

GETTING BETTER

Is the golden age of drug development over? Fat chance. Decade-by-decade comparisons show how new medicines improve on old ones. And *that's* innovation.

INNOVATION, OFTEN CALLED THE LIFE-BLOOD OF THE PHARMACEUTICAL INDUSTRY, may be drying up. If you listen to critics who see the 1980s as the zenith of pharmaceutical achievement—and the past 25 years as a gradual (or even steep) decline in pharma's fortunes—this conclusion would seem beyond debate. Of the 487 drugs that entered the market between 1998 and 2003, FDA considered nearly four in five no better than the drugs they replaced. More than three in five were not even new molecular entities. Instead of innovative drugs, these critics contend, the industry produced “me-too” drugs—and not enough of them. The number of new drugs approved by FDA reached a high of 53 in 1996, but by 2002 the number of new approvals dwindled to 17, despite quicker evaluation procedures at FDA and a new high in research spending.

What's the other side of the argument? How about the common-sense observation that drug therapies in certain fields—HIV/AIDS and blood-borne fungal infections might be two of the most obvious—have made great leaps forward during the past quarter century, saving lives that surely would have been lost before new treatments came along. Even in fields that have progressed slowly, many observers believe that new drugs

BY ALBERT I. WERTHEIMER AND FENG-HUA LOH

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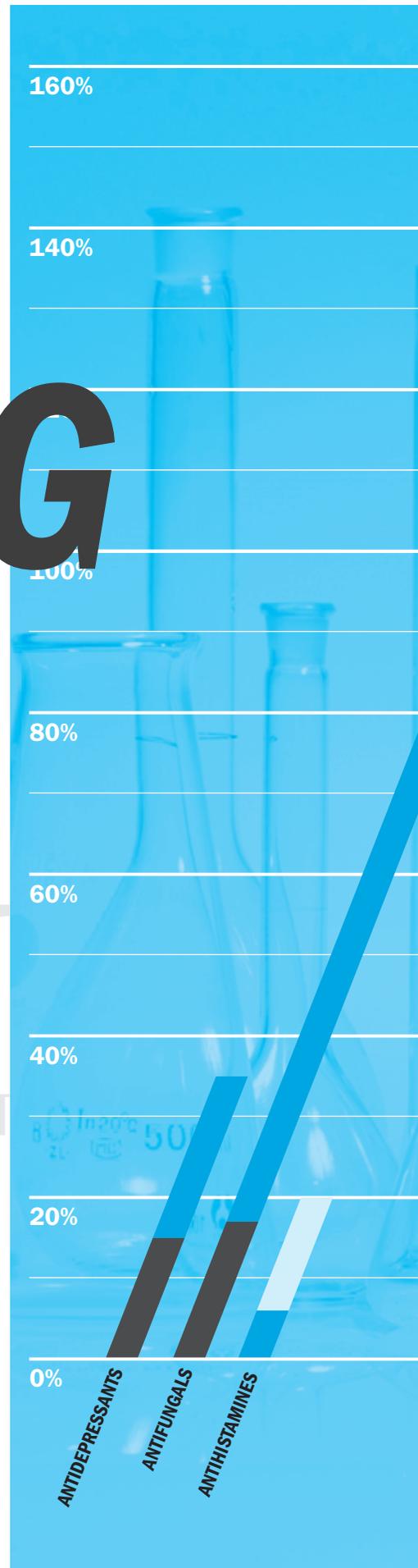
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ANTIDEPRESSANTS

ANTIFUNGALS

ANTIHISTAMINES



Improvements in therapy associated with drugs introduced in the last three decades



Drugs have gotten better each decade. How much better? The experts express progress as percentage improvement over the previous class of drugs. For cumulative improvement, they add percentages. So medicine from the 2000s may be 50 percent better than 1990s' drugs, but 140 percent better than products from the 1980s.



improve on old ones, if only because they reduce uncomfortable side effects or are easier to deliver.

Researchers at the Center for Pharmaceutical Health Services Research at Temple University attempted to make sense of these intuitive notions of innovative progress. First, they searched archival literature for specific pharmaceutical advances in 17 disease areas. Then, to assess how significant these gains were, the research team appealed to a focus panel of eight pharmacists and two physicians, all from Temple University, who are active practitioners and educators.

