
How the drug industry distorts medicine and politics. **America's Other Drug Problem**

By **ARNOLD S. RELMAN** and **MARCIA ANGELL**

THE AMERICAN HEALTH care system cannot live without the pharmaceutical industry, but it may not be able to live with it either, unless the industry is greatly reformed. For better and for worse, this enormous and hugely profitable enterprise has become a dominating presence in American life. It uses its great wealth and influence to ensure favorable government policies. It has also, with the acquiescence of a medical profession addicted to drug company largesse, assumed a role in directing medical treatment, clinical research, and physician education that is totally inappropriate for a profit-driven industry. Like most other for-profit corporations, drug companies are impelled primarily by the financial aspirations of their investors and executives. This incentive may serve useful social purposes in the distribution of ordinary goods in most markets, but prescription drugs are not like ordinary goods, and the market for drugs is not like other markets. The misconception that drugs and their market are like other goods and markets explains most of the serious problems with the pharmaceutical industry today.

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Drug Costs

THE RISING COSTS of drugs are the immediate public issue. Expenditures on prescription drugs—now roughly \$170 billion per year—constitute a rapidly growing fraction of our \$1.4 trillion health care bill. Greater overall use of drugs, higher prices for new drugs, and steady increases in the prices of existing drugs all contribute to an annual inflation in drug expenditures of 14 percent (down from a high of 18 percent in 1999). Within a few years, this surge in costs will probably make drugs the second largest component of our national health care budget, after hospitalization. According to statistics kept by the Center for Medicare and Medicaid Services, American expenditures on prescription drugs, expressed as a percentage of GDP, were virtually steady between 1960 and 1980 but increased rapidly soon thereafter, and by 2000 they had almost tripled.

Last year, a prescription for one of the twenty top-selling brand-name drugs—which is usually for a one-month supply—cost on average about \$100. Prices for prescription drugs are on average much higher in the United States than anywhere else in the world. Many patients, particularly the elderly, take several drugs, so drug costs have become a heavy burden for them; but the costs of prescription drugs are now a major problem for all who must pay for them. That includes government and private insurance plans, and uninsured and partly insured individuals.

Resistance to escalating drug expendi-

tures is growing among all the purchasers, and the media is full of critical stories and commentaries. So far, however, none of this has had a noticeable impact on rising drug expenditures. The pharmaceutical industry has been fighting effectively against all efforts to control prices or to limit the markets for its expensive new brand-name drugs. It channels these efforts and most of its public relations and lobbying activities through its trade association, the Pharmaceutical Research and Manufacturers of America (PhRMA). PhRMA's membership includes virtually all American manufacturers of brand-name drugs, and many foreign manufacturers as well. With a full-time staff of 120 in its Washington offices and hundreds of lobbyists working the halls of federal and state government, and with a core budget of some \$60 million and large additional subsidies from the industry for special projects, PhRMA conducts an extensive, virtually nonstop campaign on behalf of its clients. This is in addition to the millions spent in Washington by individual pharmaceutical firms promoting their own business objectives.

PhRMA adamantly opposes any regulation of expenditures for brand-name drugs. It argues that high prices simply reflect the very high costs of discovering and developing new drugs. Any form of price control, it claims, would eat into the industry's research and development budget, and thereby choke off the pipeline that brings the public important new drugs. Generic drugs are different, it points out, because they are merely copies of brand-

name drugs whose exclusive marketing rights have expired, and therefore their manufacturers do not have high research costs. Moreover, PhRMA contends that high profits are a necessary incentive for undertaking the risky and arduous business of discovering innovative drugs. These drugs are vital to the health of Americans, according to the industry, and it would be disastrously shortsighted to lessen the incentives to find them. PhRMA also maintains that, whatever the expenditures for prescription drugs, we get more than our money's worth. According to this argument, the output of the industry's research laboratories not only cures disease and extends and improves people's lives, but probably even saves money by avoiding hospitalizations and other more expensive kinds of treatment. In sum, the industry portrays itself as an exemplar of science-based free enterprise, primarily dedicated to discovering—through costly and risky research—new treatments for disease. It wants the public to believe the catchy slogan of the pharmaceutical giant Pfizer: "Life is our life's work."

THE RHETORIC IS stirring, but the arguments simply do not hold up. First, research and development (R&D) constitutes a relatively small part of the budgets of the large drug companies. Their marketing and advertising expenditures are much greater than their investment in R&D. Furthermore, they make more in profits than they spend on R&D. In fact, their profits are consistently much higher than those of any other American industry. Prices (which bear little relation to the costs of developing and manufacturing a drug) could be lowered substantially without coming close to threatening the R&D budgets of drug companies, much less their economic survival.

Second, the pharmaceutical industry is not particularly innovative, and it is growing less so each year. The great majority of new drugs coming to market these days, although patented, are not new at all. They are variations on older drugs already on the market. These are called "me-too" drugs, and they represent attempts to capitalize on the success of "blockbuster" drugs. (Blockbusters are defined here as drugs with over \$500 million in annual sales.) The few drugs that are truly innovative have usually been based on taxpayer-supported research done in nonprofit academic medical centers or at the National Institutes of Health. In fact, many drugs now sold by drug companies were licensed to them by academic medical centers or small biotechnology companies.

Third, while there is no doubt that the best of the new drugs have greatly improved or saved many lives, this is certainly not true of all of them; most add little or no medical value. The use of some drugs has saved money by reducing hospitalizations or the need for expensive procedures, but whether prescription drugs reduce total expenditures for health care in the long run is an imponderable question. As expenditures on drugs continue to rise, the answer becomes more uncertain, the industry's insistence to the contrary notwithstanding.

Far from being a "research-based industry," as it likes to call itself, the pharmaceutical industry now devotes most of its resources to functioning as a vast marketing and advertising enterprise whose best products were discovered and often partially developed elsewhere—usually at public expense. And this industry is hardly a model of free enterprise. It may be free to decide which drugs to develop and to set its own prices, but its lifeblood is government-granted monopolies—in the form of patents and FDA-approved exclusive marketing rights. Drug companies apparently see no contradiction in manipulating existing laws and regulations to stave off competition from generic and foreign manufacturers and lobbying for even more governmental protections while at the same time using free-market rhetoric to demand less government involvement in the pricing and the marketing of drugs.

The industry wants to obscure a basic fact: there is not and there cannot be anything like a free market in prescription drugs. The pharmaceutical business is, for many reasons, critically dependent on government help. That is why it spends so much on lobbying. Moreover, its sales are not determined primarily by price or by consumer choice, but by the physicians who prescribe drugs. And that is why it spends so much more to influence the behavior of doctors.

R&D Costs: How High Are They Really?

BEFORE DISCUSSING THE costs of bringing a new drug to market, we must first explain the steps in that process. The discovery of a drug candidate is usually the result of research into the molecular basis of disease, which is done primarily in academic or government laboratories. The next step is the pre-clinical phase of the R&D work, which is usually done by industry—although not necessarily by the company that ultimately sells the drug. This involves biological screening and pharmacological testing in labora-

tory animals to determine how the drug is absorbed, metabolized, and excreted, and to learn about its toxicity. According to PhRMA's annual report, approximately one-quarter to one-third of all pharmaceutical R&D expenditures are involved in finding or acquiring a new drug candidate and taking it through the pre-clinical screening phase. The industry claims that only about one in one thousand screened compounds makes it through the pre-clinical phase to the clinical phase—that is, to testing in human subjects.

To begin clinical testing, a drug must be registered with the Food and Drug Administration (FDA), which by law must ultimately approve all drugs for safety and effectiveness before they can be sold. There are four phases of clinical testing. In Phase I, the new drug is given to a few human volunteers to establish safe dosage levels and to study its metabolism and side effects. If the drug looks promising, it moves into Phase II, which involves small clinical trials at various doses in patients with the relevant medical condition. Finally, if all goes well, Phase III clinical trials are undertaken. These evaluate the safety and the effectiveness of the drug in much larger numbers of patients (hundreds or thousands of them), with the expectation of gaining FDA approval if the trials are successful. No more than one in five drug candidates entering clinical testing make it through to FDA approval and reach the market, so the chances that a drug candidate, once selected, will ever get to the market are said to be less than one in five thousand.

The total time from the beginning of pre-clinical testing of a candidate drug to FDA approval ranges from about six to ten years. That includes the time the FDA spends on review of the application for approval (called a new drug application, or NDA), which averages about 16 months. But these times are quite variable, and in special cases they can be greatly shortened. After approval of a drug, the FDA requires the manufacturer to continue its surveillance of the drug and to report unanticipated side effects. The company may also want to do additional clinical studies to gain approval for new uses or formulations of the drug. All clinical studies after the initial approval are designated as Phase IV trials.

According to PhRMA's annual report, the large drug companies last year spent approximately 15 to 17 percent of their income on R&D (before adjustment for tax deductions and credits). This figure is necessarily soft, since in general the industry's accounting for its R&D expenses leaves a lot to be desired, and there are

also differing estimates of total income. Much R&D information is considered proprietary. Individual companies report total R&D expenditures in their Securities and Exchange Commission (SEC) filings, and PhRMA's annual report gives industry-wide averages for total R&D as well as average figures for the breakdown of expenses by general R&D functions. But the companies do not make available most of the really interesting details, such as what each company spends, and for what purposes, on the development of each drug. We also do not know how much marketing is concealed under the rubric of "development," particularly in Phase IV post-approval studies. Still, one financial detail of R&D expenses has been widely publicized by the industry: the estimated average total R&D cost of each new drug brought to market. That figure is currently said to be \$802 million (in year 2000 dollars), including the amount spent on the many failures and false starts. This huge outlay, which we are told is rising rapidly with the growing expense of clinical trials, is said to justify—indeed to require—the high prices of new drugs.

