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PHARMACEUTICAL INNOVATION, MORTALITY REDUCTION, AND ECONOMIC GROWTH

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ABSTRACT

We perform an econometric investigation of the contribution of pharmaceutical innovation to mortality reduction and growth in lifetime per capita income. In both of the periods studied (1970-80 and 1980-91), there is a highly significant positive relationship across diseases between the increase in mean age at death (which is closely related to life expectancy) and rates of introduction of new, "priority" (as defined by the FDA) drugs. The estimates imply that in the absence of pharmaceutical innovation, there would have been no increase and perhaps even a small decrease in mean age at death, and that new drugs have increased life expectancy, and lifetime income, by about 0.75-1.0% per annum. The drug innovation measures are also strongly positively related to the reduction in life-years lost in both periods. Some of the more conservative estimates imply that a one-time R&D expenditure of about $15 billion subsequently saves 1.6 million life-years per year, whose annual value is about $27 billion. All age groups benefited from the arrival of new drugs in at least one of the two periods. Controlling for growth in inpatient and ambulatory care utilization either has no effect on the drug coefficient or significantly increases it.

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The U.S. has experienced substantial improvement in the average health of its population during the 20th century. The most widely-used measure of medical progress is the growth in life expectancy. Life expectancy (E) in selected years since 1920 is shown below:

1920	54
1965	70
1980	74
1995	76

The average person born in 1995 expects to live 22 years (41%) longer than the average person born in 1920.

Surely almost everyone would agree that this represents a significant improvement in the (economic) wellbeing of the average person. Yet the most widely-used measure of long-run economic growth—growth in *annual* per capita GDP (Y_A)—does not reflect this increase in life expectancy. A better measure of economic wellbeing might be (expected) *lifetime* per capita GDP (Y_L), where $Y_L = Y_A * E$.[1] The growth in lifetime income is the sum of the growth in annual income and the growth in life expectancy: $y_L = y_A + e$ (where lower-case letters denote growth rates).

This identity has two important implications. First, the growth in annual income understates "true" economic growth (i.e. lifetime income growth). During the last three decades the average annual values of y_A and e have been 2.00% and 0.27%, respectively. Hence Y_L has grown about 14% faster than Y_A. Second, a 10% increase in life expectancy has the same effect on Y_L as a 10% increase in Y_A. Factors that contribute to increased life expectancy also contribute to long-run economic growth.

While mean life expectancy is an extremely important indicator, other mortality statistics are also worthy of consideration. Table 1 presents moments and quantiles of the age distribution of deaths in the years 1970, 1980, and 1991. Mean age at death increased by about the same amount (5.4 years) during 1970-91 as life expectancy. This is not surprising, since life expectancy figures are actuarial extrapolations of average age of decedents. A less well-known fact is that the standard deviation of age at death has been declining. People tend to live longer than they used to, and there is also less uncertainty about the age of death. This is because the

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[1] Adopting Y_L as our measure of economic wellbeing implies assigning a marginal value of an additional year of life of Y_A, since $dY_L / dE = Y_A$. This valuation is roughly consistent with (although somewhat lower than) that suggested by other investigators. In 1985, U.S. per capita income (in current dollars) was $16,217. Cutler et al (1996), citing Viscusi (1993), use a "benchmark estimate" of the value of a life-year of $25,000, and upper and lower bounds of $50,000 and $10,000.

area in the bottom tail of the age distribution of deaths has sharply declined. In 1970, 5% of the population died by age 10 and 10% died by age 35; by 1991, the 5% and 10% values were 28 and 43, respectively. If people are risk averse, they are made better off by the reduction in the variance, as well as by the increase in the mean, of the age at death.

Another mortality measure widely used in health statistics is life-years lost before age 65 per population under 65 (LYL). This measure is defined as follows:

$$LYL = \{\Sigma_i \max(0, 65 - age\_death_i)\} / POP\_LT65,$$

where age_death_i is the age of death of the i^{th} decedent, and POP_LT65 is the population under 65. For example, in a population of 1000, if in a given year 2 people die at age 50, 3 people die at age 60, and 5 people die at age 65 or later, LYL = [2 (65 - 50) + 3 (65 - 60) + 5 (0)] / 1000 = 45 / 1000 = .045. This measure gives a great deal of weight to deaths that occur at early ages (especially infant mortality), and no weight at all to deaths beyond age 65. The shrinking of the lower tail of the age distribution documented in Table 1 leads us to expect the rate of decline in LYL to be faster than the rate of increase in life expectancy. The data in Table 2a confirm this: LYL declined 35% between 1970 and 1991. A substantial part of the decline in LYL was due to a reduction in infant mortality (death before the first birthday). The infant mortality rate declined by 55% over this 21-year period (see Table 2b). Infant deaths accounted for over 30% of total life-years lost in 1970; by 1991, they accounted for under 20%.[2]

The purpose of this paper is to perform detailed econometric tests of the hypothesis that the decline in mortality documented above is due, to an important extent, to the introduction and use of new drugs, i.e. to "changes in pharmaceutical technology." The creation and Food and Drug Administration approval of new drugs requires substantial investment in research and development (R&D): the Pharmaceutical Research and Manufacturers Association (PhARMA) estimates that the average pre-tax R&D cost of developing a new molecular entity was $359 million in 1990. Numerous econometric studies have shown that R&D investment has a significant positive impact on the growth in *annual* per capita income (y_A), or on total factor productivity growth.[3] And while there is considerable anecdotal and case-study evidence suggesting that pharmaceutical innovation has made important contributions to the other source

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[2] The rate of medical progress has been declining. Life expectancy increased by 3.6 years per decade between 1920 and 1965, and by only 2.0 years per decade between 1965 and 1995. Similarly, LYL decreased 25.4% from 1970 to 1980, and by only 13.4% from 1980 to 1991.

[3] See, for example, Griliches and Lichtenberg (1984) and Lichtenberg and Siegel (1991).

of lifetime income growth—increases in life expectancy—there is little systematic econometric evidence on this issue. This paper is an attempt to fill this gap in the literature.

Econometric investigations of the impact of technological change are usually hampered by lack of reliable data. In the case of pharmaceuticals, however, it is possible to identify, date, and classify every major and minor innovation since 1939 (because the industry has been strictly regulated by the FDA since then), and to measure the consumption (utilization) of about 1800 distinct drugs (molecules) since 1980. I have obtained from the Food and Drug Administration (by submitting a Freedom of Information Act request) a computerized list of all New Drug Approvals (NDAs) and Abbreviated New Drug Approvals (ANDAs) since 1939. The list includes the NDA or ANDA number, the approval date, the generic and trade names of the drug, the dosage form, route of administration, strength, applicant name, "therapeutic potential" (priority or standard), and "chemical type" (new molecular entity, new formulation, new manufacturer, etc.). This enables us to reconstruct the precise history of pharmaceutical innovation during the last almost 60 years.

