

Before it could be determined whether Taxol would prove effective as an anticancer agent, the practical problem of getting enough of the compound to perform the necessary tests became paramount. As Phase I and II trials took place over the next few years, the NCI realized that harvesting the necessary amount of bark would decimate Pacific yew populations. It was estimated that 360,000 trees would have to be destroyed annually if Taxol were used as a treatment for ovarian cancer alone.<sup>116</sup> Because of the practical and attendant financial obstacles, the NCI decided to enter into a partnership with a pharmaceutical company. NCI’s ulterior motive may actually have been to shift the problems associated with developing Taxol onto some other entity.<sup>117</sup>

In August 1989, the NCI published a CRADA Opportunity, under whose terms NCI would turn over its existing supply of Taxol as well as its research into the compound in exchange for assistance with processing and purifying it and funding further clinical trials. Only four companies responded, and BMS was

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<sup>113</sup> Ibid., 59.

<sup>114</sup> See Goozner, *The \$800 Million Pill*.

<sup>115</sup> Goodman and Walsh, *The Story of Taxol*, 93–99.

<sup>116</sup> See Stephenson, “A Tale of Taxol.”

<sup>117</sup> See Goodman and Walsh, *The Story of Taxol*, 140.

selected, at which point the problems associated with harvesting noted above came to be borne by BMS. For a number of years, scientists in France and the United States had been interested in how best to extract useful materials from the *Taxus* species without cutting the trees down. By 1989, researchers at Florida State University had developed a semisynthetic process employing yew needles and petrochemical-derived starting materials. Although the work had been done as a way of advancing chemical science, not to develop a production technique, BMS recognized it as a possible solution to the production problem and obtained a license to the patented process from Florida State. BMS started to manufacture the trademark drug Taxol in Ireland from the needles of the more plentiful European yew instead of the bark of the Pacific yew. It was approved by the FDA at the end of 1992. BMS ended its reliance on the Pacific yew entirely within a few years.<sup>118</sup>

Within three years of signing the CRADA, BMS was engaged in Taxol's large-scale production, the lack of which had hindered the development of this invaluable drug for thirty years. BMS continued to work on the process and in 2004 received the Greener Synthetic Pathways Award from the U.S. Environmental Protection Agency for replacing the semisynthetic process of making Taxol with plant-cell fermentation technology.<sup>119</sup> BMS spent a billion dollars to solve the problem of production without destruction of the yew tree inventory, and beyond that to explore and expand the medical utility of Taxol, which remains a major pharmaceutical, whether prescribed alone or in combination with other drugs for the treatment of ovarian, breast, and lung cancer as well as the AIDS-related condition of Kaposi's sarcoma.<sup>120</sup>

## Epogen

Angell argues, in summary, that the history of Epogen begins with the discovery in 1976, by Eugene Goldwasser, a researcher working at the University of Chicago, of a hormone called erythropoietin, which stimulates the production of red blood cells, a shortage of which is the cause of anemia. Another NIH-funded researcher at Columbia University invented a technique for synthesizing biologics, that is, drugs produced through the action of living cells rather than through chemical synthesis. Amgen, a start-up biotechnology company at the time, obtained a license for the technique and with it was able to achieve large-scale commercial production of the erythropoietin molecule. But before Amgen could reap huge profits from erythropoietin, it had to obtain financing by selling its rights to market Epogen in the United States for all medical uses—mainly the treatment of various cancers—other than treatment of kidney failure, and for all uses in Europe. The rights were purchased by Johnson & Johnson, which made essentially no contribution to the original development of erythropoietin. Angell summarizes the history of Epogen: “[T]here was ingenuity aplenty on the part of both Amgen and J & J in exploiting commercial opportunities, but not much of that had to do with the initial discovery of the hormone and its role in the treatment of anemia.”<sup>121</sup>

A fuller history reveals that Amgen's role was pivotal, not only in taking erythropoietin from a biological theory to a pharmaceutical product but also in beginning the biotechnology revolution. Although the biological role of erythropoietin was discovered in the 1950s and its medical potential recognized as early

<sup>118</sup> See Stephenson, “A Tale of Taxol.”

<sup>119</sup> U.S. Environmental Protection Agency, 2004 Greener Synthetic Pathways Award, *Bristol-Myers Squibb Company: Development of a Green Synthesis for Taxol Manufacture via Plant Cell Fermentation and Extraction*, at <http://www.epa.gov/greenchemistry/pubs/pgcc/winners/gspa04.html>.

<sup>120</sup> See Goozner, *The \$800 Million Pill*, 191. <sup>121</sup> Angell, *The Truth about the Drug Companies*, 60–62.