Pre-clinical and clinical testing and the other tasks required before a drug can be brought to the FDA for approval can be long, difficult, and very expensive. But \$802 million apiece? To put it in the kindest terms, that is an imaginary number. It is based on debatable accounting theory and it is premised on blind faith in the confidential information supplied by the industry to its economic consultants at the Tufts Center for the Study of Drug Development, the University of Rochester Graduate School of Business Administration, and the Department of Economics at Duke University, who arrived at this number. Over the years, these consultants have analyzed the costs of new drug development, and the \$802 million estimate represents an updating of their work.

Although this latest analysis has not yet been formally published, it was announced at a forum and a press conference last year in Philadelphia. PhRMA, leaders of the industry, and its defenders in the media have been trumpeting the results ever since. Joseph DiMasi of Tufts University, the senior author of this work, kindly sent us a draft of the manuscript describing the analysis, and he discussed his views with us in several telephone conversations. He also shared his opinions about a critical analysis of this work that

was released last year by Public Citizen, the Washington-based consumer watch group. Among Public Citizen's objections to the work of DiMasi's group, we consider the following to be most important.

First, the analysis concerns the costs only of new molecular entities (NMEs), sometimes called new chemical entities (NCEs). These are drugs whose active ingredients are newly discovered or synthesized molecules. The analysis was also restricted to NMEs developed entirely within the drug companies. The 68 drugs selected for study are never named; nor are the manufacturers or the individual costs. But NMEs are only a minority of the drugs that are newly approved. As we already noted, most are new dosage forms



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or combinations of drugs already on the market. Moreover, an increasing number of drugs are simply licensed from academic medical centers or biotechnology companies, and are not entirely developed in the drug companies. So, despite the implication by the industry that the DiMasi calculations tell us the average cost of the R&D needed for all the new drugs sold, these estimates seem to be based on sampling from a highly selected group of drugs. Full disclosure of the data, including the identity of the drugs selected for study and the costs for each, would have been important for the evaluation of the significance of this economic analysis.

Second, the final estimate of the cost per drug is not the actual out-of-pocket cost,

but what the authors call the "capitalized" cost—that is, it includes the estimated revenue that might have been generated over the long development period if the money spent on R&D had instead been invested in the equity market. This theoretically lost revenue is known as the "opportunity cost," and it is added to the industry's out-of-pocket costs of R&D. The authors seem to justify this interesting accounting maneuver on the grounds that from the perspective of investors, a pharmaceutical company is really just one kind of investment, which they chose among other possible investment options. But while this may be true for investors, surely it is not true for the pharmaceutical companies themselves. The latter have no choice but to spend money on R&D if they wish to be in the pharmaceutical business, so they have no "opportunity costs." To add the investors' opportunity costs to the company's out-of-pocket cost of developing a drug seems rather odd. DiMasi assures us that this calculation conforms with standard economic thought and accounting practice, but recent events on Wall Street make such reassurance less comforting than it might once have been. In any case, when DiMasi and his colleagues add the "opportunity cost" to their calculated out-of-pocket cost of pharmaceutical R&D (\$403 million per drug), the final estimate is approximately doubled.

Finally, the Public Citizen analysis points out that since R&D expenses are deductible from a firm's tax base, calculation of the cost of R&D should be reduced by the amount of corporate tax avoided. This tax saving would reduce the net cost of R&D by a percentage equal to the corporate tax rate (currently about 34 percent). DiMasi says that the corporate tax applies to net income, and since the latter is already reduced by the R&D expenditures, there is, properly speaking, no tax saving and no need to adjust the calculation of the R&D cost that he and his colleagues are making. We are not qualified to debate the accounting terminology, but it seems to us only common sense that were it not for the full deductibility of R&D from the tax base, the pharmaceutical industry's taxes would be higher and its after-tax income would be lower. Why is it not reasonable, therefore, to deduct this difference—whether it is called a "tax saving" or not—from the out-of-pocket expenditures on R&D when calculating the net cost of

R&D to a pharmaceutical firm? The Office for Technology Assessment, whose report on this subject in 1993 is often cited incorrectly as supporting the DiMasi analysis because it also considers opportunity costs, agrees with Public Citizen's position on tax deductions.

IN SUM, WE believe that Public Citizen's criticisms are substantially correct, and we agree with the group's conclusion that even if one were blindly to accept the reliability of the unrevealed data used in the calculations, the \$802 million estimate of "capitalized" cost produced by the industry's economic consultants should be reduced to an after-tax net of less than \$266 million. But remember, that would be the average out-of-pocket R&D cost only for the new molecular entities developed entirely in-house, not the average cost of all of the drugs approved each year. Most approved drugs entering the market are not really new, or they are licensed from other sources, or both. Such drugs probably have lower R&D costs, although there are no good data on this point. We conclude that the average out-of-pocket, after-tax R&D cost of most of the drugs upon which the industry's revenue now depends was probably much lower than \$266 million (in year 2000 dollars). Tax credits for certain types of R&D would probably reduce that estimate even more.

The suspicion that average R&D costs per drug are not nearly as high as claimed is further supported by other data provided by Public Citizen. If one divides the industry-supplied estimates of total R&D expenses by the total number of drugs entering the market, making appropriate allowances for the lag time between expenditures and the date of entrance into the market, the resulting net out-of-pocket, after-tax costs would probably be less than \$100 million for each drug that was approved between 1994 and 2000. That, admittedly, is only a rough approximation, but the general conclusion seems inescapable: that the \$802 million estimate now being promoted by the industry and its partisans is much too high.

Whatever the cost of bringing each new drug to market, the total R&D expenditures of the pharmaceutical industry—according to PhRMA, now about \$30 billion for all its members in the United States and abroad—are indeed large. But they should be compared with reported expenditures on marketing and administration, which are more than twice as much as R&D expenditures. Moreover, the most important financial fact about the major pharmaceutical firms is that,

despite their expenses, they are immensely profitable. The ten American pharmaceutical companies in the Fortune 500 list last year ranked far above all other American industries in average net return, whether as a percentage of revenues (18.5 percent), of assets (16.3 percent), or of shareholders' equity (33.2 percent). (For comparison, the median net return for other industries was only 3.3 percent of revenues.) And this has generally been the case for the past two decades. A business consistently this profitable cannot by any stretch of language be described as "risky" or as needing special protection of its revenues.

How Innovative Is the Pharmaceutical Industry?

THE PHARMACEUTICAL INDUSTRY justifies its extraordinary profits largely by the claim that they are necessary as an incentive to continue its vital research. The implication is that if the public wants new cures for diseases, it should give the industry free rein. It is important, then, to ask just how innovative the pharmaceutical industry really is. We think the answer is not very. Drug companies greatly exaggerate their role in the scientific work leading to the discovery of new drugs. As we have already noted, the development of important new drugs is usually the culmination of many discoveries in basic science laboratories outside the pharmaceutical industry. This work increases the understanding of the molecular basis of disease and thereby identifies promising targets and models for the design of new drugs. Most of this groundbreaking research, done with support from the National Institutes of Health (NIH) or other institutions, appears in scientific journals before the big companies become involved. The industry is certainly not the major engine of discovery and medical progress that it would have the public believe. Public investment in research has been primarily responsible for the great medical advances society is enjoying, and this is likely to be so in the future as well.

A general idea of the relative contribution of the pharmaceutical industry to the underlying medical research that leads to the development of new drugs can be gained from a recent study published in the journal *Health Affairs*. The study reported that in 1998 only about 15 percent of the scientific articles cited in patent applications for clinical medicine came from industry research, while 54 percent came from academic centers, 13 percent from government, and the rest from vari-

ous other public and nonprofit institutions. Remember that these are patent applications for all new drugs and medical innovations, not simply for those ultimately judged to be clinically important. Had the data been limited to only major breakthrough drugs, the industry's role would undoubtedly have looked even smaller.

The relatively small contribution of industry is also clear from an unpublished internal document produced by the NIH in February 2000, which was obtained by Public Citizen through the Freedom of Information Act. The NIH had selected the five top-selling drugs in 1995 (Zantac, Zovirax, Capoten, Vasotec, and Prozac) and found that 16 of the 17 key scientific papers leading to the discovery and development of these drugs came from outside the industry. Looking at all the relevant published research, not just at the key studies, 85 percent came from American taxpayer-supported laboratories or foreign academic laboratories. While it is true that academic scientists may have more incentive to publish their research results than do their colleagues in industry, these data are persuasive: publicly funded medical research is by far the major source of pharmaceutical innovation—not the industry itself.

A MORE CONCRETE appreciation of the relative contributions of outside scientific laboratories and the drug industry can be gained by considering the histories of three important, groundbreaking drugs that have appeared on the market during the past two decades.

Zidovudine, commonly known as AZT, was first marketed in the United States in 1987 by the company then called Burroughs Wellcome Co., which is now part of a much larger firm called Glaxo-SmithKline. AZT, sold under the brand name Retrovir, was the first drug shown to be effective in suppressing HIV infection. It has recently been joined by several other effective drugs, but it usually remains part of the combination drug therapy still in use. The AZT molecule was first synthesized at the Michigan Cancer Foundation in 1964 as a possible treatment for cancer and was studied in many laboratories for that purpose. In 1974, in a German basic science laboratory, it was found to be effective against experimental viral infections in mice. In 1983–1984, U.S. government-supported research at the NIH and at Duke University showed that this molecule also suppressed the AIDS virus in human cells in test tubes and, later, that it was effective in patients.

