A Decade of Innovation

Advances in the Treatment of Rare Diseases
Contained within these pages are the realized hopes and dreams of millions of Americans affected by rare diseases. *A Decade of Innovation* doesn’t just describe a period of stunning medical advances, it documents a brief window in time during which people without hope learned to believe again that they might have a future. This book tells the stories of numerous individuals and the remarkable legislation—the Orphan Drug Act of 1983—that has given them back their lives. The National Organization for Rare Disorders (NORD) is grateful to PhRMA for focusing this spotlight on rare diseases. We look forward to continued partnership with all those involved in the rapidly unfolding drama of bringing safe and effective new treatments to market for the 25 million Americans with rare diseases.

Abby S. Meyers  
President  
NORD

Carolyn Asbury, PhD  
Chairman, Board of Directors  
NORD

Genetic Alliance applauds these advances in treating rare diseases. We are grateful that the continuum of basic science to medical services is infused with the time, energy, and resources of many talented individuals, particularly those who are part of the member companies of PhRMA. Genetic Alliance members, 600 disease advocacy organizations, representing over 1,000 diseases, look forward to the day they too will celebrate a treatment. Meanwhile, we stand beside you in gratitude and support your marvelous accomplishments.

Sharon F. Terry  
President and CEO  
Genetic Alliance
## RARE DISEASES

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In the last 10 years, biopharmaceutical companies have made great progress in the fight against rare diseases. Over 160 drugs were approved during the past decade (1995–2005) to treat rare or “orphan” diseases that affect 200,000 or fewer people in the United States. This compares with 108 approvals in the decade before (1984–1994) and fewer than 10 in the 1970s. Each of these medicines offers hope and relief to patients with diseases that often have no other treatment options.

According to the National Institutes of Health Office of Rare Diseases, there are 6,000–7,000 rare diseases affecting a total of 25 million Americans. One in every 10 Americans receives a diagnosis of a rare disease. This population is particularly in need of medicines because, as the FDA estimates, 85–90 percent of rare diseases are serious or life-threatening.

Why has the number of orphan drugs being approved grown so much in recent years? One factor is advances in science; a better understanding of molecular and genetic causes of disease has given us new tools to explore rare diseases, which are often more complex than more common diseases. Another factor is the huge and growing investment in research and development in general, as well as in orphan diseases specifically. The Orphan Drug Act, passed in 1983, provided tax relief and some marketing exclusivity for companies who develop an orphan drug. This legislation is credited with the explosion in drug approvals for rare diseases after the Act was passed in 1983.

Today, the number of new drugs in development for rare diseases continues to rise. This report highlights some of the many important drugs for rare diseases that have been approved in the last decade. These medicines have meant a completely different life today for many patients with rare diseases compared with just a few years ago. And, scientists are working each day to make the coming decades as bright as the last was for patients with rare diseases.
Fabry Disease

Patients with Fabry disease are deficient in a particular enzyme involved in the breakdown of fats, which causes a buildup of fat in their blood vessels and organs. The symptoms of this potentially fatal genetic disorder are diverse and can make diagnosis difficult. They include burning sensations in the hands and feet, skin rash, excessive sweating, fever, severe gastrointestinal problems after eating, and cloudiness of the eye. Fabry disease patients often survive into adulthood but are at increased risk of strokes, heart attack and heart disease, digestive problems, and kidney failure. Fabry disease affects an estimated 1 in 117,000 people, most of whom are male.

PHARMACEUTICAL ADVANCES

■ The First to Attack Fabry Disease at Its Root
Agalsidase beta, approved in 2003, is the first drug that treats the cause of Fabry disease rather than lessening its symptoms. This enzyme replacement reduces the accumulated fat within the blood vessels and organs and decreases the symptoms of the disease.

Gaucher Disease

Gaucher disease, another rare metabolic disorder, is a deficiency of the enzyme glucocerebrosidase, which breaks down and recycles glucosylceramide. The deficiency causes quantities of this fatty substance to accumulate in the spleen, liver, lungs, bone marrow, and, in rare cases, the brain. This buildup results in bruising, clotting difficulties, fatigue, enlargement of the liver and spleen, weakening of the skeleton, and in some instances, lung and kidney impairment.