The panelists—drawn from internal medicine, cardiology, endocrinology, ambulatory care, emergency/critical care, primary care, infectious diseases, and pulmonary disease—were asked to classify each new drug into one of three general levels of improvement over the therapies they replaced:

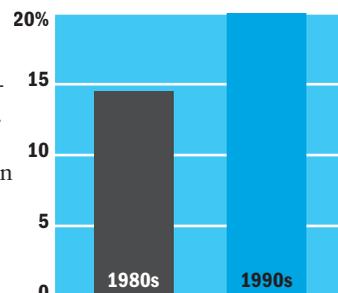
- 1. MAJOR BREAKTHROUGH:** Drugs for conditions with no available treatment.
 - 2. SUBSTANTIAL IMPROVEMENT:** Drugs that moved therapy closer to treatment goals by increasing effectiveness.
 - 3. SOME IMPROVEMENT:** Equally effective drugs that reduced adverse reactions or cut the number of monitoring tests.
- Assigning a drug to a category does not capture its impact without considering the adequacy of existing treatments; the clinical, social, and economic burdens of the disease; and the degree to which each new treatment improves on its predecessor.

Each of the following charts presents the panel's view on innovation in a disease area. In each case, the height of the bar graph represents the panel's consensus score for the percentage improvement over the immediately preceding time period.

How meaningful were the therapeutic advances since the early 1980s? For all 17 disease categories, the panelists found families of drugs that offered advantages—often big advantages—over previous therapies. The results are subjective, but the convergence of views lends credence to the findings and confirms the common-sense view that drug treatments have improved over the past 25 years, resulting in a general improvement in the quality of resources available to treat important medical conditions.

////// ANTIDEPRESSANTS

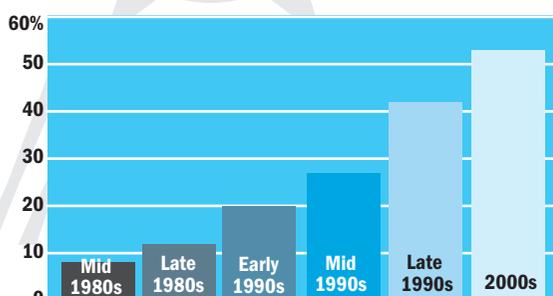
Antidepressant therapy once included opium and various other addictive drugs, not to mention the ever-popular electric shock treatment. MAO Inhibitors (MAOIs) were the first class of drugs specifically designed for depression. In the 1950s, tricyclic antidepressants (TCAs) were introduced. After TCAs, a succession of more selective treatments appeared, including selective serotonin reuptake inhibitors (SSRIs), serotonin antagonist/reuptake inhibitors (SARIs), dopamine reuptake blockers, and selective serotonin/norepinephrine reuptake inhibitors (SSNRIs). New classes of treatment include norepinephrine reuptake inhibitors (NRIs), which have fewer side effects than SSRIs and are safer for the elderly, as well as selective serotonin reuptake enhancers (SSREs), which are structurally similar to tricyclic antidepressants but work differently.



1980s Major breakthrough with selective serotonin reuptake inhibitors (SSRIs). Serotonin antagonist/reuptake inhibitors (SARIs) have fewer side effects. **1990s** Bupropion, a dopamine reuptake-blocking compound, causes fewer side effects. Venlafaxine, a selective serotonin/norepinephrine reuptake inhibitor (SSNRI), and mirtazapine, a noradrenergic and specific serotonergic antidepressant (NaSSA), are approved.

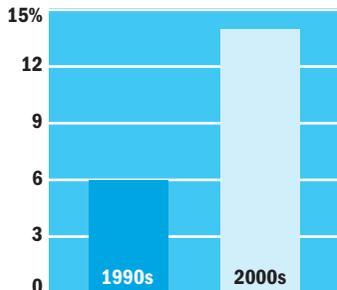
HOW TO READ THESE CHARTS Each of the following charts presents the panel's view on innovation in a disease area. In each case, the height of the bar graph represents the panel's consensus score for the percentage improvement over the immediately preceding time period.