Encouraged by the Stevenson-Wydler and Bayh-Dole Acts of 1980 (more about Bayh-Dole later), NIH-supported scientists began to collaborate with Burroughs Wellcome. By 1985, the company was able to obtain a patent on the use of AZT in the treatment of AIDS and to proceed with clinical trials that enabled it to receive FDA approval after an expedited review that required only four months—one of the shortest on record. This history shows that the drug treatment of AIDS, certainly one of the major public health advances in our time, began with basic pre-clinical work conducted almost entirely outside the drug industry and largely supported by taxpayers.

ERYTHROPOIETIN, WHICH IS marketed by Amgen under the name Epogen, is a protein hormone normally produced in healthy kidneys that stimulates red blood cell production. Technically, it is a “biological,” not a “drug,” because it is a natural substance made in the body. We include it in our discussion because Amgen is an important member of PhRMA, and because many pharmaceutical firms sell biologicals as well as drugs. Erythropoietin was discovered through a long series of investigations in academic laboratories that began in the 1960s and was largely supported by the NIH. This work established that the severe anemia characteristic of chronic kidney disease was largely caused by the failure of the damaged kidneys to manufacture erythropoietin. The isolation and the definitive chemical identification of the substance was finally accomplished by a scientist at the University of Chicago in 1976, but the university did not patent the molecule or initiate any efforts to develop it for clinical use.

To use erythropoietin in the treatment of anemia requires a safe, efficient method of biosynthesis, and this was Amgen's contribution. The task of the company's scientists was facilitated by a recombinant gene technique that was developed and patented at Columbia University (again with NIH support). Amgen, then a small biotechnology start-up company, licensed the technique from Columbia, used it to develop a practical method for recombinant synthesis of erythropoietin, and patented the biosynthetic molecule. By 1987, Amgen had completed its first clinical trials and was able to show that Epogen was safe and effective in treating anemia in patients with kidney failure—a major medical advance in the field.

With FDA approval, Epogen has been widely and successfully used, and now generates for Amgen more than \$2 billion

in annual sales—mainly from Medicare, which pays for the treatment of kidney failure. Thus, it turns out that taxpayers pay whatever Amgen charges for a drug discovered largely through taxpayer-supported research. For license of its recombinant gene patent, Columbia receives 1 percent of all sales from Amgen.

IMATINIB MESYLATE, MARKETED as Gleevec, is a new molecule that was synthesized in the early 1990s in the chemistry laboratories of the Swiss pharmaceutical firm Novartis and has recently been shown to be spectacularly successful in the treatment of a type of blood cancer called chronic myeloid leukemia (CML). This form of leukemia affects about 20,000 adults in the United States at any given time, and it is usually fatal after about three to five years. The story of imatinib is particularly instructive and worth telling in some detail.

The long trail of basic scientific research leading to the development of this drug began back in 1960 with the discovery of a characteristic abnormal-looking chromosome in patients with CML. Subsequent work showed that the abnormal-looking chromosome is due to the breakage and the subsequent rejoining of parts of two chromosomes. Later studies from many

different laboratories showed that this rejoining creates a new gene that directs the production of an abnormal enzyme, which causes white blood cells to become malignant. Other work had shown that similar types of enzymes were probably involved in a variety of other cancers, although not as directly; so chemists in Israel and in the laboratories of Novartis independently set about synthesizing molecules that would inhibit the action of these abnormal enzymes. Novartis patented several such inhibitor molecules in 1994 and added them to its collection of potentially useful drug candidates.

There was apparently no immediate interest at Novartis in determining whether any of these new inhibitors might be clinically useful in the treatment of CML until Dr. Brian J. Druker, a clinical research physician in hematology at the Oregon Health Sciences University in Portland, became interested in their possible use for this purpose. Much of the rest of this story we learned from Druker. Working with a scientist at Novartis, he obtained a small supply of several of the company's most promising enzyme inhibitors. He found that imatinib was the most potent in suppressing the growth of malignant CML blood cells in culture, and furthermore that it had no effect at all on normal

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blood cells. Such specific action is almost unheard of in cancer treatment, and Druker urged the company to explore this exciting lead. But there was little corporate enthusiasm for undertaking further clinical work on imatinib. Druker nevertheless persisted, and Novartis finally agreed to support cautious, limited tests of the drug in Druker's clinic and two other sites. By 1999, Druker was able to report spectacularly successful preliminary results before a large national meeting of American hematologists. The news about imatinib's remarkable effectiveness in CML quickly became public, and it aroused great interest. The company then decided to proceed with large-scale clinical trials to determine whether the drug was safe enough and effective enough to warrant FDA approval and general use in CML. Last year, once the positive clinical evidence was in hand, the FDA quickly gave its approval.

SO NOVARTIS'S R&D investment in testing imatinib for the treatment of CML was made several years after there was already good scientific evidence to suggest that it might be useful. Druker told us that he did not know how much the company's initial reticence was due to its finding that the drug had toxic effects in dogs at high doses; but given the relatively small number of patients with CML, he believes that a purely business calculation of the size of the likely market also played a role. In any case, the great initial success of this new drug in CML has sparked exploration, in clinical centers and laboratories around the world, of a similar approach to the treatment of other cancers. In the meantime, clinical studies to determine imatinib's long-term effects on CML continue. For most patients starting on Gleevec, Novartis now charges \$25,000 for a year's supply of the drug, and the current expectation is that these patients will have to be on treatment for at least several years, with or without supplemental therapy.

How did the company decide on Gleevec's walloping price? We do not know, but in this connection it is interesting to consider the comment made last year by Raymond V. Gilmartin, the influential chairman and CEO of Merck, at the press conference announcing the latest R&D cost estimate by DiMasi and his colleagues. Referring to the \$802 million per drug estimate, Gilmartin remarked: "The price of medicines isn't determined by their research costs. Instead, it is determined by their value in preventing and treating disease. Whether Merck spends \$500 million or \$1 billion developing a

medicine, it is the doctor, the patient, and those paying for our medicines who will determine its true value." Since those who pay for a drug are not usually able to judge its value in comparison with other drugs or other forms of treatment, and since those who can make that judgment—the doctors—do not pay for the drug, we do not understand Gilmartin's comment. Taken literally, it would mean that the high prices of today's me-too drugs reflect their medical value—which seems very unlikely. Could he really be saying that the price is simply determined by whatever the market will bear?

THESE THREE STORIES about drug development could be multiplied many times and all the stories would make the same point: the discovery of the important and innovative drugs in the past few decades usually began with basic scientific work at NIH or academic research laboratories, supported by government grants. There have been exceptions, but the pharmaceutical industry has so far devoted most of its R&D resources not to scientific discovery, but to the practical application of discoveries generated at taxpayer expense and to the development of variations on or new uses for drugs already on the market.

All of this makes good business sense for the pharmaceutical industry if, like most industries, it is primarily interested in immediate profits. The kind of wide-ranging, open-ended, and relatively undirected basic research into the molecular biology of disease that is done mainly with NIH support is very expensive, and its results are unpredictable. Whether a given line of investigation will quickly (or ever) lead to the development of a new drug cannot be known in advance. But this kind of research is the only way in which genuine medical progress is made. Pharmaceutical companies, pressured by investors to keep delivering profitable new products—whether they are medically important or not—must use less risky strategies. They use their R&D dollars to imitate top-selling drugs already on the market or to find new uses for their own blockbusters.

That me-too's have come to dominate the new drug market is documented very clearly by the FDA, which classifies drugs under review by their likely therapeutic value and by whether they are NMEs or simply re-formulations and combinations of old drugs. Over the twelve-year period beginning in 1990, 1,035 drugs were approved, and of these only 23 percent were classified as likely to be a "significant improvement" on products already on the market. (In our own judgment as physi-

cians, even many of these drugs would be more accurately described as modest, incremental improvements.) All the others were classified as appearing to have "therapeutic qualities similar to those of one or more already marketed drugs." Moreover, just 15 percent of the approved drugs were classified as both a significant improvement and an NME. Last year, the FDA approved 66 drugs for the entire drug industry. The agency classified only ten as a significant improvement, and only seven of these were NMEs. So the already small percentage of newly marketed drug products that are really novel and important seems to be dropping still further, with me-too's becoming the rule. This trend has continued during the current year.

INDUSTRY SPOKESPEOPLE sometimes justify the growing profusion of brand-name me-too drugs by arguing that they increase market competition and keep prices down. For this reason, they object to the term "monopoly" as applied to the exclusive marketing rights conferred by patents or FDA approval. But me-too drugs are not promoted on the basis of price. Instead, they are marketed as being especially effective—usually in total disregard of the facts. There is little evidence of price competition. Thus, although the availability of multiple similar brand-name drugs may have some modulating effect on prices, it is certainly not nearly as great as the price competition that results when unpatented generic drugs enter the market.

Other apologists claim that in drug therapy one size does not fit all. Very similar drugs, they say, may vary in their effects from patient to patient, so it is important to have choices among them. But there is a paucity of evidence to support the notion that if a particular drug does not work for a patient, a virtually identical one will. It might occasionally be useful to have a new, long-acting version of an identical short-acting drug that is already on the market. But we think most experts would agree that there is little or no rationale for having four or more me-too drugs, as is now the case in many fields. There are now five patented statins (a type of cholesterol-lowering drug) on the market, four patented anti-depressants of the so-called SSRI (selective serotonin reuptake inhibitor) type, and seven patented angiotensin blocking agents (drugs to treat high blood pressure and heart failure). We are aware of no good studies establishing the clinical need for so many.

Blockbusters have one thing in common besides their high sales: they are usually treatments for very common lifelong

conditions. The conditions are not so serious that they are lethal, but they do not go away either. Sometimes they are little more than annoyances, like hay fever. Consequently, large numbers of people may take drugs for these conditions for years, and that is why the markets are so large. People with uncommon or acute diseases are generally not of much interest to drug companies. The major difficulty in launching a me-too blockbuster, however, is in persuading doctors and patients that it is better than the others, since the evidence is at best marginal. Unfortunately, the FDA will approve a me-too drug on the basis of clinical trials comparing it not with an older drug of the same type, but with a placebo or a drug of another type. Drug companies would rather not have a head-to-head comparison, because they might lose. To launch a me-too drug successfully, then, requires a lot of marketing, which largely explains the industry's mammoth marketing expenditures.

