By Frank R. Lichtenberg

[Longer]

Through

In recent years, economists have generally accepted the idea that traditional measures of economic growth significantly understate the true growth rate. One reason is that GDP statistics do not account for important intangible benefits of modern life – notably, increased leisure, better health and longer life. Consider longevity. The average person born in 1995 can expect to live a remarkable 22 years longer than his or her counterpart born in 1920.

Assaying the value of extended life spans may, on first reflection, seem a task for philosophers rather than economists. But many economic studies have leapt the conceptual gap by inferring how much people value their own lives from evidence of how much they are willing to spend for small increases in safety (say, by buying home smoke detectors) and how much they are

willing to sacrifice in safety (say, by working in dangerous occupations like mining) in return for higher wages. Prof. William Nordhaus of Yale has argued persuasively that the underestimation of economic growth resulting from failure to translate increased longevity into GDP is substantial – that, adjusted for the value added by those extra years, the American economy grew twice as fast during the 20th century as the measured rate showed.

The forces driving increased longevity are not obvious. But there are clues in broader research on economic growth.

The work of the Nobel Prize-winning economist Robert Solow, which includes the most widely accepted theoretical analysis of economic growth, implies that technological progress has generated most of the gain in per-person income. And while early research assumed that the rate of technological progress was somehow determined from outside the system, more recent growth models recognize that technological progress depends on investment in research and development, and on the creation of new products and processes.

Indeed, there is abundant evidence that growth in conventionally defined per capita output is positively related to cumulative investments in research and development. For example, the manufacturing industries that invest most heavily in R&D generally have the highest rates of growth of output per worker. Here, I ask whether the unmeasured half of economic growth – the portion related to the increase in longevity – can also be explained by a specific sort of technological progress: the development and use of new drugs.

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EARLIER EVIDENCE

The Pharmaceutical Research and Manufacturers Association, the industry trade group usually referred to as PhRMA, provides an anecdotal account of the contribution of drug innovation to medical progress in this century:

> 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 among the homeless and immunosuppressed 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 dying. Today, most patients can recover in 6 to 12 months if given the full and proper course of antibiotics.
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> Pharmaceutical discoveries since the 1950s have revolutionized therapy for chronic as well as acute conditions. From 1965 to 1995, cardiovascular drugs like anti-hypertensives, diuretics, beta blockers and ACE inhibitors drastically reduced deaths from hypertension, hypertensive heart disease and ischemic heart disease.
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> 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 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.

Three economists, David Cutler, Mark McClellan and Joe Newhouse studied a single but very important pathology – heart attacks – by compiling results about the effect of various treatments on mortality. They found that changes in the medical treatments used in the management of myocardial infarctions (the most common form of heart attack) accounted for approximately 55 percent of the reduction in mortality that occurred in cases between 1975 and 1995, with the bulk of this improvement coming from pharmaceuticals. Three drug therapies – aspirin, thrombolytics and beta blockers – resulted in the largest gains. They also noted that "the long-term improvement in mortality may be even more substantial than the acute improvements."