This rare genetic disorder is classified into three different types based on clinical severity and course, and by the presence or absence of neurological complications. An estimated 6,000 individuals in the United States have Gaucher disease.

PHARMACEUTICAL ADVANCES

■ Oral Treatment for Patients who Need Another Option
For patients who cannot receive the standard enzyme treatment due to allergies, hypersensitivity, or poor venous access, miglustat, an oral treatment, was approved in 2003 for treatment of mild to moderate disease. Miglustat works by reducing the production of glucosylceramide so that the available glucocerebrosidase enzymes are not overwhelmed and are able to properly break down the substance and clear it from the body. Miglustat is proven to decrease the size of the liver and spleen and increase platelet and hemoglobin levels, which decreases bruising and fatigue.
Many Symptoms, One Disease

Donna never expected an eye exam would change her family’s outlook on life. After an eye doctor noticed clouding in her 8-year-old daughter’s eyes, Donna and her two sons were checked for similar symptoms. All four had corneal opacities. Donna and her children were sent to genetic counseling where doctors confirmed that they had Fabry disease. 

Not all Fabry disease diagnoses are as fast as Donna’s due to the wide variety of symptoms associated with the disease. Patients with the disease experience problems ranging from stomach cramps and vomiting to body aches and heat intolerance. Another patient, Adrian, had symptoms that baffled doctors for years before he was diagnosed. He eventually visited a rheumatologist who was able to make sense of his symptoms, and get him proper medical treatment for the disease.

Today, Fabry disease patients depend upon both enzyme replacement therapy (ERT) and symptom management to manage the disease. While ERT does not cure Fabry disease, it can reduce the symptoms of the disease, giving patients like Donna and Adrian a second chance at a normal life.

Patients with mucopolysaccharidosis VI (MPS VI), also known as Maroteaux-Lamy syndrome, face many health problems, which can be devastating depending on the severity of the disease.

In MPS VI, patients lack a particular enzyme called arylsulfatase B, which breaks down and recycles glycosaminoglycan (GAG), a complex sugar. GAGs are used to provide structure for various tissues including bones, cartilage, skin, and airways. When GAGs accumulate, however, they can cause a variety of symptoms including thickening of the nose, lips, and tongue; breathing problems due to narrowed airways; short stature; frequent ear infections leading to hearing loss; heart disease as a result of malfunctioning heart valves, thickening of the heart muscle, and narrowed blood vessels; and stiff joints. Because the signs and symptoms are so varied, diagnosis is often difficult and delayed. The disease is also quite rare; approximately 1,100 people worldwide have MPS VI.

PHARMACEUTICAL ADVANCES

First Therapy Targeted Toward Cause of Devastating Genetic Disorder

Approved in 2005, galsulfase is the first enzyme replacement therapy for MPS VI to treat the cause of the disorder by breaking down the built-up stores of GAGs instead of improving symptoms related to the disease. Because of the problems associated with the disease, patients with MPS VI often become tired easily and cannot withstand long periods of physical activity. In clinical trials, galsulfase was shown to improve the walking and stair-climbing capacity of patients.

Between 85 and 90 percent of orphan diseases are serious or life-threatening.
Bosentan, the first in a new class of medicines called endothelin-receptor antagonists, was approved in 2001 for the treatment of primary pulmonary hypertension to improve exercise ability and to decrease the rate of disease progression. Taken orally twice a day, it works by decreasing the stiffness of the blood vessels as well as widening them to allow blood to flow more easily.28

Treprostinil was approved in 2002 for patients with the New York Heart Association (NYHA) Class II—IV pulmonary arterial hypertension.29 Heart disease patients are classified according to the NYHA classification system, which is based on the capacity of patients with heart diseases to participate in physical activities, with Class IV disease resulting in discomfort with any activity and symptoms of the disease occurring even at rest. In other words, treprostinil treats patients with moderate to severe PAH, those who experience limitations on physical activity as a result of the disease. Administered by continuous infusion, treprostinil works by dilating the arteries and preventing blood clot formation.30