Testing Drugs on People

THE ONLY WAY to determine a new drug's safety, effectiveness, and—if this important question is asked—its relative efficacy compared with existing drugs is through properly designed and conducted clinical trials, that is, tests on people. These trials represent the third phase of the R&D process that we have described, and they are the most expensive part of clinical development. Before the FDA will consider approving a new drug for marketing, the manufacturer must present the results of at least one (and usually more) Phase III trials for review by the agency as part of the new drug application. Although the FDA usually reviews the results of the trials submitted to it very carefully, it cannot guarantee the integrity of the work, so it is essential that clinical trials be well designed and executed without bias or manipulation of the results.

Until the past decade, around 80 percent of clinical trials were conducted on patients at academic medical centers and teaching hospitals under the direction of medical faculty, who usually initiated the application for support of the trial. Most of these trials were supported by grants from a pharmaceutical company to the academic institution, although some were funded by the NIH. The design and execution of the studies and the collection, interpretation, and reporting of the data were all the primary responsibility of the academic team, made up of experts in the field. They had no financial ties to the company or to the drug being tested,

although part of their salary might have been paid from the grant as compensation for the time that they invested in the trial.

As the number and the size of clinical trials have grown and the industry's need for faster results and access to large numbers of patients has rapidly increased, more and more trials (over half of them) have been shifted to private-practice settings outside the academic centers, where pharmaceutical firms or their contractors have assumed direct responsibility for the conduct of the clinical studies. A large new industry has arisen to serve the pharmaceutical firms' needs. It consists mainly of companies called contract research organizations (CROs), which are hired by the drug companies to organize and to conduct clinical trials. Often working through other companies, they employ physicians in private practice to recruit patients as subjects for the studies. There are reportedly now over one thousand CROs worldwide, and they generated an estimated \$7 billion in revenues last year from their contracts with the pharmaceutical and biotechnology industries. Although the physicians they hire to recruit patients also help with the conduct of clinical trials, the results of the studies are analyzed and interpreted by the companies. Control over most clinical trials is now largely in the hands of the pharmaceutical industry, and the influence of the academic centers and their clinical faculty is greatly reduced—even in trials conducted at those centers. These dramatic changes have transformed the entire system for the development and the marketing of new drugs, with troubling consequences.

In an effort to recapture income from the pharmaceutical industry, most of the leading academic centers have set up clinical-trials offices to provide the industry with the same quick, comprehensive services that the drug firms have been getting from the CROs and other private research businesses. These centers now openly court the pharmaceutical industry, offering the services of their clinical faculties, access to patients, and help with the design, the conduct, and the analysis of clinical trials. Although some of the stronger academic institutions still insist on faculty control of the studies and the reporting of results, the pendulum of power has shifted. Drug companies have increasing control over the evaluation of their own products. A very recent increase in NIH support of clinical trials may now be starting to reduce the dependence of major academic centers on contracts with the pharmaceutical industry.

Adding to the problem are the growing

financial ties of clinical faculty with the pharmaceutical industry. Almost every academic expert who might be qualified to direct a clinical trial now is paid by one or more firms as a consultant or a speaker. Some medical schools have policies limiting these ties and preventing faculty with financial connections to a company from doing clinical research on that company's drugs, but many medical schools do not, and virtually all of them allow exceptions to their generally lenient rules. The consequence is that the public can no longer assume that clinical reports from academic centers are written by physicians who have no vested interests in the results. About the best to be hoped for is that these interests will be disclosed in the published reports, and that any bias resulting from these financial connections will be balanced by reports from other companies and researchers with competing interests. But the point is that the public can no longer be confident that the testing of new drugs is unbiased.

THE PERVERSIVE CONNECTIONS between the pharmaceutical industry and academia are not limited to clinical trials. Virtually every research-intensive medical center in the country now has contractual ties with one or more drug firms, usually involving subsidies for or collaborations with particular research programs and faculty. In return, the firms gain information about new findings before publication, hands-on laboratory education for their research personnel, and rights of first refusal on patents for the products of this research. Drug companies are even beginning to locate their new research laboratories near academic centers to facilitate such relationships. Merck is now building a large new research facility on land in Boston immediately adjacent to the Harvard Medical School (the first such facility in an area previously reserved for academic and clinical institutions), and Novartis has leased two research facilities in Cambridge close to MIT, joining several biotechnology companies already there.

We do not doubt that collaboration in basic research between academic centers and industry, with appropriate safeguards to preserve the integrity and the independence of academic institutions and their faculties, can be very useful. Yet physical proximity and close economic ties between the industry and the academy have a serious drawback. They can involve academic centers and their faculty too deeply in commercial enterprises, at the expense of their traditional missions of education, patient care, and free-ranging research.

They also threaten the objectivity that is the essential hallmark of good scientific research and medical education. Recently the Association of American Medical Colleges (AAMC) suggested guidelines for managing financial conflicts of interest, but these guidelines are not binding, and they do not address the fundamental issue of whether medical schools and their faculties should have such extensive ties with industry in the first place.

Marketing: Where the Action Is

ACCORDING TO DATA published in their SEC reports for 2001, the big drug companies spent on average about 35 percent of their income on what most of them call “marketing and administration.” At least one major company, Novartis, separates these two functions in its report, assigning 36 percent of total income to “marketing and distribution” and 5 percent to “administration and general overhead.” It is unlikely that other companies differ very much from Novartis in this relative weighting. Still, not much is known about the exact distribution of expenditures within the “marketing” category. Whatever the exact figures, it seems clear that marketing and related activities account for the largest part of the industry’s expenses. They certainly are far greater than the expenses for R&D or manufacturing. By following the money, we conclude that marketing, not the search for new drugs and their development for clinical practice, is the most important focus for the industry. This conclusion is also supported by the distribution of employees as reported by PhRMA. More than one-third of the industry’s workforce is employed in marketing, much more than in R&D, manufacturing, or administration.

If the industry argues that drug prices necessarily reflect its high costs for R&D, then what can it say about its much higher costs for sales promotion? Those who pay for prescription drugs are paying for marketing, too. But if the current crop of new drugs were as valuable as the industry would like us to believe, and if there were not so many me-too drugs, surely it would not be necessary to spend so much money pushing them. A genuinely important new drug, such as Gleevec, does not have to be marketed widely. Cancer doctors treating patients with CML will know about this drug and use it. No sales pitch is needed.

Still, the extravagant expenditures on drug marketing and their effect on drug prices are not the worst part of this story. What should be of even greater concern

is the effect of the industry’s marketing and advertising money on the independence and the trustworthiness of the medical profession. As a learned profession, medicine has a fiduciary responsibility to patients in particular and to society in general to provide expert, unbiased advice on the use of drugs, based on the best available scientific information. Also, the profession has an obligation to educate its own practitioners about the selection and discriminating use of the best and most cost-effective drugs—old and new, patented and generic. This should be largely the responsibility of medical schools, resident training programs in hospitals, and the postgraduate or continuing medical education (CME) courses organized by professional societies, schools, and hospitals. The latter are required for renewal of doctors’ licenses.

But the professional bodies that ought to be responsible for CME have been more or less co-opted by the pharmaceutical industry. There are guidelines, agreed to by the industry and the professional institutions, that are supposed to protect against commercial influence on the content of this education, but most of these guidelines are general and vague. They require that the medical institutions accepting industry support merely approve the CME programs, although the company paying the costs usually recommends the speakers—who, more often than not, are consultants for the company. The softness of the guidelines is hardly surprising, given the fact that they were drafted in 1992 by a task force consisting almost equally of representatives of industry and of the medical profession. They were adopted with only minor changes by the American Medical Association (AMA) and the national professional organization responsible for regulating CME.

The drug companies pay the piper, and by one means or another they call the tune; and the tune is keyed to their sales pitch. The results are clearly demonstrated by published studies showing that industry sponsorship of CME is usually followed by increased prescribing of the sponsor’s products. Were there not clear marketing and sales benefits for the sponsoring companies, they would not spend the huge sums that they do on supporting these activities. Most companies pay for medical education from their marketing budgets: this fact should speak for itself.

Perhaps the clearest indication that what the industry calls “education” is really intended to promote sales is the growth of “medical education and communication companies,” or MECCs. MECCs are for-profit businesses hired by drug companies

to prepare teaching programs and procure medical speakers. The drug companies offer these programs to hospitals or medical groups that are accredited to provide CME. Many MECCs are also officially approved by the medical profession’s CME accrediting body to award education credits on their own. The MECCs are candid in their advertising to their drug industry clients. They say their purpose is to increase their clients’ sales through professional “education”—and that is what they do. If any further demonstration were needed of the true purpose of what the industry calls “medical education,” it was clearly supplied by a recent front-page article in *The New York Times*, with an accompanying report on the PBS program *Now with Bill Moyers*. According to these sources, three of the largest advertising agencies handling pharmaceutical accounts are now investing in companies that do contract research and prepare “educational” packages for the drug industry. This astonishingly incestuous arrangement makes it clear that research and education have both become subordinate to sales promotion.