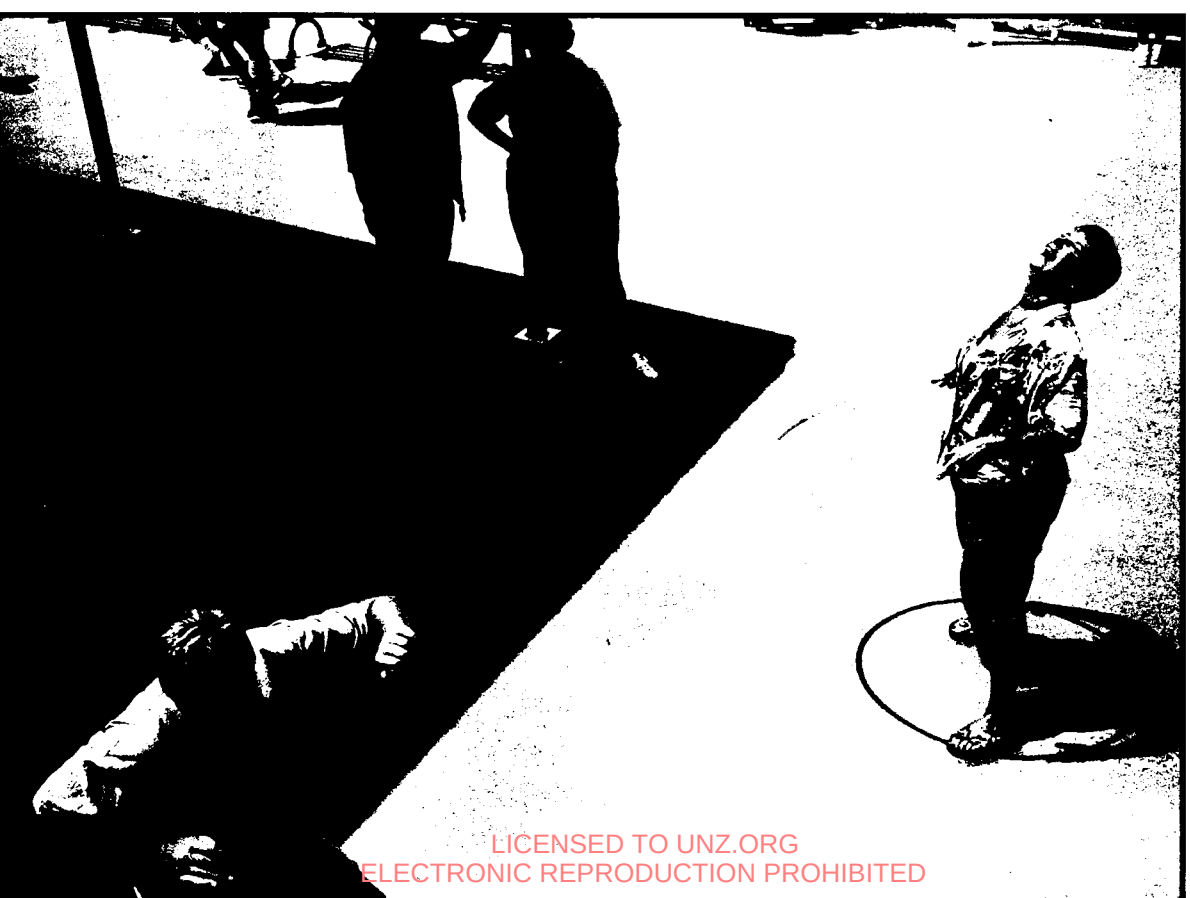
Many innovations have improved the treatment of patients with substantial damage to the heart from the attacks, including drug therapies like ACE inhibitors and anticoagulation therapy, but it is difficult to quantify these important effects. The findings of Cutler, McClellan and Newhouse are especially provocative, since they observe, "the important question is whether [the] results generalize to other types of medical care."

Two other economists, Ted Frech and

NUMBER OF NEW MOLECULAR ENTITIES APPROVED BY THE FDA

PERIOD	FREQUENCY	PERCENT	CUMULATIVE FREQUENCY	CUMULATIVE PERCENT
1940-1944	2	0.18	3	0.27
1945-1949	11	0.98	14	1.25
1950-1954	116	10.37	130	11.62
1955-1959	142	12.69	272	24.31
1960-1964	100	8.94	372	33.24
1965-1969	53	4.74	425	37.98
1970-1974	81	7.24	506	45.22
1975-1979	92	8.22	598	53.44
1980-1984	98	8.76	696	62.2
1985-1989	106	9.47	802	71.67
1990-1994	114	10.19	916	81.86
1995-1999	177	15.82	1093	97.68

NOTE: Year of approval unknown for 15 new molecular entities. Total does not add up to 100 percent due to rounding error.
SOURCE: Author's calculations, based on unpublished FDA data.