////// ANTIFUNGALS



MID 1980s Imidazole family is introduced. Ketoconazole, the first agent in this class, is widely used to treat systemic fungal infections, and represents a major step forward in decreasing dependence on amphotericin B. **LATE 1980s** Griseofulvin concentrates in newly formed cells of skin, hair, and nails, and inhibits growth of fungi. As the skin, hair, or nail is replaced, the fungus is shed. **EARLY 1990s** Fluconazole, the first of a new subclass of triazole antifungal agents, is considered the most effective treatment for vaginal candidiasis. **MID 1990s** Lipid form of Ampho-teracin B is approved. **LATE 1990s** Terbinafine, now the drug of choice for fungal nail infections, also can be used for ringworm infections. **2000s** The first of a new class of echinocandins, caspofungin acetate, is effective against aspergillosis.

The number of compromised immune systems has risen dramatically in 25 years, thanks to AIDS and new cancer therapies. Weaker immune systems fueled fungal infections and spurred the rapid development of new antifungals. Amphotericin B deoxycholate, the gold standard for the treatment of blood-borne fungal conditions, has been around since 1960. The lipid formulation was approved in 1995, which lacks the kidney-toxic profile of its predecessor. Flucytosine, available since 1973, is the only antimetabolite drug in this class, and remains in clinical use as a part of combination therapies. Additional antifungals have emerged since then, such as the azoles (fluconazole and itraconazole) and the squalene epoxidase inhibitors (terbinafine), which reduce toxicity, enhance efficacy, and shorten therapy. The newest class: the echinocandins, which block fungal-cell-wall synthesis and are indicated for patients unresponsive to the older agents. The first drug of this class is caspofungin, approved in January 2001. Nikkomyacin Z, a quinone that interrupts the exoskeletal structure synthesis, is currently under FDA review.



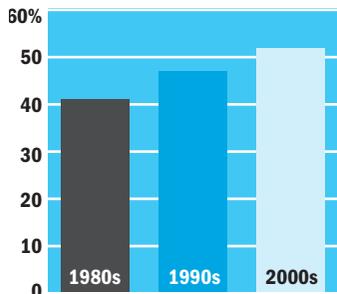
1990s Selective H1 blockers offer a better alternative to older non-selective histamine blockers, which cause sedation, as well as impaired cognition. **2000s** Third-generation antihistamines have no cardiac toxicities and excellent safety profiles.

ANTIHISTAMINES

Compared with the classic antihistamines, the newer, second-generation antihistamines offer brighter hopes of effective treatment. Their efficacy, lack of side effects, and longer duration of action, are significant improvements. These new antihistamines are absorbed more rapidly in the gastrointestinal tract, so they work faster and last longer. The recent, third-generation antihistamines are as effective as their predecessors but have no cardiac side effects. Azelastine nasal spray was approved in 2000, providing patients with an alternative delivery system and increased convenience.

New drugs, like the oxazolidones, attack bacteria with multiple resistances to familiar antibiotics.

ANTIMICROBIALS



1980s Fluorinated quinolones are more potent and less toxic. **1990s** Newer macrolides are available. Clarithromycin and azithromycin are safe, well tolerated, and convenient. **2000s** Daptomycin, a lipopeptide with rapid activity and effectiveness against resistant strains, is approved.

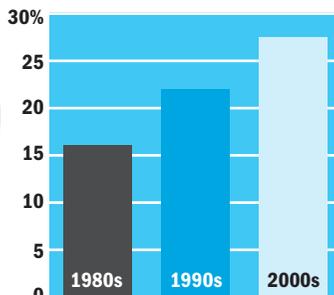
Treatment with commercially available antibiotics began in the 1950s. Over time, antibiotics have revolutionized healthcare, saving millions of lives and extending life expectancies. The newest antibiotics are the ketolides, which are the latest structural derivatives of erythromycin to be added to the macrolide family. The first ketolide is telithromycin, approved in April 2004 for certain bacterial respiratory infections. Other new antibiotics include the oxazolidones, which have a unique mechanism of antibacterial action and activity against bacteria with multiple resistances to other antibiotics. Linezolid, the first approved oxazolidone, was the first antibiotic agent introduced for the treatment of methicillin-

resistant *Staphylococcus aureus* (MRSA) infections, for which there were very limited treatment options otherwise. Daptomycin is the first product in another new class of antibiotics called lipopeptides. Phage therapy may prove an effective future treatment. This therapy uses viruses to attack specific bacteria and has proven effective against MRSA.