THE LARGEST SINGLE piece of the known drug-marketing budget is spent on the direct promotion of drugs to doctors by representatives of drug firms. (This is called “detailing.”) There are some 88,000 sales representatives throughout the country, who are paid more than \$7 billion per year by the drug companies to visit doctors in hospitals and offices to pitch their employers’ products. The number and the ubiquity of these salespeople have increased greatly over the past few years. They roam the halls of almost every sizable hospital in the country seeking opportunities to talk with the medical staff and offering gifts (such as books, golf balls, and tickets to sporting events), drug samples, and free meals. In many teaching hospitals, drug representatives regularly provide lunches for the resident staff in order to gain their ear. They attend conferences, they are invited into operating and procedure rooms, and sometimes they are even present when physicians examine patients in clinics or at the bedside.

Sales representatives also regularly visit doctors in their offices, often armed with information about the doctor’s prescribing habits obtained from local drugstores. (There are firms that buy this information from pharmacies and sell it to drug companies.) They make themselves welcome by taking practitioners to dinner in fine restaurants, where company-selected and -paid experts sometimes give talks, and they distribute favors and gifts of all kinds

to doctors and their office staffs. Free samples of drugs for physicians to give to their patients are a major gift item provided by representatives of large drug companies. Industry sources say they spend about \$8 billion per year on free samples. These samples are an effective way to get doctors and patients committed to the continued use of the sampled product—usually an expensive, newly approved drug, with a long period of exclusivity ahead of it.

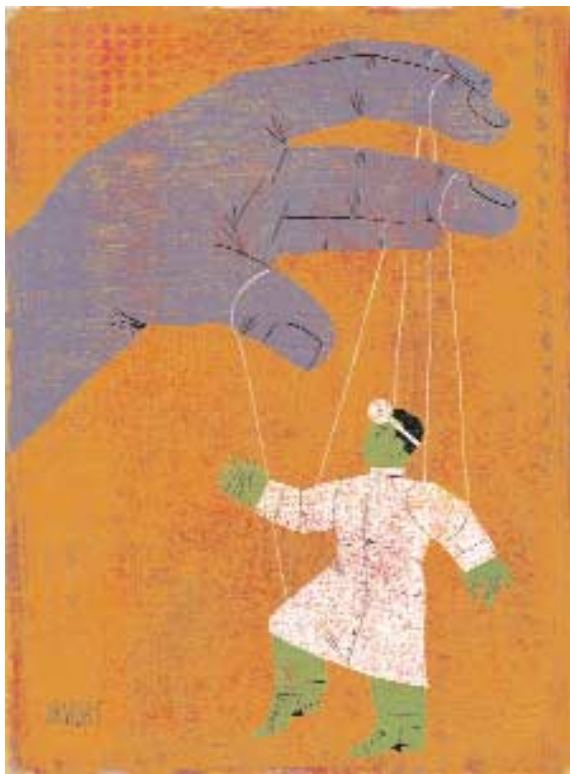
Sometimes doctors are even paid to prescribe the product and to report on the results, under the guise of participating in a company's continuing "Phase IV" research. How much of this kind of drug promotion masquerades as R&D is an interesting but unanswered question. Recently, according to an article in *American Medical News*, at least two new businesses in the Cincinnati area have been established to broker meetings between drug representatives and physicians in office practice. One such business charges drug firms \$105 for each ten-minute meeting with a doctor—of which \$50 goes to the doctor and \$5 to a charity selected by the doctor from a list of five.

An effective marketing technique used by many drug firms is to focus on so-called "opinion leaders" in a particular medical specialty. These are prominent experts, usually on medical faculties and hospital staffs, who write papers, contribute to textbooks, and give talks at medical meetings—all of which influence the use of drugs in their fields. Companies shower special favors on these physicians, offer them honoraria as consultants and speakers, and often pay for them to attend conferences in posh resorts ostensibly to seek their advice or to coach them in public speaking. In many medical specialties these days, it is almost impossible to find an expert who is not receiving payments from one or more drug companies in the field. Disclosure of these arrangements is said to be an adequate remedy for the conflicts of interest, but many observers worry about the loss of professional objectivity and independence that such financial ties produce, regardless of whether they are disclosed.

At medical meetings, drug companies are allowed to present symposia or other types of educational programs—with free lunches or dinners—to supplement the programs presented under the sponsoring society's auspices. The latter are themselves often supported by drug firms. The atmosphere at many large medical meet-

ings resembles a bazaar, dominated by the presence of garish drug company exhibits and friendly salespeople eager to ply physicians with samples, gifts, and services while they pitch their company's drugs. In the exhibit areas adjacent to the meeting rooms, physicians wander through a carnival-like scene. Many carry large canvas bags, bearing drug company logos, stuffed with goodies. To some senior physicians who have watched the atmosphere at these meetings evolve from the sober professionalism of a few decades ago to the trade-show hucksterism of today, it is a dispiriting spectacle.

The cumulative effect of all of this is to blur the crucial distinction between drug marketing and professional education.



Medical education worthy of the name requires an unbiased analysis of all the available evidence, led by experts who have no vested interest in the drugs that they are discussing. That is how medical meetings used to be, and that is how they ought to be, but it is most assuredly not what the companies want to support. They are not philanthropists. They need to sell their drugs; and experience has shown that when they organize "educational programs," when they pay for sales representatives to shower favors on physicians while touting the company's products, and when they spend huge sums on creating trade shows at medical meetings, the sales of their products increase. We would like to know how much all of this costs, but the industry

prefers to keep these matters secret.

This kind of promotion masquerading as "education" is what largely accounts for the market success of new and expensive drugs that are not significantly different or better than less expensive existing drugs. And for this both the industry and the medical profession must take responsibility. Although there has been criticism from some members of the profession, medical societies and associations have taken no effective steps to oppose these practices. Most of the profession, it seems, finds it difficult to break the habit of taking money and gifts from the drug industry. Over a decade ago the AMA issued guidelines on accepting gifts from industry, but they were voluntary and quite permissive. They have not been observed in practice nor monitored by the AMA. PhRMA recently issued guidelines of its own, which closely follow those of the AMA, but, not surprisingly, they are also voluntary and permissive. It remains to be seen whether this latest effort will have any significant effect on drug-industry practices or will prove to be just another public relations ploy.

The Office of the Inspector General (OIG) of the Department of Health and Human Services recently placed in *The Federal Register* for comment a draft of proposed guidelines for ethical and legal relationships between the pharmaceutical industry on the one hand and physicians, pharmacists, and various purchasers of drugs on the other. The OIG notes that many of the existing practices involving gifts and payments to physicians are intended to influence the prescribing of a drug company's products and may potentially violate federal anti-kickback laws. It urges drug companies to review existing laws and regulations to avoid civil and criminal penalties. The code recently adopted by industry, to which we have already referred, is a minimum standard that certainly ought to be met, the OIG says, but mere compliance with that code does not guarantee protection against persecution for illegal conduct. Although they are only general recommendations, not regulations, the tone of these proposed guidelines from the OIG is stern. It remains to be seen what will happen to them when the drug industry and other interested parties weigh in. In any event, the introduction of such guidelines suggests a rising concern about the influence of the industry on the

prescribing behavior of physicians and the costs of prescription drugs.

About the only organized sector of the medical profession that seems genuinely concerned about this issue is the national organization of medical students, the American Medical Student Association. Last spring, this group voted for a total ban on the acceptance of all drug-industry gifts and favors to medical students. It was a brave and laudable gesture, but its impact on practicing physicians and their organizations is doubtful. Recently we attended the annual meeting of the state medical society of Massachusetts, where student delegates urged their elders to pass a similar resolution that would apply to physicians. It was decisively defeated in favor of a resolution that recommended further study of the issue.

ONE OF THE most important developments in the marketing of prescription drugs is the recent explosion in direct-to-consumer (DTC) advertising. In 1997, the FDA changed its policies to allow DTC advertising without the requirement that it include medical details on the side effects of drugs. Since then, DTC advertising has burgeoned and is now estimated to be a nearly \$3 billion industry. Drug firms now spend about as much on this advertising as they do on advertising to physicians in medical journals and other professional media. Advertisements for blockbuster drugs that are prescribed for common complaints such as allergy, heartburn, arthritis, “erectile dysfunction,” depression, and anxiety are seen everywhere. Often celebrities—former politicians, famous athletes, movie stars—endorse the product. Consumers are urged to “ask your doctor” if a certain drug “would be right for you,” and to “be sure to tell your doctor if you have kidney or liver problems” or some other medical condition—something we would hope doctors already knew or could find out for themselves.

A variant on the use of celebrities for the promotion of brand-name pharmaceuticals recently attracted much comment in the news. It seems that celebrities are being paid by drug companies to appear on television news and talk shows and enthusiastically mention their use of a particular drug. Audiences are not informed about the financial arrangement, and are thus allowed to assume that the celebrities are simply volunteering their personal experience. Embarrassed by these revelations, networks are now scrambling to require full disclosure.

Drug companies have been delighted

with the effect of DTC advertising on their sales. Advocates like to describe this obvious form of selling as “education,” just as they describe their advertising to doctors. But drug companies, owing to their clear conflict of interest, are not the ones to educate people about the drugs that they are selling. DTC ads mainly benefit the bottom line of the drug industry, not the public. They mislead consumers more than they inform them, and they pressure physicians to prescribe new, expensive, and often marginally helpful drugs, although a more conservative option might be better for the patient. That is probably why DTC ads are not permitted in other advanced countries less in the thrall of the pharmaceutical industry.

Market Exclusivity: Gaming the System

AS WE EMPHASIZED earlier, the lifeblood of the pharmaceutical industry is government-granted monopolies, in the form of patents and FDA approval for exclusive marketing. The two forms of exclusivity operate largely independently, almost as backups for each other. Both make it illegal, for a specified time, for competitors to sell the same drug. Stretching that privileged time by a variety of stratagems is arguably the most innovative activity of today’s drug companies. For blockbuster drugs, it is certainly the most lucrative. Once a company loses its exclusive marketing rights and opens itself to competition from generic drugs, prices often fall rapidly to about one-fifth of what they were. For blockbusters, that can mean a yearly sales loss of hundreds of millions of dollars.