LONGER LIVING

Richard Miller, recently examined the relationship between pharmaceutical expenditures per capita and life expectancy, using data for 21 OECD countries. They found a significant positive relationship between drug outlays and life expectancy at age 40, and a yet-stronger one at age 60. Note, however, that since older people tend to consume more drugs, it is difficult to untangle cause from effect: the correlation between drug use and life expectancy may reflect the effect of longevity on pharmaceutical expenditures, as well as the effect of pharmaceutical expenditure on life expectancy.

Clinical trials have provided a great deal of evidence about the impact of new drugs on mortality. One such study was the West of Scotland Coronary Prevention Study of some 6,600 ostensibly healthy men aged 45 through 64. The results indicated that the cholesterol-lowering drug 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," the study reported, adding, "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."

Evidence from clinical trials is of great scientific value, but some experts argue that the results cannot simply be extrapolated to real-world experience. Nor docs there appear to be any way to combine the clinical-trial evidence in ways that shed light on the aggregate contribution of pharmaceutical innovation to mortality reduction.

GETTING TO THE NUMBERS

Estimating the impact of technological change is usually hampered by the lack of reliable data. In the case of drugs, however, it is possible to identify, date and classify every innovation since 1939 (because the industry has been strictly regulated by the FDA since that year), and to measure the rate of utilization of about 900 distinct drugs since 1980. The FDA supplied me with a list of all new drug approvals since 1939, along with other information about the drugs' origins and use. This allowed a detailed inventory of pharmaceutical innovation during the last six decades.

I obtained data on market shares of indi-

vidual drugs from the 1980 and 1991 National Ambulatory Medical Care Surveys (NAMCS), which counted visits to doctors' offices, and the 1993 National Hospital Ambulatory Medical Care Survey (NHAMCS), which counted visits to hospitals' outpatient and emergency facilities. These surveys allowed me to estimate the number of prescriptions, by specific chemical, as well as by diagnosis, since 1980.

Almost half of some 1,100 new molecular entities that the FDA has approved since its inception were approved after 1980. It is therefore not surprising that the mix of prescribed drugs changed considerably between 1980 and 1994. Half of the drugs that were among the top 20 prescribed in 1980 were no longer in the top 20 by 1994. Similarly, half of the top 20 drugs in 1994 were not in the top 20 in 1980. Some of them, like the asthma reliever albuterol, had not yet been approved by the FDA in 1980.

I analyzed the relationship across diseases between the long-term reduction in life-years lost before age 75 and the relative utilization of new pharmaceutical products. In other words, I investigated whether there were above-average reductions in mortality from diseases for which there was above-average utilization of new drugs. Combining data from the FDA and the NAMCS, it is possible to calculate disease-specific measures of pharmaceutical innovation – that is, innovation relevant to each disease – since NAMCS reveals the use of each drug for each disease.

This approach controls for the effects of general trends – changes in wealth, nutrition and sanitation – that affect average mortality.