We obtain data on the utilization (market shares) of various drugs from the 1980 and 1991 National Ambulatory Medical Care Surveys (NAMCS), which survey doctor-office visits, and the 1993 National Hospital Ambulatory Medical Care Survey (NHAMCS), which surveys visits to hospital outpatient departments and emergency departments.[4] These surveys enable us to estimate the number of drug "mentions" (prescriptions), by molecule, in 1980 and subsequent years. By combining the FDA and NAMCS data, I can calculate *disease-specific* measures of pharmaceutical innovation, i.e. quantify the amount of innovation relevant to each disease, since NAMCS reveals the relative frequency with which each drug is used for each disease.

The overall econometric approach is to estimate the relationship, across diseases, between the extent of pharmaceutical innovation and changes in mortality (e.g., the increase in mean age at death or the reduction in life-years lost). For this approach to be successful, there must be significant cross-disease variation in these variables. Diseases are indeed quite heterogeneous with respect to the rate of progress. The percentage reduction in LYL from 1980 to 1991 of four (ICD9 2-digit) diseases are shown below.

Rickettsioses and other arthropod-borne diseases	136%
Diseases of esophagus, stomach, and duodenum	31
Cerebrovascular disease	18

[4] The National Center for Health Statistics first administered the NHAMCS in 1992. Unfortunately, there are no publicly-available data on pharmaceutical utilization in an inpatient setting.

Chronic obstructive pulmonary disease and allied conditions	-16

There is also substantial variation across drug classes (which to some extent correspond to diseases) with respect to both the amount and timing of drug approvals. Table 3 shows the history of new molecular entities approved within several selected drug classes. The first anticoagulant/thrombolytic drug (heparin) approved by the FDA was in 1942. In contrast, the first cephalosporin (cephalexin) was approved in 1971, and the first antianginal drug (nodolol) was approved in 1979. No antigout drugs have been approved since allopurinol was in 1966.

In the next section we briefly review some existing evidence about the impact of pharmaceutical innovation on mortality. In section III we present a simple econometric model for estimating this impact, describe our procedures for constructing the variables included in this model, and discuss issues pertaining to estimation and interpretation of parameter estimates. Estimates of the model and their economic implications are discussed in Section IV. The final section contains a summary and conclusions.

II. Previous evidence

PhARMA (1998) provides an informal, anecdotal account of the contribution of drug innovation to medical progress in this century. We simply quote their account here:

> Antibiotics and vaccines played a major role in the near eradication of major diseases of the 1920s, including syphilis, diphtheria, whooping cough, measles, and polio. Since 1920, the combined death rate from influenza and pneumonia has been reduced by 85 percent. Despite a recent resurgence of tuberculosis (TB) among the homeless and immuno-suppressed populations, antibiotics have reduced the number of TB deaths to one tenth the levels experienced in the 1960s. Before antibiotics, the typical TB patient was forced to spend three to four years in a sanitarium and faced a 30 to 50 percent chance of death. Today most patients can recover in 6 to 12 months given the full and proper course of antibiotics.
>
> Pharmaceutical discoveries since the 1950s have revolutionized therapy for chronic as well as acute conditions. From 1965 to 1995 cardiovascular drugs such as antihypertensives, diuretics, beta blockers, and ACE inhibitors drastically reduced deaths from hypertension, hypertensive heart disease, and ischemic heart disease.[5]
>
> Similarly, H2 blockers, proton pump inhibitors and combination therapies cut deaths from ulcers by more than 60 percent. Anti-inflammatory therapies and bronchodilators reduced deaths from emphysema by 31 percent and provided relief for

[5] Dustan et al (1996) arrive at a similar conclusion: "In the past 2 decades, deaths from stroke have decreased by 59% and deaths from heart attack by 53%. An important component of this dramatic change has been the increased use of antihypertensive drugs."

> those with asthma. Had no progress been made against disease between 1960 and 1990, roughly 335,000 more people would have died in 1990 alone.
>
> Since 1960, vaccines have greatly reduced the incidence of childhood diseases—many of which once killed or disabled thousands of American children. Likewise, vaccines for Hepatitis B introduced during the 1980s now protect a new generation of American children from a leading cause of liver disease.

Brand new evidence indicates that new drug therapies have sharply reduced fatalities from AIDS:

> AIDS deaths in New York City plummeted by 48 percent last year, accelerating earlier gains attributed to improved drug therapies...the declines crossed sex and racial lines, suggesting that the new therapies were reaching all segments of the AIDS population. National figures for the first six months of 1997 also showed a similar sharp decline, 44 percent, from the corresponding period of 1996...Theoretically, the decline in AIDS deaths could have resulted from prevention efforts or some unknown factor...But the likeliest explanation is expanded use of combinations of newer and older drugs that began to be introduced in recent years, New York City and Federal health officials said.[6]

The anecdotal evidence about the impact of new drugs on mortality is in stark contrast to econometric evidence presented by Skinner and Wennberg (1998) about the relationship between medical expenditure *in general* and outcomes.[7] They analyzed this relationship using both a 20% sample of all Medicare enrollees and a 5% sample of very ill Medicare patients hospitalized with heart attack (AMI), stroke, gastrointestinal bleeding, and lung cancer. Per capita medical expenditures vary considerably across regions. For example, average Medicare expenditures on elderly patients in the last six months of life are twice as high in Miami as they are in Minneapolis, and the average number of visits to specialists is five times as high. However intensive econometric analysis provided "no evidence that higher levels of spending translates into extended survival."[8]

Perhaps the best evidence of the impact on mortality of new drugs comes from clinical trials, of which there have undoubtedly been thousands. One such study was the West of Scotland Coronary Prevention Study of 6595 ostensibly healthy men aged 45 through 64. The results of the study indicated that the cholesterol-lowering drug

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[6] "AIDS Deaths Drop 48% in New York," *New York Times*, February 3, 1998, p. A1.

[7] Pharmaceutical expenditure accounts for only about 10% of total U.S. health expenditure.

[8] Lichtenberg's (1998) analysis of longitudinal quinquennial country-level data for a sample of 17 OECD countries during the period 1960-90 also found no significant effect of either inpatient or ambulatory expenditure on mortality. I did, however, find significant effects of pharmaceutical consumption on both life expectancy at age 40 and life-years lost.