Antiviral agents are another important class of antimicrobials. Antiviral agents have been developed to treat and prevent influenza (both A and B) since the 1990s. Of these, M2 inhibitors, including amantadine and rimantadine, offer prevention and protection against influenza A. Neuraminidase inhibitors, including zanamivir and oseltamivir, are newer agents designed to broadly inhibit both influenza A and B.

ARTHRITIS

Arthritis and other rheumatic conditions are among the most prevalent chronic conditions in the United States, affecting approximately 38 million people. Arthritis treatments have come a long way since the 1960s, when treatments were designed to relieve pain but not to prevent inflammation. Non-steroidal anti-inflammatory drugs (NSAIDs) alleviate pain with few side effects. Salicylates, such as aspirin, increase the risk of ulcers. In the 1980s, disease-modifying anti-rheumatic drugs



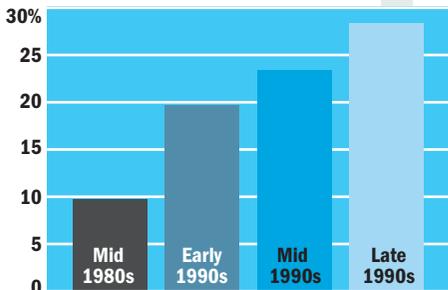
1980s Disease-modifying anti-rheumatics, such as methotrexate, are introduced. **1990s** COX II inhibitors have fewer GI effects than the first generation NSAIDs. **2000s** Etanercept and infliximab target tumor necrosis factor-alpha (TNF-alpha), which is responsible for inflammation. Anakinra, an IL-1 receptor agonist, is genetically engineered to prevent inflammatory substances from activation.

(DMARDs) became available. The DMARDs work to reduce the body's defense mechanisms and prevent it from attacking its own cells. Recently, biological response modifiers were developed to target tumor necrosis factor (TNF), one of the hormones that activates cells responsible for inflammation. Adalimumab is the first human monoclonal antibody approved by FDA to reduce symptoms of arthritis and inhibit the progression of structural damage in adults. Abatacept, a T-cell regulatory protein that inhibits cells that launch the immune response, received FDA approval in December 2005.

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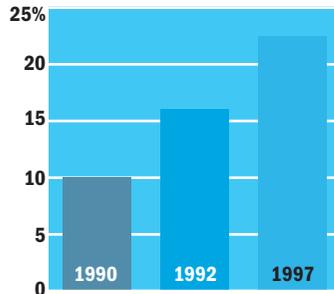
//// ASTHMA

There are approximately 17 million asthmatics in the United States. Asthma prevalence, morbidity, and mortality are increasing around the world. Data show that treatment for upper-airway diseases is associated with a reduced frequency of asthma-related emergency-department visits. There are two major forms of medication for asthma, which either relieve symptoms or prevent asthma attacks. Both aim to avoid permanent damage to the lungs. The introduction of inhaled steroids via metered-dose inhalers (MDIs) has brought relief for numerous patients, minimiz-



MID 1980s Approval of short-acting beta-agonists, such as albuterol, which remain the primary treatment of acute asthma attacks. **EARLY 1990s** Beclomethasone, the first inhaled corticosteroid, is approved for asthma. **MID 1990s** New anticholinergics, such as ipratropium bromide and glycopyrrolate, are introduced. They are used in conjunction with beta-agonists to produce more rapid improvements. **LATE 1990s** The leukotriene modifiers are shown to reduce the need for steroids. They provide oral therapy with fairly rapid onset of action.

ing the complications of long-term steroid use. The newest class of treatment is the anti-IgE antibodies (MoAb), which lessen severe asthma symptoms and reduce the need for rescue medications. Omalizumab, the first in this class, was approved in June 2003.



1990 Non-selective alpha-blockers become a non-invasive option. **1992** Finasteride is approved. It has fewer side effects than its competitors. **1997** The first selective alpha-blocker becomes available, which lowers the risk of hypotension.