<sup>121</sup> Angell, *The Truth about the Drug Companies*, 60–62.

as the mid-1970s, ten years later a major problem remained: “[T]he routine administration of erythropoietin for the treatment of anemia in patients with renal failure has hitherto been impossible because there is no source from which native human erythropoietin can be extracted in a sufficient quantity for therapeutic use.”<sup>122</sup> Amgen identified the erythropoietin gene and created a recombinant form of erythropoietin, with preliminary results reported in 1984.<sup>123</sup> More work followed in the mid-1980s. The production of a recombinant version was reported in February 1985 by a team of researchers from the biotechnology company Genetics Institute, from Kumamoto University, and from Wright State University, with support from Chugai Pharmaceuticals of Japan.<sup>124</sup> In November 1985, Amgen researchers, together with Goldwasser, who was supported by a grant from the National Heart, Lung, and Blood Institute, were able to isolate and characterize the erythropoietin gene from a human genomic library, and then to produce a biologically active recombinant human erythropoietin in Chinese hamster ovary cells.<sup>125</sup> Further development occurred under the auspices of Amgen (U.S.), Cilag (Switzerland), Kirin Brewery (Japan), and Ortho Pharmaceutical (U.S.). The patent for the production of recombinant erythropoietin was awarded to Kirin-Amgen.<sup>126</sup> Once the production problem had been solved, the path was cleared for human trials. From 1987 to 1989, reports were published on the results of trials involving small numbers of patients that were supported by Amgen, Ortho Pharmaceutical, and the

NIH.<sup>127</sup> The drug was approved in Switzerland in 1988 and in the United States in 1989.<sup>128</sup>

In contrast to Angell’s version of events, the development of Epogen entailed a long climb of thirty years, with crucial contributions from both the public and corporate for-profit sectors. There was good basic research in academia that paved the way, but the drug would not have been developed had a series of technical problems not been overcome by teamwork among industry and academic researchers working on three continents. Most telling of all is a comment by Merrill Goozner, a frequent critic of the pharmaceutical industry, about the development of Epogen: “Once Amgen could make artificial Epo, the road was clear to prove it worked in curing anemia.”<sup>129</sup>

## Gleevec

In Angell’s summary of the development of Gleevec, researchers at the University of Pennsylvania made the initial enabling discovery leading to imatinib mesylate (later called STI 571, and then branded as Gleevec) as a result of the discovery of a new chromosome, dubbed the “Philadelphia chromosome.” It was shown by work at many laboratories that this chromosome carries a gene that directs the production of an abnormal enzyme that causes white blood cells to become cancerous. Similar types of enzymes were thought to be involved in

<sup>122</sup> Winerals et al., “Effect of Human Erythropoietin Derived from Recombinant DNA on the Anaemia of Patients Maintained by Chronic Haemodialysis.”

<sup>123</sup> Lin et al., “Cloning and Expression of Monkey and Human Erythropoietin Gene.”

<sup>124</sup> See Jacobs et al., “Isolation and Characterization of Genomic and cDNA Clones of Human Erythropoietin.”

<sup>125</sup> Lin et al., “Cloning and Expression of the Human Erythropoietin Gene.”

<sup>126</sup> *Production of Recombinant Erythropoietin*, U.S. Patent No. 5441868 at <http://www.freepatentsonline.com/5441868.html>.

<sup>127</sup> See Eschbach et al., “Correction of the Anemia of End-Stage Renal Disease with Recombinant Human Erythropoietin”; and Eschbach et al., “Recombinant Human Erythropoietin in Anemic Patients with End-Stage Renal Disease.”

<sup>128</sup> New Marketed Drugs Database, Tufts Center for the Study of Drug Development, Tufts University, Boston, 2008. The data are available upon request.

<sup>129</sup> Goozner, *The \$800 Million Pill*, 28. <sup>130</sup> Angell, *The Truth about the Drug Companies*, 64. Emphasis in the original.

other cancers, so chemists in Israel and at Novartis set about synthesizing molecules that would inhibit them. Novartis patented several of these in 1994, but its management had no immediate interest in determining whether any of them might be useful in treating chronic myeloid leukemia until Brian J. Druker, from Oregon Health & Science University, in Portland, became interested in the problem. Working with Nicholas Lydon, a scientist and research program director at Novartis, Druker obtained a small supply of several of the company's most promising inhibitors and found imatinib mesylate to be the most potent. Despite concerns about its small potential market and toxicity to dogs at high doses, Druker urged Novartis to explore this exciting lead. Novartis finally agreed to support cautious, limited tests in Druker's clinic and at two other sites. By 1999, Druker was reporting spectacular preliminary results at a national meeting of hematologists, and soon the company was proceeding with large-scale clinical trials. It took only two years for the trials to be completed and the drug to be approved by the FDA. Angell concludes: "[M]ost of Novartis' research and development investment in Gleevec was made several years after there was good scientific evidence to suggest that the drug would be useful."<sup>130</sup>

Dr. Druker tells a different story: "As is the case with any drug, there is a long process before a drug reaches the stage where STI 571 has arrived. In the case of STI 571, the research effort began at Ciba-Geigy (now Novartis) in the early 1990s."<sup>131</sup> Druker goes on to thank a number of people whom he says deserve particular mention. His testimonial confirms two salient points in the Gleevec success story:

- Development of the drug traveled a long and arduous road.
- Many people working in both the for-profit and the public sector made important contributions during the development process.