Iloprost is the newest medicine for treatment of pulmonary arterial hypertension and was approved in 2004 for use by patients with NYHA Class III or IV pulmonary arterial hypertension to increase exercise ability and decrease symptoms.31 It is a novel treatment in that it is inhaled by mouth using a special nebulizer. It works by dilating the arteries and prevents blood clot formation.32

Pulmonary Hypertension

The pulmonary artery is the blood vessel that carries blood from the heart to the lungs to be re-oxygenated. In pulmonary arterial hypertension (PAH) there is continuous high blood pressure in the pulmonary artery. Possible causes of the increased pressure may include tightened muscles within the artery walls, thickened walls of the pulmonary arteries or scar tissue making the arteries narrower. Tiny blood clots may form within the smaller arteries and cause blockages. The heart, as a result, must work harder to supply the body with enough oxygen-rich blood, and over time the heart muscle weakens.

Shortness of breath is the primary symptom of PAH. People with PAH might also experience tiredness, dizziness, chest pain, or a racing pulse. As the disease progresses, energy level decreases, and these symptoms can occur even when resting.34

There are two types of pulmonary hypertension: primary and secondary. Primary pulmonary hypertension is inherited or occurs for no known reason. Secondary pulmonary hypertension is caused by another condition, such as chronic heart or lung disease or blood clots in the lungs.35 According to the American Heart Association, an estimated 500 to 1,000 new cases of pulmonary hypertension are diagnosed each year.36 Although this condition is very rare, four new orphan drugs have been approved to treat it in the last decade.

PHARMACEUTICAL ADVANCES

Helping Blood Get to the Lungs

Epoprostenol was approved in 1995 for treatment of primary pulmonary hypertension. It is an intravenously administered medicine that works by dilating the arteries, which allows more blood to flow through the vessel, and by preventing blood clot formation.37
Women with PAH Face Tough Decisions

While both men and women are at risk for pulmonary arterial hypertension (PAH), it is more likely to affect women. Approximately 60 percent of PAH patients hospitalized between 1995 and 1998 were women. Among those women, 37 percent were younger than 65.

Unfortunately, pregnancy aggravates the condition, so for women with PAH, pregnancy can be life-threatening. Within 35 days of childbirth, the death rate for new mothers with PAH is between 30 and 56 percent.37

A woman with PAH often must choose between having a family and risking her own life to have a baby.

Despite the discouraging statistics, researchers are making progress. A 2001 case study in Chest reported that epoprostenol therapy combined with an anticoagulant can improve outcomes for mother and child when used before, during, and after delivery, without negative side effects on the child.38 For nonpregnant patients, survival also appears to be increasing. Many people can manage the disorder for up to 20 years. Genetic studies and pharmaceutical research are providing hope for the development of new treatments of PAH and possibilities for a cure in the future.39

Hypotension

Hypotension is an abnormal condition in which a person's blood pressure is lower than it should be. It causes symptoms such as dizziness or lightheadedness and inadequate blood flow to the heart, brain, and other vital organs. Orthostatic hypotension results from a sudden change in body position, usually from lying down to an upright position.33 This condition affects 156,000 people34 and can be caused by certain medicines, dehydration, or heart failure/attack.35

PHARMACEUTICAL ADVANCES

■ Drug Makes Standing Up a Safe Activity

Midodrine hydrochloride is used to treat symptomatic orthostatic hypotension. It works by stimulating the blood vessels to tighten, thereby raising blood pressure. Midodrine was approved in 1996 based on its ability to increase one-minute standing systolic blood pressure.36

The Orphan Drug Act was enacted in 1983 and encourages companies to develop and manufacture drugs for rare conditions.
Finally, Remission and Better Quality of Life for Those with Painful Bowel Disease

Infliximab, the first therapy for Crohn’s disease, is a genetically engineered antibody that targets a protein that promotes inflammation in the body. Administered intravenously, infliximab decreases inflammation along the lining of the intestines and is effective in closing sores between the bowel and skin. In clinical trials, a clinical improvement or remission occurred in 65 percent of patients with severe to moderate Crohn’s disease after a single dose. The FDA estimates that this drug can help about 175,000 people in the United States.