> pravastatin reduces the risk of heart attack and death in a broad range of people, not just those with established heart disease, but also among those who are at risk for their first heart attack...Over five years, those [healthy individuals] treated with...pravastatin suffered 31 percent fewer nonfatal heart attacks and at least 28 percent fewer deaths from heart disease than a comparable group of men who received a placebo...In previous studies, pravastatin had been shown to reduce the risk of heart attack by 62 percent in patients with high cholesterol who already had heart disease.[9]

Evidence from clinical trials is extremely useful and of great scientific value, but there does not appear to be any way to summarize or combine all of this evidence to shed light on the average or aggregate contribution of pharmaceutical innovation to mortality reduction and economic growth, which is our goal.

III. Model specification and estimation

To assess the contribution of pharmaceutical innovation to the reduction in mortality of Americans, I will estimate models of the form

$$\ln (MORT_{t-k} / MORT_t) = \alpha + \beta (DRUGS_{t-k,t} / DRUGS_{.t}) + \varepsilon \qquad (1)$$

using data on a cross-section of diseases, where $MORT_t$ = a measure of mortality (e.g. mean age at death or total life-years lost) in year t; $DRUGS_{t-k,t}$ = the number of drugs prescribed in year t that received FDA approval in year t-k or later; and $DRUGS_{.t} = \Sigma_k DRUGS_{t-k,t}$ = the total number of drugs prescribed in year t. For example, if t = 1980 and k = 10, the equation becomes

$\ln (MORT_{1970} / MORT_{1980}) = \alpha + \beta (DRUGS_{1970,1980} / DRUGS_{.1980}) + \varepsilon$

The dependent variable is the percentage reduction in mortality between 1970 and 1980. The independent variable is the fraction of drugs prescribed in 1980 that were approved in 1970 or later.

The intercept (α) is usually not a parameter of much interest in regression analysis, but it is in this particular case, for it is the predicted change in mortality in the absence of any pharmaceutical innovation. Suppose that the pharmaceutical industry performed no R&D during the period 1960-70, and that, as a result, no new drugs were approved between 1970 and 1980 (in

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[9] "Benefit to healthy men is seen from cholesterol-cutting drug," *New York Times*, November 16, 1995, p. A1.

this example, we assume a 10-year lag between R&D expenditure and new drug approval). Then $DRUGS_{1970,1980} = 0$ and $E[\ln (MORT_{1970} / MORT_{1980})] = \alpha$. The total benefit of innovation is the difference between the actual change in mortality (the mean of the dependent variable) and α, the predicted change under no innovation. When MORT is defined as life-years lost, this is an *annual* benefit of innovation, since the dependent variable is the percent change in annual life-years lost.

We will estimate the model for several alternative definitions of MORT and of $DRUGS_{t-k,t}$, and two sample periods. The mortality variables we will analyze are[10]: mean age at death, life-years lost before age 65 by all decedents under 65, and by decedents in three age categories: age 0-1, age 1-25, and age 25-65. Disaggregation of total LYL into three age categories enables us to distinguish the impact of pharmaceutical innovation on infant mortality from its impact on other premature mortality. Each record in the Mortality Detail file includes a single International Classification of Diseases, Ninth Revision (ICD9) code to indicate the cause of death. We used this code to calculate the various mortality statistics by 2-digit ICD9 disease, by year.[11]

The ICD9 classification includes three kinds of codes: disease (or natural causes of death) codes (000-799), nature of injury codes (800-999), and external causes of death codes (E800-E999).[12] In the mortality files, only the first and last sets of codes are used, whereas in the ambulatory care surveys, only the first and second sets of codes are used. We therefore confine our analysis to diseases (natural causes of death).

Estimates of $DRUGS_{t-k,t}$—the number of drugs prescribed in year t that received FDA approval in year t-k or later—were obtained by combining data from several sources. The first data source was NAMCS, which contains records of 46,081 doctor-office visits in 1980 and of 33,795 visits in 1991. Each record lists the drugs prescribed (if any) by the physician. Up to five drugs may be coded. If a drug is a combination drug, its ingredients (up to five) are coded, so that as many as 25 ingredients (molecular entities) could be coded in a single record. The record

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[10] All mortality statistics were computed from the 1970, 1980, and 1991 Vital Statistics-Mortality Detail files, which constitute complete censuses of the roughly 2 million deaths per year.

[11] The calculated distribution of the log change between 1980 and 1991 of life-years lost included two extreme outliers. The mean, median, and highest and lowest five values of this distribution (N = 79) were as follows: mean = .079; median = .093; lowest = (-4.31, -1.21, -1.07, -0.61, -0.50); highest = (0.66, 0.70, 0.81, 0.86, 3.51). The lowest value was for poliomye...; the highest was for Disorder...A log change of -4.31 corresponds to a 75-fold increase in life-years lost, and a log change of 3.51 corresponds to a 33-fold decrease. We were suspicious of such extreme magnitudes, and these observations were statistically quite influential, so we excluded them from the sample.

[12] There is no direct correspondence between the nature of injury codes and the external cause of death codes, e.g. 821 does not correspond to E821.

also lists up to three diagnoses (ICD9 codes), and a "drug weight", which is used to compute population-level estimates of drug utilization from the sample data. Because multiple diagnoses may be cited in a given record, we sometimes confront the problem of "allocating" the mention of a drug across diagnoses. We adopted the simple, feasible, approach of *equal* allocation of the drug mention across the several diagnoses. For example, if two diagnoses were cited and the drug weight was 10,000, we replaced the mention of that drug by two mentions of the same drug, one for each diagnosis, each with a drug weight of 5000; this procedure does not change the population estimates of drug mentions, by molecule. We then calculated estimates of the aggregate number of prescriptions, by molecule and patient diagnosis.

To calculate the fraction of drugs that were approved by the FDA after a certain date, we linked these data to a list of all New Drug Applications since 1939 provided by the FDA. Both files included the scientific name of the drug, and the FDA file included the date the drug was first approved as a new molecular entity (NME).[13]

Table 4 shows the number of NMEs approved by the FDA from 1940 to the present. A total of 1352 NMEs have been approved. With the single exception of the 1965-69 period, the quinquennial number of NMEs approved has increased steadily over time. Figure 1 shows the distribution of drugs prescribed in 1994, by year of FDA approval. Almost half of the drugs prescribed in 1994 were approved after 1979; about a quarter were approved after 1984.