The person Druker singles out as the most important among all the people that helped him was Lydon. While Druker was working on tyrosine kinases at the Dana-Farber Cancer Institute, he came into contact with Lydon, who was interested in developing inhibitors of tyrosine kinases. Druker convinced Lydon that chronic myelogenous leukemia (CML) should be added to the targets that Novartis already was working on and that tyrosine kinase should be added to Novartis's screening program. In 1993, Druker began to look for the company with the best inhibitor of the Bcr-Abl tyrosine kinase so that he could bring it into clinical trials. His first call was to Lydon, and for the next four years they worked to keep STI 571 on the development track at Novartis.<sup>132</sup>

Only one other research group was taking the same approach, and in the medical-journal reviews of CML in the early and even mid-1990s, the use of tyrosine kinase inhibitors was identified as one of many possible approaches and not necessarily the most promising. Skepticism in the oncology community continued even after Druker and Lydon published their first paper on the subject in 1996. Finally, five years after the paper came out, ten years after work began at Novartis under Lydon, fifteen years after Druker began focusing on kinases at Dana-Farber, and thirty years after the initial work on the genetic basis of CML at the University of Chicago, Gleevec was approved by the FDA in 2001, and the "leukemia pill" became a potent weapon in the medical armamentarium.<sup>133</sup>

In her summary, Angell chastises Novartis for not investing in Gleevec until there was good scientific evidence that Gleevec might be useful. Given that resources are limited, one would hope that this is the approach taken by every company with every drug, because the alternative approach would yield a futile expenditure of massive resources and a likely loss of patients' lives. Contrary to Angell's depiction of Druker as a lone scientist whose pleas fell upon deaf ears is Druker's own testimony to the effect that the

<sup>131</sup> Druker, "A History of STI 571."

<sup>132</sup> Ibid.

<sup>133</sup> Ibid. See also Sneader, *Drug Discovery: A History*, 426.

contributions of his industry colleagues were crucial. Note the therapeutic area from which Angell selected her three accounts: Taxol and Gleevec are predominantly cancer drugs, and one important indication for Epogen is the stimulation of red-blood-cell production in patients undergoing chemotherapy. Cancer research is an area that NIH historically has emphasized more heavily than others,<sup>134</sup> but even so, the contribution of clinicians and chemists working for pharmaceutical and biotech companies was essential to the development of these three drugs for prescription by physicians. The reason for this is clear to most industry observers and public-health stakeholders: significant public research and development investment in the discovery and early development of drugs have proved to be crucial and may be socially efficient;<sup>135</sup> nonetheless, as noted by Médecins Sans Frontières: “The expertise, infrastructure and management capacity for moving these discoveries through the drug development process is concentrated in the private sector.”<sup>136</sup>

## V. CONCLUSIONS AND POLICY IMPLICATIONS

The NIH has stated that “an average of slightly more than half of each Institute’s budget supports the best research grant proposals without regard to specific applicability to a disease, but rather in expectation that their results will contribute to advances against diseases within their purview,

to research in other Institutes, and to our knowledge generally.”<sup>137</sup> This policy is consistent with a system in which public-sector and corporate pharmaceutical research efforts are complementary, with the former weighted more heavily toward the basic science of disease processes and biologics; and the latter more heavily toward the discovery, synthesis, and testing of compounds designed to exploit the knowledge yielded by the former, but with significant overlap.

The complementary nature of public and private research carries an important implication: the high rates of economic return estimated for publicly funded pharmaceutical research and development depend in substantial part on subsequent investment by private companies, without which most of the pharmaceutical products offering those benefits would not be developed. Lichtenberg estimates an annual social return from pharmaceutical innovation of 67.5 percent; other work estimates the annual social return from publicly funded research at 25 to 40 percent.<sup>138</sup> Without the scientific advances yielded by private-sector research, most drugs would not be developed, and thus the economic returns to publicly funded research would be sharply reduced. These figures strongly suggest that policies yielding a reduction in private pharmaceutical research and development would reduce sharply the economic benefits of NIH research efforts, as well as the immense medical benefits derived from the continuous development of new and improved medicines.

<sup>134</sup> See Reichert and Milne, *Public and Private Sector Contributions to the Discovery and Development of “Impact” Drugs*, 8. Note also that in addition to the treatment of anemia resulting from cancer chemotherapy, Epogen has other indications such as chronic renal failure and AIDS-related anemia.

<sup>135</sup> See Gelijns et al., “Capturing the Unexpected Benefits of Medical Research,” 695, for a discussion of factors that might shape the appropriate respective roles of public- and private-sector investment. See also Garber and Romer, “Evaluating the Federal Role in Financing Health-Related Research.”

<sup>136</sup> Médecins Sans Frontières, *Fatal Imbalance*, 18–19. Note that MSF, an independent medical humanitarian organization, often has been critical of the pharmaceutical industry.

<sup>137</sup> Quoted in Toole, “The Evolving U.S. Pharmaceutical Research Enterprise,” 5.

<sup>138</sup> See, e.g., Lichtenberg, “Pharmaceutical Innovation, Mortality Reduction, and Economic Growth,” 100–103; and citations in Joint Economic Committee, *The Benefits of Medical Research and the Role of the NIH*, 9.