Imagine needing to run to the bathroom up to 60 times a day. You might have to get up five times in the middle of dinner at a restaurant or wake up every 25 minutes in the night to use the bathroom. Patients with interstitial cystitis (IC) often need to urinate frequently and urgently, and they may have recurring pain and tenderness in the bladder and pelvic region. These symptoms can disrupt the lives of patients, making it impossible for 63 percent of them to work full time.

These unpredictable symptoms may disappear without explanation or recur with an event such as a change in diet, treatment, or menstruation. Even when symptoms disappear, they may return after days, weeks, months,
A Decade-Long Struggle with Crohn’s: John’s Story

Diseases can seem especially devastating when they strike people in their youth. At age 19, John was diagnosed with Crohn’s disease. A healthy, active teenager, John found Crohn’s disease incredibly debilitating. “My life was on hold—I was not able to work or go to college for four years.” Eating became painfully difficult; he says food felt like broken glass going through his intestines. Within a month, he had dropped from 165 to 115 pounds. “I felt like I was wearing my disease—a disease no one understood.” After 10 surgeries, John became “desperate for a solution that did not include surgery.” That solution came on his 29th birthday with his first treatment of infliximab. “It was the best birthday present I could have ever received…. I had just about given up hope, but with this treatment I felt like I had my life back.”

PHARMACEUTICAL ADVANCES

Soothing the Symptoms of Unpredictable Pelvic Pain Disorder

Pentosan polysulfate sodium was approved in 1996 and is the first and only orally administered medicine developed specifically for relief of IC symptoms. It is believed that it works by creating a buffer layer on the inside of the bladder to prevent urine from irritating the bladder wall. In clinical trials, the drug was shown to bring relief of bladder pain to 42 percent of patients who had been treated for up to six months, and 60 to 62 percent of those treated for 24 months. Patients also experienced reductions in frequency of urination.

In the decade after the Orphan Drug Act was passed, there were about 10 times as many drugs approved for rare diseases compared with the decade before.
Hyperparathyroidism

Cinacalcet is the first in a new class of drugs known as calcimimetics, now available to patients whose parathyroid glands (located behind the thyroid gland in the neck) are producing too much parathyroid hormone. Often, the cause of hyperparathyroidism is unknown, but in some cases the overactivity is caused by other conditions, such as kidney failure or parathyroid cancer. In that case, the condition is called secondary hyperparathyroidism.

Because they produce excessive parathyroid hormone, which helps the body absorb calcium from food and regulates the level of calcium in the blood, hyperparathyroidism patients have abnormally high levels of calcium in the blood (hypercalcemia). Hypercalcemia is associated with bone pain, fractures, kidney stones, and risk of cardiovascular death. According to the FDA, about 37,000 people in the United States have hypercalcemia as a result of parathyroid cancer.

PHARMACEUTICAL ADVANCES

First-In-Class Treatment Counteracts Overactive Parathyroid Glands

Cinacalcet lowers the level of parathyroid hormone and calcium by increasing the sensitivity of the calcium-sensing receptor on the surface of the parathyroid gland. In doing so, it lowers the risk of altered metabolism of calcium and phosphorus, bone pain, fractures, and risk for cardiovascular death. With cinacalcet’s 2004 approval, it became the first specific pharmaceutical therapy for hypercalcemia associated with parathyroid cancer as well as for secondary hyperparathyroidism.

Acromegaly

When a manufactured protein became available in 2003 for people with acromegaly, a hormone disorder, it marked the first in a new class of drugs that block the effect of the growth hormone. This potentially fatal disease is a result of the pituitary gland’s producing excess growth hormone. This excess hormone causes abnormally enlarged hands, feet, and facial features. Once recognized, acromegaly is treatable in most patients, but because of its slow and often insidious onset, it frequently is not diagnosed correctly.
The “Gentle Giant” with the Devastating Disease

Andre the Giant (born Andres Roussimoff) built his successful wrestling and acting career living with acromegaly. Already 6’7” at age 17, Andre began wrestling as the “Monster Eiffel Tower” in France. His enormous size, eventually 7’4” and 500 pounds, jolted Andre to the top of the wrestling world, with fans dubbing him “The Eighth Wonder of the World.”