TOP 20 DRUGS PRESCRIBED IN DOCTOR-OFFICE VISITS IN 1980 AND 1994

	PERCENT OF PRESCRIPTIONS		
RANK/DRUG	1980	1994	CLASS
1980			
1. Hydrochlorothiazide	2.9	1.4	Diuretics
2. Aspirin	2.3	1.5	General Analgesics
3. Penicillin	1.9	•	Penicillins
4. Phenylpropanolamine	1.8	1.0	Nasal Decongestants
5. Alcohol	1.8	•	Antitussives, expectorants, mucolytics
6. Erythromycin	1.7	1.2	Erythromycins and lincosamides
7. Phenylephrine	1.7	1.0	Nasal decongestants
8. Acetaminophen	1.7	3.0	General analgesics
9. Codeine	1.5	0.9	Antitussives, expectorants, mucolytics
10. Tetracycline	1.4	•	Tetracyclines
11. Pseudoephedrine	1.4	•	Nasal decongestants
12. Riboflavin	1.3	•	Vitamins, minerals
13. Digoxin	1.3	1.1	Cardiac glycosides
14. Chlorpheniramine	1.3	•	Nasal decongestants
15. Ampicillin	1.3	•	Penicillins
16. Amoxicillin	1.2	3.8	Penicillins
17. Propranolol	1.2	•	Antihypertensive agents
18. Furosemide	1.1	1.2	Diuretics
19. Ergocalciferol	1.1	•	Vitamins, minerals
20. Neomycin	1.1	•	Ocular anti-infective and anti-inflammatory agents
1980 TOTAL	**31.0**		
1994			
1. Amoxicillin	1.2	3.8	Penicillins
2. Acetaminophen	1.7	3.0	General analgesics
3. Albuterol	•	1.6	Bronchodilators, antiasthmatics
4. Aspirin	2.3	1.5	General analgesics
5. Ibuprofen	•	1.4	Antiarthritics
6. Hydrochlorothiazide	2.9	1.4	Diuretics
7. Multivitamins, general	•	1.3	Vitamins, minerals
8. Furosemide	1.1	1.2	Diuretics
9. Erythromycin	1.7	1.2	Erythromycins and lincosamides
10. Guaifenesin	•	1.2	Antitussives, expectorants, mucolytics
11. Estrogens	•	1.1	Estrogens and progestins
12. Digoxin	1.3	1.1	Cardiac glycosides
13. Prednisone	•	1.1	Adrenal corticosteroids
14. Diltiazem	•	1.0	Antianginal agents
15. Beclomethasone	•	1.0	Unclassified
16. Phenylephrine	1.7	1.0	Nasal decongestants
17. Phenylpropanolamine	1.8	1.0	Nasal decongestants
18. Triamcinolone	•	0.9	Adrenal corticosteroids
19. Codeine	1.5	0.9	Antitussives, expectorants, mucolytics
20. Levothyroxine	•	0.9	Agents used to treat thyroid disease
1994 TOTAL		**27.6**	

NOTE: • indicates not in top 20 in that year.
Total estimated number of prescriptions was 899 million in 1980 and 921 million in 1994.

The analysis of mortality change in a cross-section of diseases is analogous to the analysis of output in a cross-section of industries. Industries produce goods, while diseases are "bads." The pace of innovation varies across both industries and diseases, due in part to variation in technological opportunity.

I estimated the relationship between reductions in mortality and the introduction of new drugs for the entire period 1970-91 and for two sub-periods (1970-80 and 1980-91), as well as for different categories of disease, based on the average age at which people die from the disease. I also distinguished between drugs that the FDA says represent an advance over available therapy and what have been called "me-too" drugs. The data cover all diseases and all drugs used by patients outside hospitals, thus making it possible to draw general conclusions about the impact of new drugs on longevity – conclusions that could not be drawn from previous studies that focused on specific diseases and/or drugs.

MODELING THE IMPACT OF NEW DRUGS

The dependent variable (think of it as the effect) in my analysis is the percentage reduction in life-years lost before age 75 between 1970 and 1991. The independent variable (think cause) is the fraction of drugs prescribed in 1991 that were approved in 1970 or later. I hypothesize that the greater the percentage of drugs prescribed in 1991 that were not yet available in the baseline year (1970), the greater the reduction in mortality.

Although there is only one explicit independent variable, the model does not assume that pharmaceutical innovation is the only source of mortality reduction. Changes in mortality are likely to depend upon a variety of factors, including changes in wealth, environmental quality and the prevalence of smoking. Note, however, that if the changes in these other factors did not vary from disease to disease, their effect would be captured by the constant term in the hypothesized algebraic relationship. Thus, my estimates of the effect of pharmaceutical innovation on mortality reduction depend entirely on diseases' deviations from sample averages.