## REFERENCES

- Ahlquist, Raymond P., "A Study of the Adrenotropic Receptors," *American Journal of Physiology* 153, no. 3 (June 1948): 586–600.
- Anfinsen, C. B., et al., "Partial Purification of Human Interferon by Affinity Chromatography," *Proceedings of the National Academy of Sciences* 71, no. 8 (August 1974): 3139–42.
- Angell, Marcia, *The Truth about the Drug Companies: How They Deceive Us and What to Do about It* (New York: Random House, 2004).
- Ashiya, Mona, and Richard E. T. Smith, "Non-Insulin Therapies for Type-2 Diabetes," *Nature Reviews Drug Discovery* 6, no. 10 (October 2007): 777–78.
- Baker, Dean, *The Benefits and Savings from Publicly Funded Clinical Trials of Prescription Drugs* (Center for Economic and Policy Research, March 2008).
- Barnes, Peter J., "New Drugs for Asthma," *Nature Reviews Drug Discovery* 3, no. 10 (October 2004): 831–34.
- Barnett, Allen, and Michael J. Green, "Loratadine," in *Chronicles of Drug Discovery*, ed. Daniel Lednicer (Washington, D.C.: American Chemical Society, 1993), 3:83–99.
- Bedford, G. R., and D. N. Richardson, "Preparation and Identification of *cis* and *trans* Isomers of a Substituted Triarylethylene," *Nature* 212, no. 5063 (November 12, 1966): 733–34.
- Berkowitz, Barry A., and George Sachs, "Life Cycle of a Blockbuster Drug: Discovery and Development of Omeprazole," *Molecular Interventions* 2, no. 1 (February 2002): 6–11.
- Bhatt, Deepak L., and Eric J. Topol, "Scientific and Therapeutic Advances in Antiplatelet Therapy," *Nature Reviews Drug Discovery* 2, no. 1 (January 2003): 15–28.
- Black, J. W., W. A. M. Duncan, and R. G. Shanks, "Comparison of Some Properties of Pronethalol and Propranolol," *British Journal of Pharmacology and Chemotherapy* 25, no. 3 (December 1965): 577–91.
- Borden, Ernest C., et al., "Interferons at Age 50: Current and Future Impact on Biomedicine," *Nature Reviews Drug Discovery* 6, no. 12 (December 2007): 975–90.
- Bossert, F., and W. Vater, "Dihydropyridine: Eine neue Gruppe stark wirksamer Coronartherapeutika" (Dihydropyridine: A New Group of Strongly Effective Coronary Therapeutics), *Naturwissenschaften* 58, no. 11 (November 1971): 578.
- Brazil, Melanie, "Herpes Simplex Achilles' Helicase," *Nature Reviews Drug Discovery* 1, no. 4 (April 2002): 251.
- Bremer, Howard, Catherine Innes, and Christopher McKinney, "Academic Technology Transfer: Driving Public Use of University Research Results," Association of University Technology Managers (AUTM) Education Series, no. 6 (2004).
- Bush, Vannevar, *Science, the Endless Frontier: A Report to the President by Vannevar Bush, Director of the Office of Scientific Research and Development* (July 1945), at [www.nsf.gov/about/history/vbush1945.htm](http://www.nsf.gov/about/history/vbush1945.htm).
- Byers, Larry D., and Richard Wolfenden, "Binding of the By-Product Analog Benzylsuccinic Acid by Carboxypeptidase A," *Biochemistry* 12, no. 11 (1973): 2070–78.



Calfee, John E., and Elizabeth DuPre, "The Emerging Market Dynamics of Targeted Therapeutics," *Health Affairs* 25, no. 5 (September/October 2006): 1302–8.

Centers for Medicare and Medicaid Services, "National Health Expenditures Projections 2007–2017, Forecast Summary and Selected Tables," at [http://www.cms.hhs.gov/NationalHealthExpendData/03\\_NationalHealthAccountsProjected.asp#TopOfPage](http://www.cms.hhs.gov/NationalHealthExpendData/03_NationalHealthAccountsProjected.asp#TopOfPage), Table 11.

Cockburn, Iain M., and Rebecca M. Henderson, "Absorptive Capacity, Coauthoring Behavior, and the Organization of Research in Drug Discovery," *Journal of Industrial Economics* 46, no. 2 (June 1998): 157–82.

Cohen, Philip, and Michel Goedert, "GSK3 Inhibitors: Development and Therapeutic Potential," *Nature Reviews Drug Discovery* 3, no. 6 (June 2004): 479–97.

Comanor, William S., "The Economics of Research and Development in the Pharmaceutical Industry," in *Pharmaceutical Innovation: Incentives, Competition, and Cost-Benefit Analysis in International Perspective*, ed. Frank A. Sloan and Chee-Ruey Hsieh, 153–73 (Cambridge: Cambridge University Press, 2007).

———, "The Political Economy of the Pharmaceutical Industry," *Journal of Economic Literature* 26 (September 1986): 1178–1217.

———, "Research and Competitive Product Differentiation in the Pharmaceutical Industry in the United States," *Economica* 31 (November 1964): 372–84.

Danzon, Patricia, and Michael F. Furukawa, "International Prices and Availability of Pharmaceuticals in 2005," *Health Affairs* 27, no. 1 (January/February 2008): 221–33.

De Clercq, Erik, "Strategies in the Design of Antiviral Drugs," *Nature Reviews Drug Discovery* 1, no. 1 (January 2002): 13–25.

———, "Three Decades of Antiviral Drugs," *Nature Reviews Drug Discovery* 6, no. 12 (December 2007): 941.

DiMasi, Joseph A., "New Drug Development in the United States, 1963–1999," *Clinical Pharmacology & Therapeutics* 69, no. 5 (May 2001a): 286–96.

———, "Risks in New Drug Development: Approval Success Rates for Investigational Drugs," *Clinical Pharmacology & Therapeutics* 69, no. 5 (May 2001b): 297–307.

———, and Henry G. Grabowski, "Should the Patent System for New Medicines Be Abolished?," *Clinical Pharmacology & Therapeutics* 82, no. 5 (November 2007): 488–90.