Though he became an international icon as one of the World Wrestling Federation’s toughest wrestlers, Andre preferred to think of himself as a “gentle giant,” like his character, Fezzik, in The Princess Bride. Shortly after his death in 1993 due to the effects of acromegaly, Andre the Giant was the first wrestler ever inducted into the WWF/WWE Hall of Fame.63

Today, acromegaly is treatable with surgery, radiation, and medicines, which can help normalize levels of growth hormone and insulin-like growth factor-1 (IGF-1) in the bloodstream. There are three drugs available among three different classes to treat the condition.64

In the pipeline are potential treatments for anthrax, cystic fibrosis, and West Nile Virus, which have been granted orphan status by the FDA.62

ACROMEGALY

PHARMACEUTICAL ADVANCES

■ Manufactured Protein to Block Growth Hormone

Pegvisomant works by binding to the growth hormone receptor and blocks the effects of the growth hormone and reduces the signs and symptoms of the disorder.66 It is indicated for use in patients whose acromegaly has not responded to surgery, radiation, or other medicines.69 In clinical trials, researchers found that more than 90 percent of patients responded to the medicine.60

Acromegaly, which is most common in middle-aged adults, can lead to serious health complications such as arthritis, diabetes, high blood pressure, and increased risk of cardiovascular disease. It affects at least 40 to 60 out of every million people at any time.60

In the pipeline are potential treatments for anthrax, cystic fibrosis, and West Nile Virus, which have been granted orphan status by the FDA.62
Both neurocysticercosis and hydatid disease are parasitic diseases from worms and affect approximately 300 Americans annually.71 Neurocysticercosis, caused by pork tapeworm larvae (eggs), is usually spread through contaminated water or food. It causes cysts to develop throughout the body and can cause headaches and seizures if they develop in the brain tissue.72 It is the most common infectious cause of seizures worldwide.73

People can contract hydatid disease, also known as Echinococcus, by eating contaminated food containing Echinococcus granulosus worm eggs. The infection causes cysts in the liver first but they can also develop in the lungs, brain, bones, and other organs. If the cysts rupture, severe illness results, including fever, low blood pressure, and shock.74,75

Cryptosporidiosis and Giardiasis

Cryptosporidiosis and giardiasis, parasitic infections that cause diarrhea, mainly affect people living in developing countries around the world, but even in the United States there are cases every year.65

The parasite cryptosporidium can be found in drinking or recreational water and contaminated food. Once it enters the body it lives in the intestinal tract, but outside the body it can survive for long periods because of a tough outer shell. The parasite causes vomiting and nausea, dehydration, stomach pain, and weight loss.66 Giardiasis is an infection caused by a single-celled parasite called Giardia lamblia or, simply, Giardia. If left untreated in children, complications from these parasites include malnutrition, impaired growth, and death.69

Cryptosporidiosis and Giardiasis

Killing Parasites That Cause Dangerous Waterborne Illnesses

Nitazoxanide, an antiprotozoal approved in 2002, is used to treat children up to 11 years of age with diarrhea caused by cryptosporidiosis and giardiasis. It is the first new drug approved for giardiasis in over 40 years.68 Nitazoxanide is the only drug approved for treating cryptosporidiosis and the only drug approved for giardiasis for children one to 11 years of age. Nitazoxanide works by stopping the growth of the infecting organisms.69 The FDA estimates that nitazoxanide could help 2,500 people in the United States.70

PHARMACEUTICAL ADVANCES

First Treatment for Two Kinds of Cyst-Causing Worms

In 1996, albendazole became the first treatment approved to treat both neurocysticercosis and hydatid.76 Albendazole kills the worm by preventing it from absorbing sugar (glucose), which it needs to survive.77 This drug was found to destroy cysts in 40 to 70 percent of patients with neurocysticercosis. Among patients with hydatid disease, albendazole eliminates the cysts in about 30 percent of patients and reduces their size in an additional 40 percent of patients.75
Tuberculosis—A Disease from Antiquity