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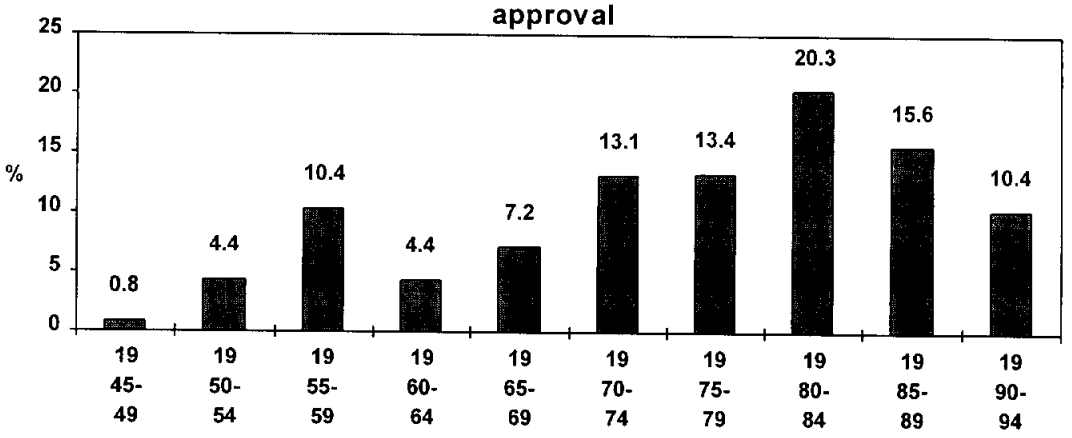
[13] The FDA data enable us to identify the dates of "minor" innovations—new formulations of existing molecules—as well as the dates of "major" innovations—new molecules. For example, approval dates of different dosage forms of the molecule aminophylline are as follows:

1940 tablet
1979 tablet, sustained action
1982 solution
1983 suppository
1991 injection

Minor as well as major innovations may confer health benefits. Unfortunately, we are unable to monitor the diffusion of minor innovations, since the drug information provided in NAMCS does not include the dosage form or route of administration of the drug prescribed, only the name of the compound.

Figure 1
Distribution of drugs prescribed in 1994, by year of FDA approval



Only patient visits to doctors' offices are covered by NAMCS. In 1992 the National Center for Health Statistics began conducting a similar survey (NHAMCS) of visits to hospital outpatient departments and emergency rooms. The number of hospital outpatient visits is believed to have grown much more rapidly during the last 10 to 15 years than the number of doctor-office visits. Doctor-office visits still accounted for more than 80% of total visits in the 1990s[14], but we sought to improve the precision of our estimates of the new-drug proportion by combining information from the NAMCS and NHAMCS surveys. We calculated the share of new drugs in total drugs prescribed in the consolidated sample as well as separately for each of the three outpatient "sectors."[15]

In the course of the approval process, the FDA classifies drugs into two categories: "priority review drugs"--drugs that appear to represent an advance over available therapy--and "standard review drugs"--drugs that appear to have therapeutic qualities similar to those of already marketed drugs.[16] One might reasonably hypothesize that it is only new priority drugs that have a significant impact on mortality, or at least that their effect is much larger than that of

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[14] Estimated annual number of outpatient visits, by venue, are as follows:

Doctors' offices	670 million
Hospital outpatient departments	63 million
Emergency rooms	90 million.

[15] Unfortunately, there is a slight temporal misalignment between the two surveys: the NAMCS data are for 1991 (the same year as the mortality data), but the NHAMCS data are for 1993.

[16] The FDA attempts to review and act on complete applications for "priority" drugs within six months of an NDA's submission date, and to review and act on NDAs for "standard" drugs within 12 months. All AIDS drugs are classified as priority drugs.

new standard drugs. We estimate versions of eq. (1) in which $DRUGS_{t-k,t}$ is defined as the number of *priority* drugs prescribed in year t that received FDA approval in year t-k or later, as well as versions in which $DRUGS_{t-k,t}$ is defined as the *total* number of (priority plus standard) drugs prescribed in year t that received FDA approval in year t-k or later. (In both cases $DRUGS_{.t}$ is defined as the total number of drugs (priority plus standard) prescribed in year t.)

We have mortality data for 1970, 1980, and 1991, and data on the vintage-distribution of drugs prescribed in both 1980 and 1991, so we can estimate eq. (1) for the two periods 1970-80 and 1980-91. The data indicate that the important (in terms of market demand) new drugs introduced in the 1970s and the 1980s were targeted at different diseases and patient populations. The top panel of Table 5 shows the percentage distribution of drugs prescribed in 1980 that were less than 10 years old, by drug class. The top three classes of new drugs were drugs used for relief of pain, antimicrobial agents, and respiratory tract drugs; together these accounted for about half of new drug prescriptions. The lower panel of Table 5 shows the percentage distribution of drugs prescribed in 1991 that were less than 11 years old, by drug class. Cardiovascular-renal drugs accounted for over a third of the new drugs prescribed in 1991, more than four times their share of new drugs in 1980; the new-drug share of hormones also increased sharply. As Table 6 indicates, the average age of patients receiving drugs varies significantly across drug classes. The average age of patients receiving drugs used for relief of pain—the largest new drug class in 1980—is 48, while the average age of patients receiving cardiovascular-renal drugs—the largest new drug class in 1991—is 66. Further calculations show that, consistent with this, the average age of patients receiving any new drug in 1980 was 44, whereas the average age of patients receiving any new drug in 1991 was 52. Since the clientele for drugs introduced in the 1980s tended to be older than the clientele for drugs introduced in the 1970s, one would expect the mortality reductions in the 1980s to be more concentrated among older patients. Since we have computed life-years lost by age group, we can test this prediction.