It is likely that changes in these other factors do vary to some extent from disease to disease. But there is no apparent reason to expect changes in most determinants of mor-

tality other than drug innovation to be correlated across diseases with drug innovation. It is not obvious, for example, why diseases for which many new drugs were developed should be the ones whose sufferers reduced smoking the most or whose wealth increased the most.

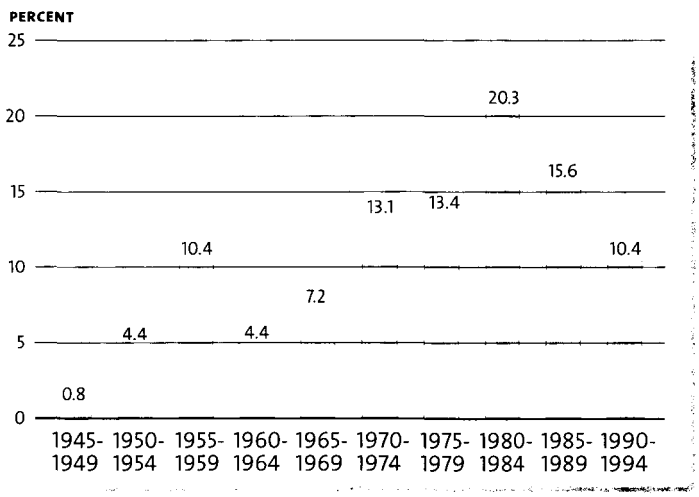
Ideally, one might estimate an expanded version of the model that includes a large number of other possible determinants of mortality change. But many of these are difficult to measure at the disease level. There are, however, several potentially relevant factors that we can measure, and will include in a more elaborate model of mortality reduction to check the sensitivity of our estimates to the inclusion of other real world factors in the analysis. They are: (1) the probability that the physician provides non-medical therapy – primarily counseling and education – to the patient, (2) the availability of a vaccine for the disease, and (3) the rate of introduction of new surgical procedures.

Estimates of the number of drugs prescribed in years following their approval by the FDA were obtained by combining data from several sources. The National Ambulatory Medical Care Survey (NAMCS) contains records from some 46,000 visits to doctors' offices in 1980 and 34,000 visits in 1991. To calculate the fraction of drugs that were approved by the FDA after a specific date, I linked the NAMCS records to the list of all new applications for drug approval. Almost half of the drugs prescribed in 1994 were approved after 1979; about a quarter were approved after 1984.

The FDA classifies new drugs as priority-review drugs, which represent an advance over available therapy, and standard-review drugs, which have therapeutic qualities similar to those of drugs on the market. The FDA's goal is to act on applications for priority drugs within six months, and to make decisions on standard drugs within one year. All AIDS drugs are classified as priority drugs.

One might expect that new priority drugs, on average, have a larger impact on mortality than new standard drugs. I tested this hypothesis by estimating versions of the model in which the new drug share is broken into two components: the shares of new priority drugs and new standard drugs in total drugs prescribed at the end of the period.

DISTRIBUTION OF DRUGS PRESCRIBED IN 1994, BY FDA APPROVAL PERIOD



Of course, new drugs may confer benefits to patients other than mortality reduction. Elsewhere, I have investigated the effect of pharmaceutical innovation on morbidity and quality of life. Note that, if new drugs do indeed reduce mortality, one should examine the impact of pharmaceutical innovation on illness reduction, controlling for mortality reduction, since new drugs are likely to keep less-healthy people alive.

LONGER LIVING

I had mortality data for 1970, 1980 and 1991, along with data on the "vintage" distribution of drugs prescribed in both 1980 and 1991. So I estimated the model for the entire 21-year period 1970-91 and for the two subperiods, 1970-80 and 1980-91. Since some drugs must be consumed for a sustained period for their full health benefits to be realized, it would not be surprising if the longer-term estimated relationship were stronger than either of the two shorter-term relationships.

Moreover, the data indicate that the important new drugs introduced in the 1970s and the 1980s, as measured by sales, were aimed at different diseases and patients. 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. By the same token, the average age of patients receiving drugs varies significantly across drug classes. The average age of patients receiving drugs used for 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.