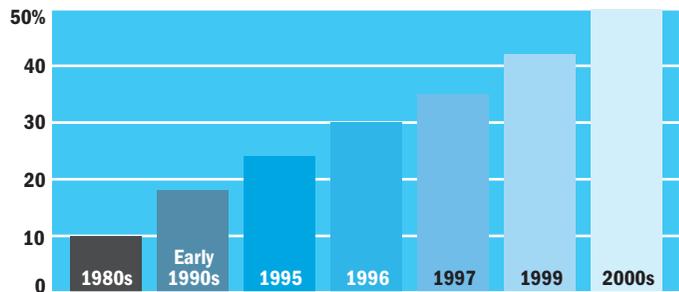
//// BENIGN PROSTATIC HYPERPLASIA

Until non-invasive drug treatment became an option in the early 1990s, the only treatment available for BPH was surgical. Some drugs reduce the size of the prostate (5-alpha-reductase inhibitors, like finasteride), while others relax the muscles that surround the prostate (alpha-blockers), to allow the flow of urine. More recently, selective alpha-blockers tamsulosin and alfuzosin have become the drugs of choice for BPH. They are more effective than finasteride, with fewer side effects. The problems of BPH may be completely eliminated at some time in the future, but, in the meantime, treatment for relief of its symptoms has never been so diverse or effective.

//// DIABETES MELLITUS

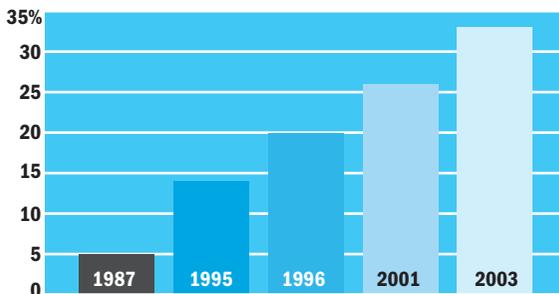
Insulin was the first and has remained the primary means of treatment for Type 1 diabetes since it first was used successfully in 1922. The advent of synthetic human insulin and several different classes of antidiabetic medications improved treatment. The second-generation sulfonylureas are at least 100 times more potent on a weight basis than the first-generation agents, and appear to produce fewer side effects. In the 1990s, biguanides, alpha-glucosidase inhibitors, meglitinides, and then thiazolidinediones, were approved in succession. Once-daily glargine is the first insulin that offers truly flat insulin levels throughout the day. In January of 2006, the first inhaled insulin was approved for the treatment of Type 1 and Type 2 diabetes.

Asthma sufferers began to take inhaled steroids with metered-dose inhalers, which dropped the risk of long-term steroid use. The newest class of treatments are the anti-IgE antibodies, which cut down severe symptoms and reduce the need for rescue drugs.



1980s Synthetic human insulin lowers the risk of adverse allergic reactions compared with animal insulin, and decreases the chance of patients needing higher and higher doses of insulin. **EARLY 1990s** Second-generation sulfonylureas are more potent and have fewer drug interactions and side effects. **1995** Metformin, the first biguanide, improves peripheral glucose uptake. **1996** Alpha-glucosidase inhibitors delay absorption of glucose. Lispro insulin, the first new insulin product in more than a decade, allows patients to take insulin right before a meal. **1997** Repaglinide, the first of the meglitinide class, is designed to manage meal-related glucose loads. **1999** Thiazolidinediones increase insulin sensitivity and glucose uptake. **2000s** Once-a-day glargine is the first insulin to offer truly flat insulin levels through the entire day for most users. Insulin aspart has faster absorption and onset, as well as shorter duration of action, compared with regular human insulin. It is used for mealtime dosing to control blood sugar elevation during meals.

HIV/AIDS



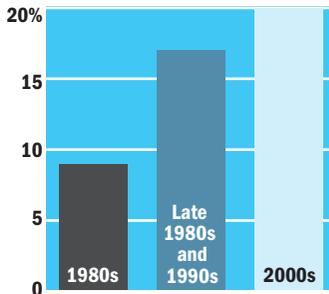
1987 Nucleoside analog reverse transcriptase inhibitor is approved (NRTI). It prevents viruses from copying properly. **1995** Other NRTIs were developed. Protease inhibitors (PIs) prevent infected cells from infecting additional cells. **1996** Non-NRTIs help patients intolerant of PIs' side effects. **2001** First nucleoside reverse transcriptase inhibitor (NtRTI) was introduced. Similar to NRTIs, it works more quickly. **2003** First fusion inhibitor is approved. It works outside the cell.