The dependent variable in eq. (1) is the log-change (growth rate) of mortality, $\ln (MORT_{t-k} / MORT_t)$. The variance of the dependent variable is strongly inversely related to the average size of the disease, $(MORT_{t-k} + MORT_t) / 2$. The growth rates of diseases affecting a relatively small number of people are likely to be much farther away (in both directions) from

the mean than those of major diseases.[17] To correct for heteroskedasticity, the equation is estimated via weighted least squares, where the weight is $(MORT_{t-k} + MORT_t) / 2$. Diseases that are responsible for larger average numbers of deaths or life-years lost are given more weight.[18]

There are a number of reasons why estimates of the parameters of eq. (1) might be biased. Several considerations imply that estimates of β will be biased towards zero, and therefore that our hypothesis tests will be strong tests. Measurement error in the new-drug proportion is perhaps the main reason to suspect downward bias. The variable we calculate $(DRUGS_{t-k,t} / DRUGS_{.t})$ may be a noisy measure of the true share of new drugs for a number of reasons: (1) Sampling error: the NAMCS survey is a random 1 in 10,000 or 1 in 16,000 sample of doctor office visits; (2) Coverage: our drug data refer only to doctor-office visits in 1980, and to outpatient visits in 1991 (no inpatient data); (3) Misallocation of drugs to diseases resulting from errors in allocation procedure described above (when there are multiple diagnoses); (4) Noncompliance: Our data refer to drugs prescribed by physicians, not drugs consumed by patients. It is estimated that only about half the medicine prescribed is taken correctly. The National Council on Patient Information & Education divides the problem of noncompliance into two categories: acts of omission and acts of commission. Acts of omission include: never filling a prescription; taking less than the prescribed dosage; taking it less frequently than prescribed; taking medicine "holidays"; stopping the regime too soon. Acts of commission include: overuse, sharing medicines, consuming food, drink or other medicines that can interact with the prescribed drug.[19]

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[17] To illustrate this, we estimated the unweighted regression of the log change between 1980 and 1991 in LYL on the share of new, priority drugs in 1991, and computed the absolute value of the residuals from this regression. We then divided the diseases into three size categories, based on the average number of LYL in 1980 and 1991. The means of the absolute residuals in each of the three size groups were:

smallest	0.322
middle	0.288
largest	0.137.

Also, there is a highly significant (p-value < .01) inverse correlation between the absolute residual and the logarithm of mean LYL.

[18] When the dependent variable is the log-change in mean age at death or the coefficient of variation of age at death, the weight used is the average of the number of deaths in years t - k and t.

[19] Compliance rates vary with the disease and setting of the patient group. According to data reported in the Journal of Clinical Pharmacy and Therapeutics, patients in homes for the aged had relatively high rates of compliance, as did patients in the first year of antihypertensive treatment. In contrast, patients taking penicillin for rheumatic fever had relatively low rates of compliance.

It is plausible that reverse causality (endogenous innovation), as well as measurement error in the independent variable, could bias estimates of β towards zero. Suppose that there is a significant anticipated increase in fatalities from a certain disease (such as AIDS), and that this prospect stimulates a high rate of development and diffusion of new drugs targeted at that disease. Behavior of this sort would reduce the probability of observing a positive relationship across diseases between mortality reduction and new drug utilization.

Estimates of β might conceivably be biased by the omission from eq. (1) of determinants of mortality change that are correlated with the new drug share. One might postulate that reductions in mortality may be partially attributable to growth in inpatient bed-days and ambulatory visits, and that these might be correlated with our drug measure. However Skinner and Wennberg's (1997) and Lichtenberg's (1998) findings suggest that these variables do not have a significant effect on mortality; moreover, Lichtenberg's (1996) results suggest that growth in inpatient bed-days is *negatively* correlated across diseases with the extent of pharmaceutical innovation. Nonetheless, we will check the robustness of our estimates by estimating a variant of eq. (1) in which we include the growth in inpatient bed-days and ambulatory visits.

We can also think of one possible reason for the least-squares estimate of β to be biased upwards, i.e. to overestimate the average contribution of pharmaceutical innovation to medical progress. Suppose that the rate of progress (P) against a disease is a deterministic, concave function of research expenditure on the disease (X) and research productivity (π): $P_i = \pi_i X_i^{\theta}$, where i denotes disease i and $0 < \theta < 1$. Taking logarithms of the progress function, $\ln P_i = \ln \pi_i + \theta \ln X_i$. Suppose that disease-specific research productivity (π_i) is unobservable. If π_i were uncorrelated with research expenditure X_i, the least-squares estimate of the elasticity of progress with respect to spending θ would be unbiased. However, as argued in Lichtenberg (1997), if decision-makers are efficiently allocating the research budget across diseases (i.e. to maximize the total number of people cured of all diseases), they should devote more research funds to diseases where research productivity is high. Therefore π_i and X_i are likely to be positively correlated, and the slope coefficient from the simple regression of $\ln P_i$ on $\ln X_i$ would overestimate θ. More progress tends to be made on diseases with high research funding in part because those are the diseases where research productivity is highest. We are examining the

relationship between progress and the new drug proportion, not research expenditure, but the latter two variables are likely to be positively correlated.[20]

IV. Empirical results

Weighted least-squares estimates of eq. (1), based on two alternative measures of mortality change, two measures of pharmaceutical innovation, and two sample periods, are presented in Table 7. The first mortality measure we examine is mean age at death. There is not a statistically significant relationship between the change in mean age at death and the overall new drug share in either period. However there is a highly significant positive relationship between the increase in mean age and the new priority drug share in both periods. The point estimate of β is four times as large in the first period as it is in the second, but the fraction of cross-disease variance in mortality change explained (R^2) is the same—7%--in the two periods. In the first period, the (weighted) mean of the dependent variable—the actual increase in mean age at death--was .101[21], and α--the predicted increase in the absence of any pharmaceutical innovation—equals -0.01 (and is insignificantly different from zero). This suggests that in the absence of pharmaceutical innovation, there would have been no increase in mean age at death; new (priority) drugs were responsible for the entire observed increase. It also implies that innovation increased life expectancy, and lifetime income, by just about 1% per annum, which appears to be a very sizable contribution to economic growth. In the second period, the actual increase in age is much smaller (.036), and the intercept is negative (-0.04) and significantly less than zero, implying that mean age at death would have declined in the absence of innovation. The estimated contribution of innovation to increased longevity during 1980-91 is .076 (= .036 - (-.04)), about three-fourths as large as it was during 1970-80.

The second mortality variable we analyze is the percentage reduction in life-years lost before age 65 by decedents of all ages. In both periods, the LYL reduction is very strongly positively related to both drug innovation measures. The relationship with new priority drugs is

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[20] We attempted to explore the relationship across drug classes between unpublished PHARMA data on R&D intensity (the ratio of R&D expenditure to sales) and our data on the share of new drugs in total prescriptions. Unfortunately, the PHARMA data are available for only eight highly aggregated drug classes (e.g. cardiovascular drugs), and we failed to find a statistically significant relationship based on such a small sample.

[21] This is a little more than twice as large as the log increase in the mean age at death figures reported in Table 1, which are means for the entire population of decedents.

slightly stronger than the relationship with all new drugs, so we will focus on the priority drug estimates. The new priority drug share explains *half* of the cross-disease variation in LYL reduction during the 1970s. The estimates imply that in the absence of innovation, LYL would have increased significantly, not declined sharply, as it actually did. The implied contribution of innovation to premature mortality reduction during 1970-80 is enormous: .54 (= .343 - (-.21)).