Patents are supposed to be granted only for discoveries or inventions that are useful, novel, and not obvious. In the past two decades, however, these three standards have been considerably relaxed, so that now nearly anything can be and is patented—including new uses, dosage forms, combinations of old drugs, even the coating of pills. In addition, as a result of a number of industry-friendly laws and regulations passed during the same two decades, the period of exclusivity has become stretched to the breaking point. In 1980, exclusivity lasted for the standard 17-year patent term (minus the time for clinical testing and FDA approval). Now, given the ingenuity of the industry’s legions of patent lawyers, it can be extended for many more years.

In 1984, Congress passed the Drug Price Competition and Patent Term Restoration Act, commonly known as the Hatch-Waxman Act. It added up to five years of

exclusivity for certain drugs to compensate for long FDA-approval times, and it also provided for three years of additional exclusivity for introducing changes in drugs already on the market, such as new dosage forms, new indications, or switches from prescription to over-the-counter status. In a misguided attempt to encourage generic manufacturers to enter the market as soon as possible, the act contained two other provisions. First, it made the FDA approval process simpler for generic companies, but it also stipulated that if a brand-name company sued a generic company for patent infringement, FDA approval of the generic drug would automatically be delayed for 30 months—whatever the merits of the lawsuit. Second, it said that the first generic company to challenge a patent would have six months of exclusivity after it finally reached the market, free from competition by other generics.

HATCH-WAXMAN HAS been a bonanza for the big drug companies. While it was meant to stimulate generic competition, it has often had exactly the opposite effect. Since the act was passed, brand-name drug companies routinely file not just one patent on their drugs, but a series of them spread throughout the life of the first patent. These secondary patents are on every conceivable attribute—never mind usefulness, novelty, or non-obviousness. The result is that generic companies are routinely charged with patent infringement, which immediately triggers 30 months of additional exclusivity. When a generic company challenges a secondary patent, the brand-name company sometimes strikes a deal with it that defers entry of the generic product into the market. Owing to the six-month exclusivity given to the first generic company that challenges a patent, other generic companies are also stopped. Through such shenanigans, exclusivity can be prolonged for years.

This sort of gaming of the system is not supposed to be possible. Under the law, only challenges to certain patents may trigger the 30-month stay on generic entry into the market. These are the patents on approved drugs that companies list with the FDA in a publication known as the Orange Book, available on the FDA website. To be listed in the Orange Book, patents are supposed to apply only to the drug itself and the use for which it was approved. Other patents related to the drug—such as those for new dosage forms or uses—are not supposed to be listed in the Orange Book.

But the FDA does not even attempt to

hold drug companies to that restriction. Instead, drug companies list any patents they choose, no matter how remote from the originally approved drug and no matter how frivolous its use. Sometimes they list virtually the same patent twice. And the secondary patents can be listed at any time, even years after the original approval. This means that there is nearly always some patent in effect that can be used as an excuse for suing generic companies, thus triggering the 30-month additional exclusivity. By filing new patents even after the first lawsuit and then suing for infringement of them, it is even possible to obtain successive 30-month stays. In the case of GlaxoSmithKline's anti-depressant drug Paxil, five lawsuits against the same generic company resulted in five 30-month stays, staggered so that, altogether, GlaxoSmithKline extended its exclusivity by over five years.

In a damning report issued in July 2002, the Federal Trade Commission (FTC) documented the widespread anti-competitive activities within the pharmaceutical industry. And it implicitly took the FDA to task for failing to enforce legal restrictions on the listing of secondary patents in the Orange Book. The FTC found evidence that Hatch-Waxman is regularly exploited to prevent generic competition, and it has taken antitrust action against several brand-name and generic drug companies that colluded to keep generic drugs off the market.

In addition to the Hatch-Waxman Act, other congressional actions have also added to the time during which companies can sell brand-name drugs without generic competition. In accord with the international GATT agreements of 1994, Congress increased the basic patent term from 17 years after issuance to 20 years after filing—which is usually longer. And the Food and Drug Administration Modernization Act (FDAMA) of 1997 added six more months of patent protection if drug companies test their drugs on children. One might think that drugs that would be used by children should be tested on them as a condition of FDA approval, but Congress seems to prefer the legislated bribery route. The effect of all this is much longer periods of exclusivity for brand-name drugs.

In 1980, the average time in which a drug could be marketed without competition was about eight years: the patent term of 17 years minus the time it took for clinical trials and FDA approval. Now it is nearly twice that, and not just because of shorter times for testing and

Near Morning

Cow's breath warms his swaddling
a brood mare snuffles her foal
crumbs of prayer
caught up in the mouse's paws
the shadows of the guests
linger along the wall
though the guests have gone

A leather drawstring pouch
embroidered with dialect
bulges with drachmas
the scent of sandalwood
a costly porcelain jar
rolled up in the rug on the back
of the little mule Ham
sleepily nibbling her fetlock
hock-deep in snow

The man has lain down
with the woman at last
It is nearly dawn
For a moment
there is a stillness
so absolute
even the stars don't blink

The infant beginning
to inhabit his body
is startled by the cold
kiss of air on his cheek
by an ember falling into ashes
a sound as soft as the step
of a friend in the garden
a serry of torches
marching across the wall.

Melissa Green

FDA approval. The companies extend their exclusivity by using every possible stratagem simultaneously, so that if one fails another might work. First, the big drug companies change their top-selling drugs in ways that will add three years' exclusivity, in accord with Hatch-Waxman. Second, they stagger multiple secondary patents, which serve as the pretext for routine lawsuits to trigger a 30-month extension. Third, nearly every blockbuster is tested on children to get the extra six months of patent protection. That is true whether the drugs are likely to be used by children or not. Fourth, brand-name companies sometimes collude with generic companies to delay their entry into the market. And fifth, when all else has failed, they can get a new patent on a trivial variation of their blockbuster and promote it as an "improved" version of the original.

THREE STORIES ARE illustrative of the many ingenious, often questionable tactics that are used to extend exclusivity. The first concerns the blockbuster Claritin—an antihistamine said to cause less drowsiness than cheaper over-the-counter drugs such as Benadryl. (Claritin costs \$80 to \$100 for one month's supply, compared with about one-tenth that for Benadryl.) It was patented by Schering-Plough in 1981, but not approved by the FDA until 1993 (after much scientific controversy about whether it was really effective at the low doses necessary to prevent drowsiness). Last year Claritin had sales of about \$2.7 billion and brought in about one-third of Schering-Plough's revenues. The 17-year patent should have expired in 1998, but, according to a story last year in *The New York Times Magazine* by Stephen Hall, Hatch-Waxman added two years, and GATT added 22 months, and pediatric testing added another six months. These three extensions added four and a half years to the drug's exclusivity—worth billions of dollars. Starting in 1998, Schering-Plough sued eight generic drug companies for infringement of one or more of its four patents listed in the Orange Book. Hall reported the company's legal costs to be about \$5 million per case—still a pittance compared with the stakes.

Back in 1987, Schering-Plough, with great foresight, patented the active metabolite of Claritin—that is, the molecule into which the body converts Claritin, which accounts entirely for the action of the drug. In December last year, it received FDA approval to market the Claritin metabolite under the name Clarinex, and began a massive promotional campaign to switch Claritin users to the new drug before Claritin was scheduled to lose its exclusivity in December 2002. To that end, it also priced Clarinex slightly below Claritin. Clarinex was approved for the treatment of year-round indoor allergies as well as seasonal outdoor allergies. That means Schering-Plough can market it as an improvement, even though it is simply what Claritin turns into after it is swallowed.

This year Schering-Plough petitioned the FDA to change Claritin from a prescription drug to an over-the-counter product. By law, the same drug at the same dose cannot be sold both ways, so the move will stop generic companies from competing in the prescription market when the patent expires. Last month the switch was approved. Claritin will probably be on drugstore shelves by the end of this year

and Clarinex will be the only prescribed Schering-Plough allergy drug. We can see from the Claritin story that drug companies leave nothing to chance. They work simultaneously on every angle that might extend the exclusive marketing life of their blockbusters.

NEXT, THE PROZAC STORY. Prozac, made by Eli Lilly, was the first of a new type of anti-depressant called SSRIs. It was developed mainly on the basis of research done outside the company. In 1987, the FDA approved Prozac for the treatment of depression; in 1994, for the treatment of obsessive-compulsive disorder; in 1996, for bulimia; and in 1999, for geriatric depression. It rapidly replaced other types of anti-depressants because of its milder side effects. Prozac soon accounted for one-quarter of Lilly's revenues, with annual sales reaching \$2.6 billion.

Like other companies in the same position, Lilly sued generic makers who hoped to enter the market. One of them, Barr Pharmaceuticals, charged that Lilly had listed essentially duplicate patents in the Orange Book. In 2000, the Court of Appeals for the Federal Circuit, which handles all patent appeals, agreed. It said Lilly had "double-patented" Prozac, and changed the expiration date from December 2003 to February 2001. The Supreme Court refused to hear an appeal, but Lilly used pediatric testing to extend the time to August 2001. Generic forms of Prozac are now on the market, and the price has come down accordingly. Usage has also dropped, as people respond to advertising for similar brand-name (and now more expensive) SSRIs such as Paxil and Zoloft, while advertising for Prozac has essentially stopped. In June 1999, however, Lilly patented Prozac Weekly, a new formulation that can be taken less often. It was approved by the FDA six months before the Prozac patent expired, and Lilly has exclusive marketing rights until 2004.