———, and Henry G. Grabowski, "The Cost of Biopharmaceutical R&D: Is Biotech Different?," *Managerial and Decision Economics* 28, nos. 4–5 (summer 2007): 469–79.

———, and Henry G. Grabowski, "Patents and R&D Incentives: Comments on the Hubbard and Love Trade Framework for Financing Pharmaceutical R&D," World Health Organization, Commission on Intellectual Property Rights, Innovation, and Public Health (June 25, 2004), at <http://www.who.int/intellectualproperty/news/en/Submission3.pdf>.

DiMasi, Joseph A., Ronald W. Hansen, and Henry G. Grabowski, "The Price of Innovation: New Estimates of Drug Development Costs," *Journal of Health Economics* 22, no. 2 (March 2003): 151–85.



DiMasi, Joseph A., and Cherie Paquette, "The Economics of Follow-On Drug Research and Development," *Pharmacoeconomics* 22, supplement 2 (2004): 1–14.

Druker, Brian J., "A History of STI 571: The Unsung Heroes," at [www.newcmldrug.com/history.htm](http://www.newcmldrug.com/history.htm).

Earl, John, and Peter Kirkpatrick, "Ezetimibe," *Nature Reviews Drug Discovery* 2, no. 2 (February 2003): 97–98.

*Encyclopedia of Chemistry*, "Duloxetine," at [www.chemie.de/lexicon/e/Duloxetine](http://www.chemie.de/lexicon/e/Duloxetine).

Eschbach, J. W., et al., "Correction of the Anemia of End-Stage Renal Disease with Recombinant Human Erythropoietin: Results of a Combined Phase I and II Clinical Trial," *New England Journal of Medicine* 316, no. 2 (January 8, 1987): 73–78.

———, "Recombinant Human Erythropoietin in Anemic Patients with End-Stage Renal Disease," *Annals of Internal Medicine* 111 (1989).

*FDA Consumer Magazine*, "Merck Withdraws Vioxx; FDA Issues Public Health Advisory," November–December 2004, at [www.fda.gov/fdac/features/2004/604\\_vioxx.html](http://www.fda.gov/fdac/features/2004/604_vioxx.html).

Fitzgerald-Bocarsly, Patricia, "The History of Interferon: An Interview with Sid Pestka," at [www.isicr.org/newsletter/isicr4.2.pdf](http://www.isicr.org/newsletter/isicr4.2.pdf).

Fleckenstein, Albrecht, *Calcium Antagonism in Heart and Smooth Muscle* (New York: John Wiley & Sons, 1983).

Flower, Rod J., "The Development of Cox-2 Inhibitors," *Nature Reviews Drug Discovery* 2, no. 3 (March 2003): 179–91.

Frick, M. H., et al., "Helsinki Heart Study: Primary-Prevention Trial with Gemfibrozil in Middle-Aged Men with Dyslipidemia," *New England Journal of Medicine* 317, no. 20 (November 12, 1987): 1237–45.

Fuchs, Victor R., and Harold C. Sox, Jr., "Physicians' Views of the Relative Importance of Thirty Medical Innovations," *Health Affairs* 20, no. 5 (September/October 2001): 30–42.

Fuller, Ray W., Kenneth W. Perry, and Bryan B. Molloy, "Effect of an Uptake Inhibitor on Serotonin Metabolism in Rat Brain," *Life Sciences* 15, no. 6 (September 15, 1974): 1161–71.

Gaddum, J. H., and Z. P. Picarelli, "Two Kinds of Tryptamine Receptor," *British Journal of Pharmacology and Chemotherapy* 12, no. 3 (September 1957): 323–28.

Garber, Alan M., and Paul M. Romer, "Evaluating the Federal Role in Financing Health-Related Research," *Proceedings of the National Academy of Sciences* 93 (November 1996): 12717–24.

Gelijns, Annetine C., Nathan Rosenberg, and Alan J. Moskowitz, "Capturing the Unexpected Benefits of Medical Research," *New England Journal of Medicine* 339, no. 10 (September 3, 1998): 693–98.

Gluck, Michael E., "Federal Policies Affecting the Cost and Availability of New Pharmaceuticals" (Georgetown University Institute for Health Care Research and Policy, July 2002).

Goodman, Jordan, and Vivien Walsh, *The Story of Taxol: Nature and Politics in the Pursuit of an Anti-Cancer Drug* (Cambridge: Cambridge University Press, 2001).

Goozner, Merrill, *The \$800 Million Pill: The Truth Behind the Cost of New Drugs* (Berkeley: University of California Press, 2004).

Grabowski, Henry, "Competition between Generic and Branded Drugs," in *Pharmaceutical Innovation: Incentives, Competition, and Cost-Benefit Analysis in International Perspective*, ed. Frank A. Sloan and Chee-Ruey Hsieh, 153–73 (Cambridge: Cambridge University Press, 2007).

Hall, Stephen S., *A Commotion in the Blood* (New York: Henry Holt, 1997).

Hara, Takuji, *Innovation in the Pharmaceutical Industry* (Northampton, MA: Edward Elgar, 2003).

Heeres, J., et al., "Antimycotic Imidazoles, Part 4: Synthesis and Antifungal Activity of Ketoconazole, A New Potent Orally Active Broad-Spectrum Antifungal Agent," *Journal of Medicinal Chemistry* 22, no. 8 (August 1979): 1003–5.