In the second period, the implied contribution is much more modest—the difference between actual and predicted (under no innovation) LYL reduction is .13--although it is still extremely large in economic terms. During the 1980s, the average number of LYL per year was 12.6 million. Pharmaceutical innovation reduced annual LYL by about 13%, or about 1.6 million. If we value a life-year at 1985 GDP per capita ($16,217)—as discussed earlier this appears to be conservative—the value of life-years saved each year is $26.6 billion. Of course, innovation costs money. Table 8 provides data on total R&D spending by U.S. pharmaceutical companies. Assuming that there is a ten-year lag from research to FDA approval and market introduction of new drugs, R&D expenditures during 1970-81 constitute the additional cost of new drugs (as opposed to existing drugs) consumed by patients during 1980-91. Total (undiscounted, current-dollar) industry R&D expenditures during the period 1970-81 were $14.6 billion. Thus, as a first approximation, a "one-time" expenditure of $14.6 billion leads to an annual gain of $26.6 billion. This should be regarded as a very rough estimate; for a number of reasons it may be either too high or too low. Industry R&D expenditure may understate the true social cost of drug development. Toole (199) presents evidence consistent with the view that the number of new molecular entities approved in a given year is positively related to *government*-funded biomedical research expenditure many (e.g. 25) years earlier, as well as to industry-funded R&D. It may therefore be appropriate to include some government-funded R&D in our cost estimate.[22] On the other hand, pharmaceutical innovation probably confers benefits other than reduced mortality, such as reduced hospitalization and surgical expenditures (see Lichtenberg (1996)), reduced workdays and schooldays lost, and improved quality of life; the above calculation does not account for these.

As discussed earlier, the (simple regression) coefficients on pharmaceutical innovation presented in Table 7 could be biased due to the omission of covariates such as the growth in inpatient and ambulatory care utilization. We have data on these covariates for the 1980-91

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[22] In 1992, about half of total health R&D expenditure in the U.S. was publicly supported, but during the last few decades, private funding has grown much more rapidly than public funding. In 1980, government R&D accounted for almost 80% of U.S. health R&D. Source: National Science Board (1993), p. 365.

period, and we estimated a generalized version of eq. (1) that includes them. The estimates are presented in Table 9. In the mean age at death equation, neither of these variables is significant, and their inclusion has virtually no effect on the drug coefficient. In the LYL equation, both the inpatient and ambulatory care coefficients are highly significant, but they have a perverse (negative) sign: diseases with the highest growth in inpatient and ambulatory utilization had the lowest rates of LYL reduction. Perhaps this is because the growth in both utilization and LYL are driven by exogenous, unobserved changes in the severity or incidence of diseases. In any case, note that inclusion of these covariates *doubles* both the coefficient on the drug variable and its t-statistic. These estimates suggest that the estimates presented in Table 7 do not overestimate the effect of new drugs on mortality change, and may indeed understate it.

The last set of estimates we wish to consider are estimates of the model of LYL reduction, by age class of decedent, for three age classes: age 0-1, 1-25, and 25-65. The results reported above indicate that pharmaceutical innovation substantially reduces total LYL before age 65, but the reduction in mortality could conceivably be confined to two or even just one of the age classes (e.g., infants). The estimates presented in Table 10 strongly suggest that this is not the case: all three age groups benefited (in terms of reduced mortality) from the arrival of new drugs in at least one of the two periods. It is true that infants are the only age class for which there is a highly significant relationship between LYL reduction and the share of new priority drugs in both periods. (This relationship is remarkably strong in the first period; the priority drug variable explains 85% of the variation across diseases in the 1970-80 decline in infant mortality.) However in both periods, innovation also makes a significant contribution to mortality reduction in one of the other two age classes. Consumption of new drugs reduced mortality among persons aged 1-25 between 1970 and 1980, and among persons aged 25-65 between 1980 and 1991. In Tables 5 and 6 we showed that the drugs introduced in the 1980s tended to be targeted at older patients than the drugs introduced in the 1970s, so the "vintage-age interaction" evident in Table 10 is not at all surprising.

V. Summary and Conclusions

There is considerable anecdotal and case-study evidence indicating that pharmaceutical innovation has played an important role in the long-term increase in life expectancy of Americans. We have attempted in this paper to provide some systematic econometric evidence

on this issue, by estimating the relationship, across diseases, between the extent of pharmaceutical innovation and changes in mortality (e.g., the increase in mean age at death or the reduction in life-years lost). This approach is feasible because the data enable us to identify, date, and classify every pharmaceutical innovation since 1939 (the industry has been strictly regulated by the FDA since then), and to measure the consumption of about 1800 distinct drugs (molecules) since 1980, and the characteristics (including diagnoses) of the patients who consume them.

We found that, in both of the two periods we studied (1970-80 and 1980-91), there was a highly significant positive relationship across diseases between the increase in mean age at death (which is closely related to life expectancy) and the share of new "priority" drugs in total drugs prescribed by doctors. (Priority drugs are drugs that appear to the FDA to represent an advance over available therapy.) Mean age at death increased in both the 1970s and the 1980s (albeit more slowly in the 1980s). Our estimates imply that in the absence of pharmaceutical innovation, there would have been no increase and perhaps even a small decrease in mean age at death; new (priority) drugs were responsible for the entire observed increase. They also imply that innovation has increased life expectancy, and lifetime income, by about 0.75-1.0% per annum, which represents a substantial contribution to economic growth.

We also examined the effect of new drug introductions on the reduction in life-years lost (LYL) before age 65. In both periods, the LYL reduction is very strongly positively related to drug innovation measures. The new priority drug share explains *half* of the cross-disease variation in LYL reduction during the 1970s. The estimates imply that in the absence of innovation, LYL would have increased significantly, not declined sharply, as it actually did. The implied contribution of innovation to premature mortality reduction during 1970-80 is enormous. In the second period, the implied contribution is much more modest, although it is still extremely large in economic terms. If we value a life-year at 1985 GDP per capita ($16,217)—which appears to be conservative—the value of life-years saved each year is $26.6 billion. The "one-time" R&D expenditure required to achieve this saving is on the order of $14.6 billion. These estimates are admittedly very rough, but they do suggest that the social rate of return to pharmaceutical R&D investment has been quite high.

The innovation-induced mortality reduction is not confined to a single age group; all age groups benefited from the arrival of new drugs in at least one of the two periods. Controlling for growth in inpatient and ambulatory care utilization either has no effect on the drug coefficient or significantly increases it.