By no coincidence, the average age of patients receiving any new drug in 1980 was 44, while the average age 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. I tested this prediction by estimating the model for different categories of diseases, classified by the mean age at which people die from the disease.

Two disease classes – malignant neoplasm (cancer) of lymphatic and hematopoietic tissue, and pneumonia and influenza – illustrated here exhibited very different patterns of mortality reduction and new-drug utilization during the 1970-91 period. Only one of the top five drugs prescribed in 1991 for the cancer class was approved after 1970, and the decline in per capita life-years lost (28 percent) was below the average for all diseases (43 percent). In contrast, all of the top five drugs prescribed to patients diagnosed with pneumonia and influenza were new drugs, and the decline in per capita life-years lost (74 percent) was well above average. The data for these two disease classes are thus consistent with the hypothesis that new drugs reduce mortality. But we need to analyze data on the full cross-section of diseases to test the theory in a disciplined way.

HARD NUMBERS

The estimates show a highly significant positive relationship between the new drug share and mortality reduction in all three periods. The magnitude and statistical significance of the effect is larger over the entire 21-year period than it is in either of the two sub-periods. This is consistent with the idea that the long-run effects of new drugs on mortality are larger than the short-run effects. More than 40 percent of the variation across diseases in the 1970-91 reduction in mortality is explained by the new drug share.

An alternative way of analyzing this relationship is to group diseases into a number of categories on the basis of the new drug share, and then calculate the average reduction in mortality for each group of diseases.

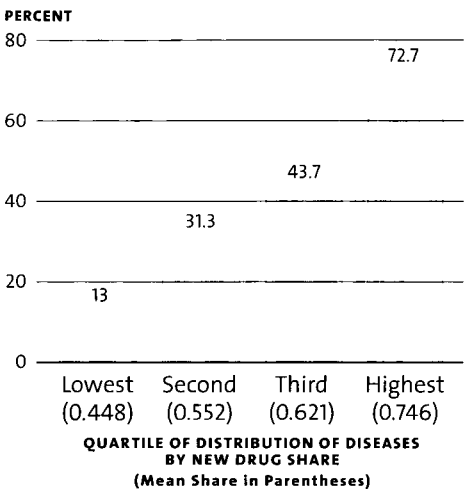
CONTROLLING FOR OTHER FACTORS

As noted earlier, the estimated effects of pharmaceutical innovation could be biased by the failure to control for other factors affecting mortality reduction. For example, educating patients about lifestyle is a potentially important source of mortality reduction. I controlled for the effect of improved patient knowledge by including the fraction of 1991 patients receiving other therapeutic services as an independent variable.

Likewise, vaccines, as well as drugs, contribute to mortality reduction. To control for the effect of vaccine availability on mortality reduction (in an admittedly imperfect way), I included a variable equal to 1 for diseases where a vaccine was available in 1991, and equal to 0 for where one was not. Including measures of counseling and education and of vaccine availability had very little effect on the estimated impact of pharmaceutical innovation on mortality reduction.

The third potential non-pharmaceutical source of mortality reduction is the rate of introduction of new surgical procedures. Using data from the 1980 and 1991 National Hospital Discharge Surveys, I constructed an index, by disease, of the rate at which new surgical procedures were introduced during the period 1980-91. Unfortunately, it does not appear to be feasible to measure the fraction of surgical procedures performed that are new, analogous to the fraction of drugs prescribed that are new, since comprehensive information on the date of introduction of all surgical procedures is not collected by the FDA. In any event, there is no statistically significant relationship between the surgery-innovation variable and mortality reduction for the 1980-91 period. Moreover, adding the surgery innovation variable to the equation has no effect on the estimate of the impact of pharmaceutical innovation.