Horrobin, David F., "Innovation in the Pharmaceutical Industry," *Journal of the Royal Society of Medicine* 93 (July 2000): 341–45.

Isaacs, Alick, and Jean Lindenmann, "Virus Interference. I. The Interferon," *Proceedings of the Royal Society of London, Series B, Biological Sciences* 147, no. 927 (September 12, 1957): 258–67.

Jackson, Shaun P., and Simone M. Schoenwaelder, "Antiplatelet Therapy: In Search of the 'Magic Bullet,' " *Nature Reviews Drug Discovery* 2, no. 10 (October 2003): 1–15.

Jacobs, Kenneth, et al., "Isolation and Characterization of Genomic and cDNA Clones of Human Erythropoietin," *Nature* 313, no. 6005 (February 28, 1985): 806–10.

Johnson, David H., "Evolution of Cisplatin-Based Chemotherapy in Non-Small Cell Lung Cancer: A Historical Perspective and the Eastern Cooperative Oncology Group Experience," *Chest* 117 (Supplement) (April 2000): 133S–137S.

Joint Economic Committee (U.S. Senate), *The Benefits of Medical Research and the Role of the NIH* (May 2000).

Jordan, V. Craig, "Tamoxifen: A Most Unlikely Pioneering Medicine," *Nature Reviews Drug Discovery* 2, no. 3 (March 2003): 205–13.

———, "Tamoxifen (ICI46474) as a Targeted Therapy to Treat and Prevent Breast Cancer," *British Journal of Pharmacology* 147, supplement 1S (January 2006): S269–S276.

Kaitin, K. I., N. R. Bryant, and L. Lasagna, "The Role of the Research-Based Pharmaceutical Industry in Medical Progress in the United States," *Journal of Clinical Pharmacology* 33, no. 5 (May 1993): 412–17.

Kaitin, Kenneth I., ed., *Growing Protocol Design Complexity Stresses Investigators, Volunteers, Tufts CSDD Impact Report* 10, no. 1 (January/February 2008).

———, and Catherine Cairns, "The New Drug Approvals of 1999, 2000, and 2001: Drug Development Trends a Decade after Passage of the Prescription Drug User Fee Act of 1992," *Drug Information Journal* 37, no. 3 (2003): 357–71.

Kamb, Alexander, et al., "Why Is Cancer Drug Discovery So Difficult?," *Nature Reviews Drug Discovery* 6, no. 23 (February 2007): 115–20.

Kneller, Robert, "The Origins of New Drugs," *Nature Biotechnology* 23, no. 5 (May 2005): 529–30.

Lednicer, Daniel, *New Drug Discovery and Development* (Hoboken, N.J.: John Wiley & Sons, 2007).

Leurs, Rob, Remko A. Bakker, Henk Timmerman, and Iwan J. P. de Esch, "The Histamine H3 Receptor: From Gene Cloning to H3 Receptor Drugs," *Nature Reviews Drug Discovery* 4, no. 2 (February 2005): 107–20.

Lichtenberg, Frank R., "The Impact of New Drugs on U.S. Longevity and Medical Expenditure, 1990–2003: Evidence from Longitudinal, Disease-Level Data," *American Economic Review* 97, no. 2 (May 2007): 438–43.

———, "Pharmaceutical Innovation, Mortality Reduction, and Economic Growth," in *Measuring the Gains from Medical Research: An Economic Approach*, ed. Kevin M. Murphy and Robert H. Topel, 74–109 (Chicago: University of Chicago Press, 2003).

———, and Bhaven N. Sampat, "The Contribution of NIH-Supported Research to Pharmaceutical-Embodied Technological Progress," manuscript, May 22, 2008.

———, and Bhaven N. Sampat, "NIH Research and Pharmaceutical Innovation," manuscript, November 26, 2007.

Lin, Fu-Kuen, et al., "Cloning and Expression of Monkey and Human Erythropoietin Gene," *Experimental Hematology* 12 (International Experimental Hematology Meeting, August 12–16, 1984): 357.

———, et al., "Cloning and Expression of the Human Erythropoietin Gene," *Proceedings of the National Academy of Sciences* 82 (November 1985): 7580–84.

Linsel-Nitschke, Patrick, and Alan R. Tall, "HDL as a Target in the Treatment of Atherosclerotic Cardiovascular Disease," *Nature Reviews Drug Discovery* 4, no. 3 (March 2005): 193–206.

Mathews, Anna Wilde, and Avery Johnson, "Drug Companies Face Political, Scientific Attacks," *Wall Street Journal*, January 23, 2008, A14.

Matthews, Tom, et al., "Enfuvirtide: The First Therapy to Inhibit the Entry of HIV-1 into Host CD4 Lymphocytes," *Nature Reviews Drug Discovery* 3, no. 3 (March 2004): 215–25.

Maxwell, Robert A., and Shohreh B. Eckhardt, *Drug Discovery: A Casebook and Analysis* (Clifton, NJ: Humana Press, 1990).

Médecins Sans Frontières, *Fatal Imbalance: The Crisis in Research and Development for Drugs for Neglected Diseases*, Access to Essential Medicines Campaign and the Drugs for Neglected Diseases Working Group (Geneva, Switzerland, September 2001).

National Institutes of Health, "A Plan to Ensure Taxpayers' Interests Are Protected" (July 2001).

New Marketed Drugs Database, Tufts Center for the Study of Drug Development (Tufts University, 2008).