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Table 1

Mean Life Expectancy and Statistics of
Age Distribution of Deaths, 1970, 1980, and 1991

	1970	1980	1991
Life expectancy at birth (years)[23]		73.7	75.5
Age at death (years)[24]			
Mean	64.6	67.7	70.0
Standard deviation	21.8	20.4	19.8
Coefficient of variation	.337	.302	.283
Median	70	72	74
25%	57	60	63
10%	35	41	43
5%	10	22	28

[23] Source: Health, United States, 1994, Table 30.
[24] Source: Author's calculations based on 1970, 1980, and 1991 Vital Statistics—Mortality Detail files.

Table 2a

Life Years Lost Before Age 65 per 100,000 population under 65 years of age, 1970-91

	1970	1980	1991	1991 / 1980
Both sexes and races	8596	6416	5556	.866
White male	9757	7612	6406	.842
Black male	20,284	14,382	14,432	1.003
White female	5527	3983	3288	.826
Black female	12,188	7927	7276	.918

Source: Health, United States, 1994, Table 32.

Table 2b

Infant vs. Total Life Years Lost, 1970-91

Year	Infant mortality rate	Infant deaths (000s)	Infant LYL	Total LYL
1970	20.0	74,620	4,850,300	15,747,872
1980	12.6	45,511	2,958,215	12,896,160
1991	8.9	36,588	2,378,220	12,250,980

Source: Health, United States, 1994, Tables 1, 6, 23, 32.

Table 3

History of New Molecular Entities Approved Within Selected Drug Classes

Drug Class: **Antianginals**

Date	Molecule	Ther_Pot	Chemtype	Applicant	Trd_Name
10dec79	Nadolol	Standard	Nme	E R Squibb	Corgard
31dec81	Nifedipine	Priority	Nme	Pfizer	Procardia
05nov82	Diltiazem	Standard	Nme	Hoechst Marion Rssl	Cardizem
22feb85	Tolazoline			Ciba	Priscoline
13may85	Dipyridamole			Danbury Pharma	Dipyridamole
28dec90	Bepridil	Priority	Nme	Johnson Rw	Vascor
31jul92	Amlodipine	Standard	Nme	Pfizer Cen Res	Norvasc

Drug Class: **Anticoagulants/Thrombolytics**

Date	Molecule	Ther_Pot	Chemtype	Applicant	Trd_Name
05feb42	Heparin			Pharmacia And Upjohn	Heparin Sodium
21jan48	Dicumarol			Abbott Labs	Dicumarol
15dec48	Protamine	Standard	New Manu.	Eli Lilly	Protamine Sulfate
04nov55	Warfarin	Standard	Nme	Dupont Merck	Coumadin
19jun62	Anisindione	Standard	Nme	Schering	Miradon
29mar93	Enoxaparin	Priority	Nme	Rhone Poulenc Rorer	Lovenox

Drug Class: **Antigout**

Date	Molecule	Ther_Pot	Chemtype	Applicant	Trd_Name

26apr51	Probenecid	Priority	Nme	MSD	Benemid
13may59	Sulfinpyrazone	Standard	Nme	Ciba	Anturane
08jun60	Colchicine	Standard	New Combi.	MSD	Colbenemi
19aug66	Allopurinol	Priority	Nme	Glaxo Wellcome	Zyloprim

Table 4

Number of New Molecular Entities Approved by FDA

Period	Frequency	Percent	Cumulative Frequency	Cumulative Percent
1940-44	4	0.3	4	0.3
1945-49	21	1.6	25	1.8
1950-54	68	5.0	93	6.9
1955-59	86	6.4	179	13.2
1960-64	101	7.5	280	20.7
1965-69	70	5.2	350	25.9
1970-74	107	7.9	457	33.8
1975-79	157	11.6	614	45.4
1980-84	174	12.9	788	58.3
1985-89	189	14.0	977	72.3
1990-94	228	16.9	1205	89.1
1995-97	147	10.9	1352	100.0

Note: year of approval unknown for 15 NMEs.
Source: Author's calculations based on unpublished FDA data.

Table 5

Percentage Distribution of Drugs Prescribed in 1980
that were less than 10 years old, by Drug Class

Drugs Used For Relief Of Pain	19.7
Antimicrobial Agents	17.1
Respiratory Tract Drugs	11.2
Psychopharmacologic Drugs	9.5
Skin/Mucous Membrane	8.7
Cardiovascular-Renal Drugs	8.6
Metabolic And Nutrient Agents	8.0
Gastrointestinal Agents	6.7
Ophthalmic Drugs	4.0
Anesthetic Drugs	2.3
Neurologic Drugs	1.7
Unclassified/Miscellaneous	1.2
Oncolytics	0.7
Antidotes	0.2
Hormones And Agents Affecting Hormonal Mechanisms	0.2
Antiparasitic Agents	0.1

Percentage Distribution of Drugs Prescribed in 1991
that were less than 11 years old, by Drug Class

Cardiovascular-Renal Drugs	36.5
Respiratory Tract Drugs	12.6
Hormones And Agents Affecting Hormonal Mechanisms	10.8
Psychopharmacologic Drugs	9.9
Antimicrobial Agents	7.3
Drugs Used For Relief Of Pain	5.9
Gastrointestinal Agents	5.1
Skin/Mucous Membrane	4.7
Metabolic And Nutrient Agents	4.5
Ophthalmic Drugs	2.5
Oncolytics	0.2
Neurologic Drugs	0.0
Otologic Drugs	0.0

Table 6

Average age (in 1991) of patients receiving drugs, by drug class

Cardiovascular-Renal Drugs	66.4
Ophthalmic Drugs	60.9
Hematologic Agents	57.6
Oncolytics	57.0
Gastrointestinal Agents	53.3
Anesthetic Drugs	52.2
Psychopharmacologic Drugs	50.9
Hormones And Agents Affecting Hormonal Mechanisms	49.5
Antiparasitic Agents	48.3
Drugs Used For Relief Of Pain	48.2
Neurologic Drugs	46.4
Unclassified/Miscellaneous	43.6
Otologic Drugs	40.7
Metabolic And Nutrient Agents	39.1
Antidotes	36.8
Skin/Mucous Membrane	36.2
Respiratory Tract Drugs	32.0
Antimicrobial Agents	29.6
Radiopharmaceutical/Contrast Media	20.4
Immunologic Agent	12.4

Source: Author's calculations based on 1991 NAMCS file.