MEAN 1970-91 REDUCTION IN LIFE-YEARS LOST
BY DISEASES GROUPED BY NEW DRUG SHARE



SOCIETY'S RETURN ON DRUG INNOVATION

On average, each new drug approved during the period 1970-91 saved 11,200 life-years in

1991 – and presumably will do so in all future years. So, by attaching costs to new drug approvals and economic value to life-years, we can calculate the social rate of return to investment in pharmaceutical innovation. Stewart Myers and Christopher Howe estimate the cost of a new drug approval to be $697 million. David Cutler et al use a benchmark estimate of the value of a life-year of $25,000. The aggregate value of 11,200 life-years, at $25,000 per year, is $280 million. The annual social rate of return to pharmaceutical innovation is thus $280 million divided by $697 million, or 40 percent – a remarkable figure.

This is a very rough estimate. On the one hand, the cost side of the estimate does not include government investments in R&D used by drugmakers. On the other, pharmaceutical innovation confers benefits beyond reduced mortality, like reduced hospitalization and surgical expenditures, reduced workdays and schooldays lost, and improved quality of life.

FIVE DRUGS MOST FREQUENTLY PRESCRIBED IN 1991 TO PATIENTS WITH TWO DIFFERENT DIAGNOSES

DRUG	PERCENT OF TOTAL PRESCRIPTIONS IN 1991	FDA APPROVAL DATE THROUGH 1970	FDA APPROVAL DATE AFTER 1970	DRUG STATUS	DRUG CLASS
DIAGNOSIS: Pneumonia and influenza (ICD9 code 48) (74% reduction in per capita life-years lost, 1970-91)					
Amoxicillin	13.34%	1/18/74	•	Priority	Antibacterial
Albuterol	10.35	5/1/81	•	Priority	Bronchodilator
Ibuprofen	6.75	9/19/74	•	Priority	Anti-inflammatory
Cefaclor	6.13	4/4/79	•	Standard	Antibacterial
Ceftriaxone	5.34	12/21/84	•	Priority	Antibacterial
DIAGNOSIS: Malignant neoplasm of lymphatic and hematopoietic tissue (ICD9 code 20) (28% reduction in per capita life-years lost, 1970-91)					
Cyclophosphamide	8.16	• 11/16/59		Priority	Antineoplastic
Prednisone	7.66	• 9/15/55		Priority	Glutocorticoid
Vincristine	5.65	3/7/84	•	Priority	Antineoplastic
Digoxin	5.13	• 11/16/54		Priority	Cardiotonic
Allopurinol	4.7	• 8/19/66		Priority	Xanthine oxidase inhibitor

Previous investigators have argued that increased longevity is an important component of economic growth. And my estimates suggest that pharmaceutical innovation has contributed heavily to gains in life expectancy. More than 45 percent of the variation across diseases in the 1970-91 reduction in mortality can be attributed to the introduction of drugs. The average percentage reduction in life-years lost for the 19 diseases with the highest relative utilization of new drugs was over five times as great as the average percentage reduction in life-years lost for the 19 diseases with the lowest relative utilization of new drugs.

Stepping back, these are simply remarkable numbers. There seems little doubt that innovation in pharmaceuticals has been spectacularly valuable to society. M

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THE King IS Dead

In 1948, the world of electronics was shaken, but not stirred, by the invention of the transistor at Bell Laboratories. Hardly anyone noticed, including AT&T, then the parent of Bell Labs. Four years later, Akio Morita visited the United States and saw in this small, crudely made electronic component the potential for a whole new world of radio. He went back to Japan and formed Sony. In the United States, calmer minds pondered the future of the transistor, laying out a supremely rational approach to developing this product gradually for specialty niches.

The king of electronic components at the time was RCA, followed by Sylvania and General Electric. It was clear that their dominance of the business – which was then mainly vacuum tubes – would give them the scale, the technology and the marketing wherewithal to control the fledgling transistor business. Within 20 years, however, none of these players was even ranked among the leaders in the industry, which was now the great-grandchild of the transistor business and dominated by producers of dynamic random access memories and microprocessors – Texas Instruments, Fairchild and