Ng, Rick, *Drugs: From Discovery to Approval* (Hoboken, N.J.: John Wiley & Sons, 2004).

Olbe, Lars, Enar Carlsson, and Per Lindberg, "A Proton-Pump Inhibitor Expedition: The Case Histories of Omeprazole and Esomeprazole," *Nature Reviews Drug Discovery* 2, no. 2 (February 2003): 132–39.

Patchett, Arthur A., "Enalapril and Lisinopril," in *Chronicles of Drug Discovery*, ed. Daniel Lednicer (Washington, D.C.: American Chemical Society, 1993), 3:125–62.

Patton, John S., and Peter R. Byron, "Inhaling Medicines: Delivering Drugs to the Body through the Lungs," *Nature Reviews Drug Discovery* 6, no. 1 (January 2007): 67–74.

Payne, David J., et al., "Drugs for Bad Bugs: Confronting the Challenges of Antibacterial Discovery," *Nature Reviews Drug Discovery* 6, no. 1 (January 2007): 29–40.

Pieters, Toine, *Interferon: The Science and Selling of a Miracle Drug* (New York: Routledge, 2005).

*Production of Recombinant Erythropoietin*, U.S. Patent no. 5441868, at <http://www.freepatentsonline.com/5441868.html>.

Rasmusson, Gary H., et al., "Azasteroids: Structure-Activity Relationships for Inhibition of 5 $\alpha$ -Reductase and of Androgen Receptor Binding," *Journal of Medicinal Chemistry* 29, no. 11 (November 1986): 2298–2315.

Reichert, Janice M., and Christopher-Paul Milne, *Public and Private Sector Contributions to the Discovery and Development of "Impact" Drugs* (Tufts Center for the Study of Drug Development, May 2002).

Reid, Ian C., and Caroline A. Stewart, "How Antidepressants Work," *British Journal of Psychiatry* 178 (2001): 299–303.

Roden, Dan M., and Alfred L. George, Jr., "The Genetic Basis of Variability in Drug Responses," *Nature Reviews Drug Discovery* 1, no. 1 (January 2002): 37–44.

Rosenberg, Barnett, et al., "Platinum Compounds: A New Class of Potent Antitumour Agents," *Nature* 222, no. 5191 (April 26, 1969): 385–86.

Ryan, Charles W., et al., "Chemistry of Cephalosporin Antibiotics," *Journal of Medicinal Chemistry* 12, no. 2 (March 1969): 310–13.

Schacht, Wendy H., "The Bayh-Dole Act: Selected Issues in Patent Policy and the Commercialization of Technology," Congressional Research Service, RL32076 (December 8, 2006).

———, "Federal R&D, Drug Discovery, and Pricing: Insights from the NIH-University-Industry Relationship," Congressional Research Service, RL30585 (June 19, 2000).

Scriabine, Alexander, "Discovery and Development of Major Drugs Currently in Use," in *Pharmaceutical Innovation*, ed. Ralph Landau et al., 148–270 (Philadelphia: Chemical Heritage Press, 1999).

———, "The Role of Biotechnology in Drug Development," in *Pharmaceutical Innovation*, ed. Ralph Landau et al., 271–97 (Philadelphia: Chemical Heritage Press, 1999).

Skolnick, Phil, "Antidepressants for the New Millennium," *European Journal of Pharmacology* 375, nos. 1–3 (June 1999): 31–40.

Smith, Pamela W., "The National Institutes of Health (NIH): Organization, Funding, and Congressional Issues," Congressional Research Service, RL33695 (October 19, 2006).

Sneader, Walter, *Drug Discovery: A History* (West Sussex: John Wiley & Sons, 2005).

Stephenson, Frank, "A Tale of Taxol," *Research in Review*, Office of Research (Florida State University, fall 2002), at <http://rinr.dsu.edu/fall2002/taxol.html>.

Terrett, Nicholas K., et al., "Sildenafil (VIAGRA™), A Potent and Selective Inhibitor of Type 5 cGMP Phosphodiesterase with Utility for the Treatment of Male Erectile Dysfunction," *Bioorganic & Medicinal Chemistry Letters* 6, no. 15 (August 6, 1996): 1819–24.

Thorp, J. M., and W. S. Waring, "Modification of Metabolism and Distribution of Lipids by Ethyl Chlorophenxyisobutyrate," *Nature* 194, no. 4832 (June 9, 1962): 948–49.

Tobert, Jonathan A., "Lovastatin and Beyond: The History of the HMG-CoA Reductase Inhibitors," *Nature Reviews Drug Discovery* 2, no. 7 (July 2003): 517–26.

Toole, Andrew A., "Does Public Scientific Research Complement Private Investment in Research and Development in the Pharmaceutical Industry?," *Journal of Law and Economics* 50, no. 1 (February 2007): 81–104.

———, "The Evolving U.S. Pharmaceutical Research Enterprise," monograph, Pfizer, *Economic Realities in Health Care Policy* 4, no. 1 (2005).

———, "The Impact of Public Basic Research on Industrial Innovation: Evidence from the Pharmaceutical Industry," working paper (Rutgers University, May 9, 2008).

Trusheim, Mark R., Ernst R. Berndt, and Frank L. Douglas, "Stratified Medicine: Strategic and Economic Implications of Combining Drugs and Clinical Biomarkers," *Nature Reviews Drug Discovery* 6, no. 4 (April 2007): 287–93.