Seven years into the modern era of HIV/AIDS treatment, the outlook for people with HIV infections continues to improve. As the number of classes of antiviral medications grows, clinicians are shifting from monotherapy to combination therapy with two or more classes. The revolutionary practice of combination therapy, known as highly active anti-retroviral therapy (HAART), dramatically increases survival and decreases mortality. The therapy usually includes one nucleoside analog, one protease inhibitor, and either a second nucleoside analog or a non-nucleoside reverse transcriptase inhibitor (Non-NRTI). For many patients, HAART has turned HIV into a chronic controllable illness. In 2003, the first fusion inhibitor, enfuvirtide, was approved to block HIV's ability to infect healthy CD4 cells. When used with other anti-HIV medicines, enfuvirtide can reduce the amount of HIV in the blood and increase the number of CD4 cells.

Diuretics have been used to treat high blood pressure since the 1960s. New drug classes led to combination therapies.

For more on HIV/AIDS, see "Generation Epidemic," by Mark Senak, in the Viewpoint section beginning on page 89.

HYPERCHOLESTEROLEMIA



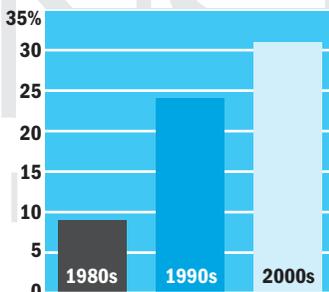
1980s Gemfibrozil, the first safe fibric acid derivative, is approved for lowering LDL and increasing HDL levels. **LATE 1980s and 1990s** Lovastatin, the first HMG-CoA reductase inhibitor or "statin," is approved. Other statins are marketed, making them the most widely prescribed cholesterol-lowering class. **2000s** Ezetimibe, the first in a new class that inhibits the intestinal absorption of cholesterol, is approved.

has a different method of action than any of the previously available drugs. It helps block the absorption of cholesterol that comes from food. It can be used independently, but it works best with statins.

Numerous medications are now available to help lower the level of low-density lipoprotein (LDL or "bad cholesterol") and triglycerides in the blood while increasing the levels of high-density lipoprotein (HDL or "good cholesterol"). Statins, or HMG-CoA reductase inhibitors, were a major advancement and have become the most widely prescribed class of drugs.

Recently, ezetimibe was approved, which

HYPERTENSION



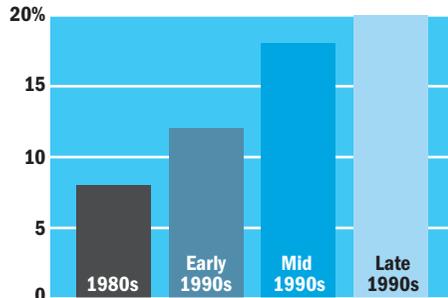
1980s The first ACE inhibitor, captopril, is introduced. **1990s** Calcium channel blockers are approved. **2000s** Angiotensin II receptor blockers become available.

angiotensin II receptor blockers (ARBs), which have functions similar to ACE inhibitors but work better. The many treatment options available today utilize single agents or various combinations of agents to individualize treatment for patients' medical conditions.

It is estimated that more than 50 million Americans have high blood pressure. Diuretics, discovered in the 1960s, remain an effective treatment option. Other options include beta-blockers, calcium channel blockers, and angiotensin-converting enzyme (ACE) inhibitors. The most recently introduced agents are the

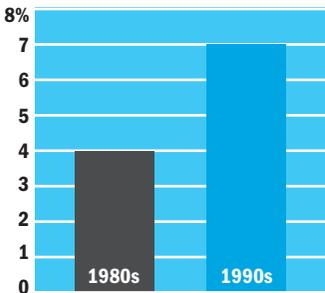
////// IMMUNOSUPPRESSANTS

Immunosuppressive therapy is responsible for great strides in the prevention of organ rejection. Corticosteroids have been the backbone of maintenance immune suppression since the early 1960s. The development of azathioprine in 1957 led directly to the use of immunosuppressant drugs in patients with kidney grafts, resulting in the one-year survival of related donor transplants reaching 80 percent in 1963. The next major advance was the discovery, in the late 1970s, of cyclosporin, which is now the front-line immunosuppressant drug. The most significant development of the past three decades were the macrolide immunosuppressants, which selectively inhibit T cells.