The most ingenious move to extend the life of Prozac was the creation of Sarafem—which is the identical drug in the identical dose, but colored pink and lavender instead of green, and taken for a new indication. In 1990, Dr. Richard Wurtman, the director of MIT's Clinical Research Center, and his wife, Dr. Judith Wurtman, took out a patent on SSRIs for the treatment of premenstrual syndrome. This is called a "method of use" patent. According to a CNN report on July 13, 2000, they tried to license the use to Eli Lilly, but the company was not interested—then. So they licensed it to Interneuron Pharmaceuticals, a small biotechnology company

co-founded by Richard Wurtman, which is now called Indevus Pharmaceuticals. In 1997, Lilly, faced with the imminent loss of Prozac's exclusivity, decided to license its use for premenstrual syndrome from Interneuron—reportedly for \$2 million plus a percentage of sales. Lilly renamed Prozac "Sarafem," colored it pink and lavender, and got FDA approval to market it for "premenstrual dysphoric disorder," which is not yet officially recognized as a distinct disorder in the psychiatric diagnostic manual. The Wurtmans and MIT get a portion of Indevus's royalties.

Sarafem's exclusivity was supposed to last until July 2003, but Lilly received a six-month extension because it tested the drug on children—which cannot have been scientifically very illuminating, since these "children" must have been beyond the age of menarche and therefore very nearly adults. Sarafem was priced slightly higher than the identical drug when it was called Prozac. Now that generic Prozac is on the market, Sarafem costs three and a half times as much—\$8.70 per pill at our local drugstore, compared with \$2.50 for the generic.

FINALLY, CONSIDER THE heartburn drug Prilosec, made by the British pharmaceutical firm AstraZeneca. This story was recently told in great detail in an article by Gardiner Harris in *The Wall Street Journal*. Prilosec was the number-one drug in the world, with sales of about \$6 billion per year, until its patent expired in October 2001 after a six-month extension for pediatric testing. Like Schering-Plough and Lilly, AstraZeneca looked ahead. It sued generic companies for infringement of its layers of patents—eleven are listed in the Orange Book. To date, there is still no generic drug on the market: a delay worth billions to the company. At our local drugstore, Prilosec continues to sell for a whopping \$6 per pill. And, like Schering-Plough, AstraZeneca patented a spin-off of its blockbuster drug. Prilosec consists of a mixture of two forms (or isomers) of the same molecule, only one of which is active. The company patented the active form, named it Nexium, and got FDA approval to market it just in time to switch people over to it before Prilosec's exclusivity ran out. This maneuver is very similar to Schering-Plough's Claritin story, except that users were switched to an isomer rather than a metabolite. (Lilly was even more audacious, since Sarafem is identical to Prozac.)

AstraZeneca launched a massive advertising campaign to persuade Prilosec users and their doctors that Nexium was some-

how better, even though there is every scientific reason to expect that a double dose of Prilosec would be equivalent to Nexium. (This was never tested.) Very quickly, according to Harris, Nexium became the most heavily advertised drug in the United States. The media were blanketed with Nexium ads: "Today's purple pill is Nexium. From the makers of Prilosec." To help with the switch, AstraZeneca priced Nexium slightly below Prilosec, gave discounts to managed-care plans, bargained doctors with free samples, and even offered coupons in newspapers. The campaign reportedly cost the company \$500 million in 2001.

Influencing Government

NONE OF THESE maneuvers to lengthen the lives of blockbuster drugs—all of which add to drug costs—could have occurred without the help of Congress. The drug industry has the largest lobby in Washington. In 2000, according to Public Citizen, it employed 625 lobbyists (more than one for each member of Congress) at a cost of \$92.3 million—including 460 hired from 134 Washington lobbying firms. These lobbyists were extremely well connected. They included 21 former members of Congress and others of no doubt equal or greater influence, such as Haley Barbour, the former chairman of the Republican National Committee; Linda Daschle, the wife of outgoing Senate Majority Leader Tom Daschle; Scott Hatch, son of Senator Orrin Hatch; and Anthony Podesta, former counsel to Senator Ted Kennedy and brother of President Clinton's former chief of staff.

In addition, the industry made generous political contributions in the 1999–2000 election cycle, including \$20 million in direct campaign contributions plus \$65 million in soft money. Most of that money went to support Republicans, but these companies have cash enough to spread around. The top recipient in the past decade, according to government ethics watchdog Common Cause, was Hatch, a Republican, but powerful Democrats from states that are home to major drug companies, such as New Jersey Senator Robert Torricelli and Connecticut Senator Joseph Lieberman, also did well. As just one example of the industry's influence, in 1999 Torricelli introduced a bill to give Claritin and six other drugs a chance to lengthen their patents. According to Common Cause, this bill was introduced a day after Schering-Plough made a \$50,000 contribution to the Democratic Senatorial Campaign Committee, which

Torricelli chaired. Hatch held hearings on the bill, despite the fact that Schering-Plough is one of the companies that employed the lobbying firm for which his son worked. As it turned out, the bill was apparently too embarrassing even for Congress, and nothing came of it. Drug companies also influence political campaigns by funding and sometimes creating supposed grassroots organizations, such as Citizens for Better Medicare, to promote drug company interests in media ads and on websites.

One of the most important congressional actions affecting not only the pharmaceutical industry, but also the academic medical centers and the biotechnology industry, was the Bayh-Dole Act of 1980. According to this act and related legislation, academic institutions could patent the fruits of government-funded research and license them to private industry for royalties. The law applied not just to biomedical research, but that is where it saw its greatest application. Virtually overnight, Bayh-Dole made drug companies and academic institutions partners, both benefiting from taxpayer subsidies. The original purpose of Bayh-Dole was to encourage "technology transfer," the translation of basic discoveries into practical use. Accordingly, it stipulated that the products of the research must be made "available to the public on reasonable terms." It also stipulated that the government agency that funded the research (usually the NIH) should be informed by grantee institutions of all such patent and licensing arrangements. These provisions were never enforced. Last year, at the behest of Senator Ron Wyden, the NIH attempted to account for its contributions to a list of 47 blockbusters on the market. The fact that four of them (Taxol, Epogen, Procrit, and Neupogen) were developed largely with public funding was widely publicized. What was not so widely publicized was the fact that the NIH did not seem to know one way or the other about many of the other 43 drugs.

Whether the Bayh-Dole Act has been an overall success is controversial. Certainly the number of biomedical patents increased rapidly after it was passed. But many critics say that the effect of the legislation has often been opposite to its purpose. By encouraging thickets of licenses on every aspect of new technologies and producing a proprietary culture of secrecy, it may actually have slowed technology transfer and the exploration of new scientific leads. And it has certainly done nothing to ensure that drugs licensed from academic institutions are available "on reasonable terms."

In the past year or so, public dismay with high drug prices has begun to have an effect in Congress. In July, the Senate passed a bill introduced by Charles Schumer and John McCain that would prevent many of the abuses of Hatch-Waxman. It also included an amendment to permit the commercial re-importation of prescription drugs from Canada. (Congress passed a re-importation bill during the Clinton administration, but it was not signed by the president.) It did not pass the House, and there is every reason to doubt that anything like it will, given the implacable opposition of the drug industry.

THE TRICKIEST ISSUE for Congress concerning the pharmaceutical industry has to do with growing public pressure for a Medicare drug benefit. Everyone agrees that something has to be done to relieve senior citizens of the heavy burden of paying for prescription drugs out-of-pocket, and everyone, including the pharmaceutical industry, is on record as favoring some sort of extension of Medicare to cover outpatient prescription drugs. Widely differing versions of bills to provide such coverage passed the House and Senate this year, but could not be reconciled. The House version (the one favored by the pharmaceutical industry) proposed that coverage for prescriptions be paid in part by a set contribution from Medicare administered through private insurers. The Senate version was more generous, and provided for direct reimbursements by Medicare—without the intermediary of a private insurance plan.

Political posturing on both sides obscured a critical question in this debate: how much influence should the agency administering the program have on the approved list of covered drugs and on the prices paid to the manufacturers? A program administered directly through Medicare would probably drive harder bargains and involve more regulations than a program contracted out to private insurers, and these policies would very likely spread to drug benefit programs in the private sector as well. This is a prospect that the drug industry, understandably, greatly fears, and that is undoubtedly why drug companies contributed an estimated \$30 million in the recent campaign, most of which went to Republican candidates and Republican-leaning special-interest groups. The Republican victory now ensures that if a Medicare prescription-drug benefit ever does emerge from the 108th Congress, it will certainly be much more to the industry's liking than the version that passed the Senate earlier this year.

Like Congress, the FDA is also on the

industry's payroll. In 1992, Congress passed the Prescription Drug User Fee Act (PDUFA), which required drug companies to pay user fees to the FDA, but stipulated that they would be used only to speed up approval of drugs. These fees now account for about half the budget of the FDA's Center for Drug Evaluation and Research. This makes the FDA dependent on the industry it regulates.

For the industry, the fees are easily outweighed by the increased sales that come from getting faster approval, and by its greater clout with the agency. PDUFA has to be renewed by Congress every five years. In this year's version, which was tacked onto a bioterrorism bill, the fees were increased substantially. Although a small fraction can be used to monitor drug safety, the lion's share is earmarked to further speed drug approval. Yet the faster the approval, the more likely that dangerous drugs will reach the market. Indeed, over the decade since PDUFA was enacted, 13 prescription drugs have had to be withdrawn from the market because they were found to be dangerous—but not before they caused hundreds of deaths.

The FDA is also subject to industry pressures through its 18 standing advisory committees on drug approvals. These committees, which consist of outside experts in various specialties, are charged with reviewing new drug applications and making recommendations to the agency about approval. Many members of these committees have financial or other connections to interested companies. For example, three of the eight members of the FDA's Psychopharmacologic Advisory Committee, which recommended approval of Sarafem, reportedly had ties to Lilly.