Turk, Boris, "Targeting Proteases: Successes, Failures, and Future Prospects," *Nature Reviews Drug Discovery* 5, no. 9 (September 2006): 785–99.

U.S. Department of Health and Human Services, *Critical Path Opportunities Report*, Food and Drug Administration (Washington, D.C., March 2006), at [http://www.fda.gov/oc/initiatives/criticalpath/reports/opp\\_report.pdf](http://www.fda.gov/oc/initiatives/criticalpath/reports/opp_report.pdf).

U.S. Environmental Protection Agency, 2004 Greener Synthetic Pathways Award, *Bristol-Myers Squibb Company: Development of a Green Synthesis for Taxol Manufacture via Plant Cell Fermentation and Extraction*, at <http://www.epa.gov/greenchemistry/pubs/pgcc/winners/gspa04.html>.

U.S. Food and Drug Administration, "FDA Approves Allegra-D, Manufacturer to Withdraw Seldane from Marketplace," December 29, 1997, at [www.fda.gov/bbs/topics/ANSWERS/ANS00843.html](http://www.fda.gov/bbs/topics/ANSWERS/ANS00843.html).

U.S. General Accounting Office, *Agencies' Rights to Federally Sponsored Biomedical Inventions*, GAO-03-536 (July 2003).

Waitekus, Anatheia B., and Peter Kirkpatrick, "Duloxetine Hydrochloride," *Nature Reviews Drug Discovery* 3, no. 11 (November 2004): 907–8.

Wastila, Linda J., and Louis Lasagna, "The History of Zidovudine," *Journal of Clinical Research and Pharmacoepidemiology* 4 (1990).

Winerals, Christopher G., et al., "Effect of Human Erythropoietin Derived from Recombinant DNA on the Anaemia of Patients Maintained by Chronic Haemodialysis," *The Lancet* 328, no. 8517 (November 1986): 1175–78.

Wong, David T., et al., "LY227942, An Inhibitor of Serotonin and Norepinephrine Uptake: Biochemical Pharmacology of a Potential Antidepressant Drug," *Life Sciences*, 43, no. 24 (1988): 2049–57.

———, et al., "A Selective Inhibitor of Serotonin Uptake: Lilly 110140," *Life Sciences* 15, no. 3 (August 1, 1974): 471–79.

———, Kenneth W. Perry, and Frank P. Bymaster, "The Discovery of Fluoxetine Hydrochloride (Prozac)," *Nature Reviews Drug Discovery* 4, no. 9 (September 2005): 764–74.

Wong, Ma-Li, and Julio Licinio, "From Monoamines to Genomic Targets: A Paradigm Shift for Drug Discovery in Depression," *Nature Reviews Drug Discovery* 3, no. 2 (February 2004): 136–51.

Zinner, Darren E., "Medical R&D at the Turn of the Millennium," *Health Affairs* 20, no. 5 (September/October 2001): 202–9.

Zycher, Benjamin, "The Human Cost of Federal Price Negotiations: The Medicare Prescription Drug Benefit and Pharmaceutical Innovation," *Medical Progress Report no. 3* (Center for Medical Progress, Manhattan Institute for Policy Research, October 2006).

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## ACKNOWLEDGEMENTS

Sincere thanks for helpful comments are due to Joshua P. Cohen, William S. Comanor, Arthur Daemmrigh, Laurence A. Dougharty, Frank L. Douglas, Leonard S. Levy, Robert E. Litan, Henry I. Miller, Mark Rohrbaugh, Richard I. Shader, Bert Spilker, Thomas P. Stossel, Andrew A. Toole, and Grace-Marie Turner, none of whom bears responsibility for any remaining errors or omissions.

The authors would like to thank also the Ewing Marion Kauffman Foundation for its generous financial support.

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*Findings presented in Manhattan Institute publications are those of our scholars and are not influenced by the individuals, foundations, and corporations that support the Manhattan Institute and its research.*

## FELLOWS

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The Center for Medical Progress (CMP) is dedicated to articulating the importance of medical progress and the connection between free-market institutions and making medical progress both possible and widely available throughout the world. The research and writing of CMP senior fellows David Gratzer, Regina Herzlinger, Paul Howard, Peter Huber, Thomas Stossel, and Benjamin Zycher encourage the development of market-based policy alternatives to sustain medical progress and promote medical innovation.

CMP fellows are published in prominent publications such as the *Wall Street Journal*, the *Washington Post*, *National Review*, and the *Weekly Standard*. In 2006 and 2007, Gratzer and Herzlinger each released a book examining health care in the United States. Gratzer's *The Cure: How Capitalism Can Save American Health Care* received nationwide acclaim, leading the *Wall Street Journal* to recommend that "our nation's policy makers read *The Cure*" and prompting the *Washington Post* to describe Gratzer's work as "an artful job of concisely laying out what ails the U.S. system and how things got to be that way."

Herzlinger, the Nancy R. McPherson Professor of Business Administration Chair at the Harvard Business School, is widely recognized throughout the business and policy communities for her innovative research in health care. Her newest book, *Who Killed Health Care?: America's \$2 Trillion Medical Problem—and the Consumer-Driven Cure*, exposes the motives and methods of those who have crippled America's health-care system. Zycher is researching the economic and political effects of regulation, government spending, taxation, and the economics of the pharmaceutical sector.

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