1980s Cyclosporin is approved. It greatly improved graft survival in all areas of transplantation. **EARLY 1990s** Tacrolimus, very similar to cyclosporin, is 10 to 100 times more potent on a per-gram basis. **MID 1990s** Mycophenolate mofetil (MMF) is approved for use in combination with cyclosporin A and prednisone for the prevention of acute renal allograft rejection. **LATE 1990s** Basiliximab, daclizumab, thymoglobuline, and rapamune are approved. These are effective as a combination therapy with cyclosporin.

Progress has been slow in the migraine field. Ergotamine and aspirin are beginning a second century as front-line therapies. In the 1990s, new drugs helped to prevent, not just treat, migraine attacks. Triptans abort headaches and relieve nausea. Valproex, an epilepsy drug, was approved to prevent migraine headaches.



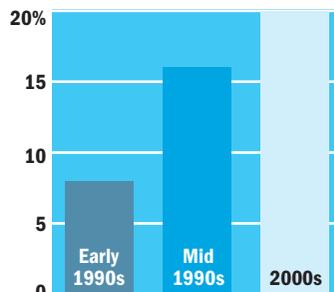
////// MIGRAINE

It is estimated that the average migraine sufferer in the United States loses 13 days of work and eight days of leisure time a year due to migraine attacks. Ergotamine and aspirin have been used to treat migraines for approximately 100 years. Medications for other disorders that have shown effectiveness are beta-blockers, antidepressants, and calcium channel blockers. A relatively new group of drugs called triptans was introduced in the mid-1990s. These drugs are effective in aborting migraines and relieving nausea. Sumatriptan was the first drug approved in this class. However, newer triptans developed after sumatriptan have reduced side effects and caused less risk for recurrence. Valproex, which is indicated for epilepsy, was the first drug approved for the prevention of migraines. Its intravenous form is being investigated. It has been shown to promptly abort an attack of an ongoing intractable migraine headache without producing significant side effects.

1980s Treatment varies. Analgesics, such as aspirin and ergotamine, are used, which alleviate symptoms but do not prevent attacks. **1990s** Sumatriptan, the first of the selective 5HT₁ antagonists, is approved. Once-a-day valproex is approved for prevention. The extended-release formulation of valproex soon followed.

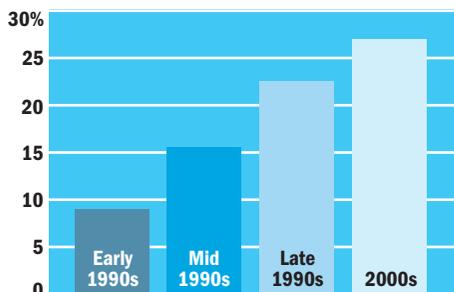
////// MULTIPLE SCLEROSIS

Until the 1970s, MS was considered an allergy; treatment consisted of antihistamines, vitamins, and steroids. Then MS was recategorized as an autoimmune reaction; treatment focused on preventing destructive immune responses with steroids and immune system regulators. Now, disease management improves quality of life for most patients. Since 1993, there have been five different products approved to treat MS. Many symptomatic treatments are available, as well as therapies that protect neurons and prevent attacks on them. New treatments include natalizumab, approved in 2004, as the first in a new class of drugs known as SAM (selective adhesion molecule) inhibitors. These drugs block penetration into the brain, which decreases damage.



EARLY 1990s Betaseron, an interferon beta-1b, is approved as the first drug to alter the underlying course of relapsing-remitting MS. **MID 1990s** Glatiramer acetate is approved to suppress the immune system's attack on neurons. Interferon beta-1a is shown to slow the rate of progression of disability in relapsing-remitting MS. **2000s** Mitoxantrone is the first therapy approved in the United States for secondary-progressive MS, and offers new treatment options for worsening effects of the disease.