Table 7

Weighted least-squares estimates of the model $Y = \alpha + \beta X + \varepsilon$, for alternative measures of mortality change (Y), pharmaceutical innovation (X), and sample periods

	X = New drug share of total number of drugs prescribed at end of period		X = New "priority" drug share of total number of drugs prescribed at end of period	
	1970-80	1980-91	1970-80	1980-91
Dependent variable (Y):				
Percentage increase in mean age at death	$\beta = 0.50$ (1.18) $\alpha = .028$ (0.37) $Y = .101$ $R^2 = .02$	$\beta = -.035$ (0.49) $\alpha = .051$ (1.63) $Y = .036$ $R^2 = .00$	$\beta = 1.19$ (2.28) $\alpha = -0.01$ (0.18) $Y = .101$ $R^2 = .07$	$\beta = 0.30$ (2.34) $\alpha = -0.04$ (5.31) $Y = .036$ $R^2 = .07$
Percentage reduction in age 0-65 life years lost	$\beta = 3.17$ (5.78) $\alpha = -0.22$ (1.88) $Y = .343$ $R^2 = .32$	$\beta = 0.44$ (2.84) $\alpha = -.081$ (1.28) $Y = .088$ $R^2 = .10$	$\beta = 4.27$ (8.39) $\alpha = -0.21$ (2.40) $Y = .343$ $R^2 = .50$	$\beta = 0.55$ (3.10) $\alpha = -.044$ (0.92) $Y = .088$ $R^2 = .12$

Table 8

Domestic U.S. R&D and R&D Abroad, Ethical Pharmaceuticals, Research-based Pharmaceutical Companies, 1970-97

Year	Domestic U.S. R&D ($ mil.)	Annual Percent Change	R&D Abroad ($ mil.)	Annual Percent Change	Total R&D ($ mil.)	Annual Percent Change
*1997	15,045.1	12.5	3,816.0	7.8	18,861.1	11.5
*1996	13,378.5	12.7	3,539.6	6.2	16,918.1	11.2
1995	11,874.0	7.0	3,333.5	**	15,207.4	**
1994	11,101.6	6.0	2,347.8	3.8	13,449.4	5.6
1993	10,477.1	12.5	2,262.9	5.0	12,740.0	11.1
1992	9,312.1	17.4	2,155.8	21.3	11,467.9	18.2
1991	7,928.6	16.5	1,776.8	9.9	9,705.4	15.3
1990	6,802.9	13.0	1,617.4	23.6	8,420.3	14.9
1989	6,021.4	15.0	1,308.6	0.4	7,330.0	12.1
1988	5,233.9	16.2	1,303.6	30.6	6,537.5	18.8
1987	4,504.1	16.2	998.1	15.4	5,502.2	16.1
1986	3,875.0	14.7	865.1	23.8	4,740.1	16.2
1985	3,378.7	13.3	698.9	17.2	4,077.6	13.9
1984	2,982.4	11.6	596.4	9.2	3,578.8	11.2
1983	2,671.3	17.7	546.3	8.2	3,217.6	16.0
1982	2,268.7	21.3	505.0	7.7	2,773.7	18.6
1981	1,870.4	20.7	469.1	9.7	2,339.5	18.4
1980	1,549.2	16.7	427.5	42.8	1,976.7	21.5
1979	1,327.4	13.8	299.4	25.9	1,626.8	15.9
1978	1,166.1	9.7	237.9	11.6	1,404.0	10.0
1977	1,063.0	8.1	213.1	18.2	1,276.1	9.7
1976	983.4	8.8	180.3	14.1	1,163.7	9.6
1975	903.5	13.9	158.0	7.0	1,061.5	12.8
1974	793.1	12.0	147.7	26.3	940.8	14.0
1973	708.1	8.1	116.9	64.0	825.0	13.6
1972	654.8	4.5	71.3	24.9	726.1	6.2
1971	626.7	10.7	57.1	9.2	683.8	10.6
1970	566.2	---	52.3	---	618.5	---

* Estimated
** R&D Abroad affected by merger and acquisition activity.

Notes:
1. Ethical pharmaceuticals only. Domestic U.S. R&D includes expenditures within the United States by research-based pharmaceutical companies. R&D Abroad includes expenditures outside the United States by U.S.-owned research-based pharmaceutical companies.
2. Totals may not add exactly due to rounding.

Source: Pharmaceutical Research and Manufacturers of America, PhRMA Annual Survey, 1997 (http://www.phrma.org/facts/data/R&D.html)

Table 9

The effect of controlling for growth in hospital bed-days and doctor-office visits on the priority drug share coefficient

Dependent variable:	Percentage increase in mean age at death, 1980-91		Percentage reduction in life years lost, 1980-91	
Column:	(1)	(2)	(3)	(4)
Regressor:				
New "priority" drug share of total number of drugs prescribed in 1991	0.30 (2.34)	0.28 (2.08)	0.55 (3.10)	1.114 (6.05)
Percentage increase in number of hospital bed-days, 1980-91		.029 (1.31)		-0.171 (3.48)
Percentage increase in number of doctor-office visits, 1980-91		.039 (1.48)		-0.307 (5.01)
R^2	.07	.12	.12	.39

Table 10

Weighted least-squares estimates of model of LYL reduction, by age of decedent

	X = New drug share of total number of drugs prescribed at end of period		X = New "priority" drug share of total number of drugs prescribed at end of period	
	1970-80	1980-91	1970-80	1980-91
Dependent variable (Y): percentage reduction in life years lost, by age of decedent:				
Age 0-1	β = 7.02 (15.6) α = -0.91 (8.21) Y = .585 R^2 = .80	β = 0.21 (1.44) α = .105 (1.69) Y = .185 R^2 = .03	β = 6.87 (17.5) α = -0.67 (7.62) Y = .585 R^2 = .83	β = 0.39 (3.15) α = .071 (1.59) Y = .185 R^2 = .14
Age 1-25	β = 1.66 (2.68) α = .075 (0.60) Y = .366 R^2 = .09	β = -.068 (0.28) α = .268 (3.17) Y = .246 R^2 = .00	β = 1.92 (2.93) α = 0.15 (1.59) Y = .366 R^2 = .11	β = -0.28 (0.75) α = .030 (3.72) Y = .246 R^2 = .01
Age 25-65	β = -.153 (0.36) α = .194 (2.42) Y = .170 R^2 = .00	β =.986 (4.61) α = -0.37 (4.17) Y = .021 R^2 = .24	β = 0.27 (0.45) α = .145 (1.96) Y = .170 R^2 = .00	β = 1.47 (3.16) α = -0.31 (2.86) Y = .021 R^2 = .12