The influence of the pharmaceutical industry on government clearly reaches into the Bush administration. Defense Secretary Donald Rumsfeld was CEO, president, and chairman of G. D. Searle, a major drug firm that recently merged with Pharmacia, which is now in the process of merging with Pfizer. Mitchell E. Daniels, White House budget director, was senior vice president of Eli Lilly. Bush *père* was on Lilly's board of directors before becoming president. When added to the industry's large contributions to the Bush campaign in 2000, these connections could well have had something to do with the last-minute withdrawal of Dr. Alastair Wood's nomination as FDA commissioner earlier this year.

Wood, a widely respected professor of clinical pharmacology at Vanderbilt University in Nashville (and a former colleague of ours on the editorial staff of

The New England Journal of Medicine), reportedly was warmly recommended by Senator Bill Frist and Health and Human Services Secretary Tommy Thompson. But he was also known as a supporter of strong regulatory action by the FDA and had evidently ruffled feathers among drug industry executives and other champions of a “free market” for drugs, including the editors of *The Wall Street Journal*. According to an article last May in *The Boston Globe*, the result was behind-the-scenes pressure on the White House, which led to an abrupt change of heart. Frist was quoted as saying that “there was a great deal of concern that he [Wood] put too much emphasis on [drug] safety.” And Dr. Raymond Woosley, also a distinguished clinical pharmacologist and an earlier candidate for the post (who opted instead for a major academic position), remarked, “It is pretty clear that anyone who has said anything that industry doesn’t like isn’t going to make it.”

Dr. Mark McLellan, the newly confirmed commissioner, evidently was not opposed—he may even have been supported—by industry, but he has not taken public stands on any of the critical issues discussed here that might have influenced the views of the pharmaceutical companies. He is both a physician and an economist who has served recently on the president’s Board of Economic Advisers, but he has no experience in drug regulation or clinical pharmacology, so he has much to learn about his new job. Morale at the FDA is said to be very low, and it remains to be seen whether the young commissioner can improve it with the policies and management style he will bring to this critical task. Only time will tell whether he intends to stand up to the pressures from the industry and from a Congress that is now more friendly to the industry than ever before.

What Should Be Done?

THE PHARMACEUTICAL INDUSTRY dominates just about every aspect of the American health care system that is related to its business interests. It uses its wealth and its political clout to influence all who might check or monitor its activities—including physicians, professional and academic institutions, Congress, and the FDA. Hiding behind a screen of public relations and advertising, it expects consumers to sit still for its excesses, with the clearly implied threat that otherwise it will be forced to stop producing its medical miracles.

What reforms might remedy the situation and direct the industry toward more

socially useful behavior? First, the laws and regulations relating to the patenting of drugs and the granting of exclusive marketing rights need to be changed. The U.S. patent system is based on Article I, section 8, of the Constitution: “Congress shall have power ... to promote the progress of science and useful arts, by securing for limited times to authors and inventors the exclusive right to their respective writings and discoveries.” Patents were supposed to protect the intellectual property rights of inventors while enabling them to share information that others might use to advance the field, all in the public interest. But in the modern pharmaceutical business, as we have shown, the system is being grossly abused to allow companies to patent drugs that cannot reasonably be called new inventions, and to permit extensions of exclusivity on the flimsiest of legal pretexts.

The system has allowed the companies to flood the market with expensive me-too drugs and absurdly trivial variations on existing products. The system has also been used by the companies to delay, and sometimes to prevent altogether, competition from generic drugs. There is no question that modifications of Hatch-Waxman are needed. The FTC and Schumer and McCain are correct in their criticisms of the system, and we certainly support the general thrust of their proposals for reform. But more is needed. The whole patent system needs a new look, in view of the recent relaxation of standards for both usefulness and originality. The issues are technical and complicated, and the details of the needed changes will require careful consideration by experts to avoid making a bad situation even worse. We suggest study by a commission of experts (free of industry control) before any legislative or regulatory action is taken, but the completion of the study and the enactment of reforms deserve a high congressional priority.

STRENGTHENING THE FDA and improving its operations also should be a high priority for Congress. The FDA needs more help from congressional appropriations in meeting its growing responsibilities. Its dependence on user fees from industry should be replaced by adequate government support. This is an agency with an agenda of enormous importance to the public health, and it should not have to depend on the industry it is supposed to be regulating, any more than the SEC, for example, should have to depend on contributions from publicly traded corporations.

Of crucial importance, FDA regulations

should be changed to require that new drug applications include evidence not only of the safety and the efficacy of a new drug, but also of the drug’s effectiveness in relation to existing products of the same type. Approval should depend in part on whether the new drug adds something useful in terms of greater effectiveness, greater safety, fewer side effects, or substantially greater convenience. The FDA should be allowed reasonable flexibility in its judgments, of course; but it should not approve drugs that on balance offer trivial advantages or no advantages at all over products already available, and may even be worse. That policy change alone would dramatically improve the medical value of new prescription drugs, since drug companies would have no incentive to turn out me-too drugs and would have to shift their R&D emphasis to finding more innovative ones.

The requirements for membership on FDA advisory committees, upon which the agency depends for advice in the evaluation and approval of new drugs, should be strengthened to avoid conflicts of interest. Given the pervasiveness of the financial ties with the drug industry that now exist among clinical experts in most fields, it is admittedly difficult to find qualified consultants without such conflicts. But the task is not impossible, and the agency should be required to show that it is making every reasonable effort. Without unbiased experts, the FDA cannot get the help it needs to withstand the pressures from industry to approve drugs that really ought not to be allowed on the market or to keep drugs on the market that ought to be withdrawn.

We have already explained why we believe that direct-to-consumer ads are not in the public interest. The FDA should reverse its policy and prohibit such ads in the future, or at least greatly restrict their use. The drug industry and the advertising agencies, which have a financial interest in such ads, will strongly resist, so any such action would probably require a congressional mandate. For reasons of public health and safety, however, the FDA is acknowledged to have purview over pharmaceutical advertising, so there is no question of an unfettered “right to commercial free speech” in this case. The issue is how, and how much, it should be regulated.

Reforms are also needed in the current system for conducting clinical trials. The drug industry should not control the medical evaluation of its own products. The industry has a legitimate interest in seeing that these clinical trials are carried out, and it should pay for most of them. But the

design and the conduct of the trials, and the collection, the analysis, and the interpretation of the results, should be the responsibility of the independent clinical investigators who do the work—not of the sponsoring drug companies. This will require stringent oversight or elimination of the hired businesses that conduct clinical trials for the drug companies, as well as substantial reforms at the academic centers and teaching hospitals that would then carry out most of the studies. Perhaps drug-company trials might best be monitored through some centralized, not-for-profit institution that could be a repository for contract proposals from the companies and an intermediary for the distribution of funds. What should be avoided in any case is the market competition among academic centers for drug-company business. This threatens to transform our medical centers into commercial enterprises, with the inevitable weakening of their commitments to education, clinical care, and unrestricted research. Guidelines such as those recently promulgated by the AAMC will be helpful in preventing this transformation, but the outright elimination of a commercial market for clinical trials would probably be most effective.

IN DEVISING REMEDIES for the problems described here, we must not lose sight of the fact that the prescription-drug industry can sell only the drugs that doctors are willing to prescribe. We have noted the costly and excessive lengths to which drug companies go to influence the prescribing behavior of physicians. But this is done only with the acquiescence of the doctors and their professional associations and educational institutions. If the drug industry presumes to take responsibility for the “education” of physicians, it is because the profession allows—or even invites—the industry to do so. In so doing, the profession abdicates its responsibility to act as fiduciaries and advisers for patients. The profession must take the necessary steps to end its financial and intellectual reliance on the pharmaceutical industry. We believe that many physicians (including medical educators) share this view but hesitate to voice it publicly. The public should be able to get trustworthy expert advice from physicians on what drugs are safe and effective and which of these, if any, are needed for optimal and cost-effective treatment. This is unlikely if much of the profession and its institutions are in the industry’s pocket.

Finally, we note that most of the reforms we have suggested are intended to improve the quality of prescription drugs

and the discrimination with which they are prescribed. Most would probably also reduce expenditures. But the greatest contribution to the control of prescription-drug costs could come from the bargaining power of large purchasers. The largest potential purchaser is the government—through Medicare, Medicaid, and the Veterans Affairs System. If payment for all the drugs used by the patients in these programs were to be negotiated by the government, there is no doubt that major savings would be achieved, particularly if physicians were also to use formularies that limit the routine use of me-too drugs. Such measures would undoubtedly spread to the private insurance system. However, with Republicans now in control of Congress, federal policies will probably become even friendlier to the pharma-

ceutical industry.

Prescription drugs are an essential part of modern medical care. Americans need good new drugs at reasonable prices. Yet the pharmaceutical industry is failing to meet that need. There is a widening gap between its rhetoric and its practices. Neither the medical profession nor government has so far done much to remedy the situation, but sooner or later they will have to act. The increased conservative complexion of the new Congress and the growing dependence of physicians on pharmaceutical money will probably delay such action. Nevertheless, the public is aroused and some kind of reform seems ultimately inevitable. The consequences of continuing to allow an essential industry to put profits above the public interest are simply too grave. ■

Medications do not have a chance to fight health problems if they are taken improperly or not taken at all. Non-adherence to medications costs thousands of lives and billions of dollars each year in the United States alone, according to the New England Healthcare Institute. Researchers fight America's 'other drug problem'. by University of Missouri-Columbia. The graph depicts a patient's medication-taking habits: the scattered dots illustrate irregular adherence (before the intervention), followed by consistent dots that depict improved adherence immediately after beginning the Continuous Self-Improvement strategy. Credit: MU. Medications do not have a chance to fight health problems if they are taken improperly or not taken at all.