OSTEOPOROSIS

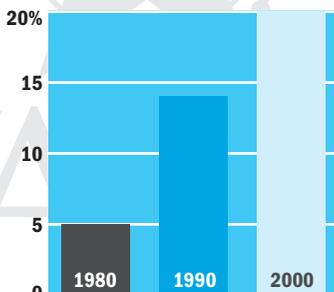


EARLY 1990s One-tablet hormone replacement therapies are indicated to help prevent osteoporosis in women at risk. **MID 1990s** Selective estrogen receptor modulators (SERMs), like raloxifene and tamoxifen, provide the beneficial effects of estrogens without their potential disadvantages. **LATE 1990s** New bisphosphonates prevent further bone loss, reduce the number of fractures during the first few years, and increase bone density. **2000s** Teriparatide is approved. It is a form of the parathyroid hormone, stimulates new bone formation, and significantly increases bone mineral density.

Osteoporosis treatment has evolved immensely over the past 20 years. Hormones and vitamin supplements were typical therapeutic regimens until calcitonin was accepted as an effective treatment in the 1980s. In the 1990s, selective estrogen receptor modulators (SERMs) were developed to provide the benefits of estrogen without their potential disadvantages. The bisphosphonates, a new class of drugs, were equally effective and caused fewer side effects. In December 2002, teriparatide, a form of the parathyroid hormone, became the first approved agent for stimulating new bone formation. In March 2005, FDA approved ibandronate sodium, the first once-monthly oral bisphosphonate. It is equally effective but more convenient than the once-daily or once-weekly bisphosphonates.

SCHIZOPHRENIA

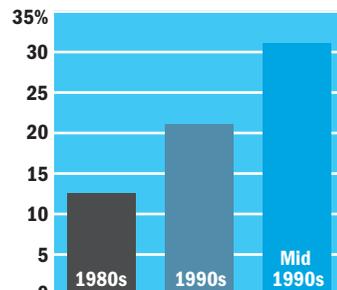
Antipsychotic medications have been available since the mid-1950s, and appear to have helped a vast number of patients to improve. Though available on the market as treatment for other conditions, a number of atypical antipsychotic drugs were approved for schizophrenia over the last two decades. Clozapine was the first of this kind and has been shown to be more effective than other antipsychotics; however, periodic blood work is needed due to the risk of agranulocytosis. The atypical antipsychotics that were developed after clozapine have shown a decreased incidence of side effects, such as extrapyramidal side effects (EPS) and tardive dyskinesia (TD). However, they have been more likely to induce weight gain. The more recently approved ziprasidone and arapiprazole have been associated with little or no weight gain.



1980s Phenothiazines are plagued by debilitating side effects. **1990s** Clozapine is approved for schizophrenia and is shown to be more effective than other antipsychotics. Quetiapine, olanzapine, and risperidone—approved later—are typically safer and better tolerated. **2000s** Ziprasidone is approved. It differs from other antipsychotics in that it is associated with little or no weight gain.

PEPTIC ULCER DISEASE

Until the 1970s, the options available to treat peptic ulcer disease were antacids, lifestyle changes, and surgery. In the late 1970s, the H2 antagonists became available. Since then, understanding of the role of the bacterium *Helicobacter pylori* in the disease has advanced the treatment of peptic ulcer disease. New treatments include proton pump inhibitors (PPIs), antisecretory agents, and antibiotics that target *H. pylori*.



1980s Prostaglandins, like misoprostol and sucralfate, are introduced. **1990s** Proton pump inhibitors become available. Omeprazole and then lansoprazole are approved. **MID 1990s** The bacterium *H. pylori* is identified as the primary cause of ulcer disease. Antibiotics offer a new, effective cure for ulcers.

The atypical antipsychotics developed after clozapine decreased side effects but induced weight gain.

Our panel's findings support the common-sense view that the pharmaceutical industry has made significant therapeutic progress in the past quarter century. A large number of new drugs have proven superior to pharma's previous offerings. In fact, some new compounds treat conditions for which no therapies existed. Could the pharmaceutical industry have done more? Perhaps. One could argue that firms paid insufficient attention to orphan diseases, to women's problems, or to conditions encountered in the tropics. And yes, it is true that some new products represent only incremental progress. But let us not be distracted. If we measure the basics, however subjectively, it is clear that in most therapeutic areas, patients are better off. ④