Tuberculosis has ravaged human culture since ancient times. Egyptian mummies tell the story of deadly tuberculosis infections thousands of years ago. Fragments of the spinal columns of mummies dating back to 2400 B.C. show evidence of damage caused by the bacteria. Later, around 460 B.C., Hippocrates wrote that tuberculosis was the most widespread disease of the time in Greece and was nearly always fatal.85 Today, tuberculosis infections still occur in all parts of the world, but mankind is fighting back. Scientists are using the vast knowledge and powerful tools that the Egyptians could not have dreamed of to develop new treatments for this age-old foe.

Tuberculosis (TB) is still the most common cause of death and morbidity in the world, killing 30 million people worldwide in the 1990s, according to the WHO.79 In the United States, fortunately, it is a rare condition affecting just 15,000 people in 2003.80

TB is a contagious bacterial infection that primarily affects the lungs but can attack any part of the body. It is caused by Mycobacterium tuberculosis and is typically spread through the air from a cough or sneeze of someone who is infected with the bacteria. If not treated properly, TB can be fatal.

PHARMACEUTICAL ADVANCES

Modern Treatment for Ancient “Consumption”

In 1998, the first new drug to treat TB in 25 years, rifapentine, was approved for treatment of pulmonary tuberculosis. It works by stopping the cell multiplication process of the bacteria and is used in combination with other anti-tuberculosis drugs to treat pulmonary tuberculosis.81 Before rifapentine was approved, the health care community was worried about resistance to older drugs that was developing over time. This treatment offers another tool to fight tuberculosis. Also, the dosing regimen for this drug is simpler than other drugs, so patients are more likely to take it.82

In the last decade (1995–2005), over 160 orphan drugs were approved, compared with 108 from 1984 to 1994 and only 10 in the decade prior to the passage of the Orphan Drug Act in 1983.83
Thrombocytopenia

Thrombocytopenia is caused by too few platelets in the blood, which are responsible for forming clots along with clotting factors if damage occurs to the blood vessels. Patients with this disorder bleed even with minor injuries, and in severe cases with no injury at all. This deficiency of platelets can be caused by a few factors, including low platelet production by the bone marrow, infection, other diseases, or sometimes drugs. Heparin, a drug used to prevent blood clots and to “thin” blood by inhibiting clotting factors in situations such as acute coronary syndromes including heart attacks, can cause thrombocytopenia in some patients.

Hemophilia B

Hemophilia B is a rare congenital disorder caused by the lack of clotting Factor IX, a type of protein that works with platelets to form clots when damage to a blood vessel occurs. Hemophilia B affects approximately 18,000 Americans. People with this disease bleed excessively and for longer than other people. It can be life-threatening.

PHARMACEUTICAL ADVANCES

Alternative Blood-Thinning Treatment

In 1998, lepirudin was introduced as the first alternative to heparin for patients who experience heparin-induced thrombocytopenia. Lepirudin is a derivative of the saliva of a medicinal leech, a bloodsucking aquatic worm that is sometimes used in blood withdrawal. Lepirudin blocks thrombin, which is an enzyme that aids in clot formation. Lepirudin also promotes a rapid increase of platelets. The FDA estimates that 180,000 people could benefit from this new drug.

PHARMACEUTICAL ADVANCES

DNA-Derived Clotting Factor: A Better Treatment Option for Patients

Recombinant human Factor IX was approved in 1997 for the prevention and control of excessive, potentially life-threatening bleeding in hemophilia B patients. Recombinant DNA-derived clotting factors are lab-produced using Chinese hamster ovary cells that have been modified to express the human Factor IX gene. The advantage of recombinant human Factor IX over other sources of Factor IX is that it is free from the risk of transmitting human viruses.
Leprosy

Leprosy is an infectious disease caused by the bacteria *Mycobacterium leprae* with symptoms of disfiguring skin lesions and sensory loss in the skin, muscle weakness, and progressive debilitation caused by peripheral nerve damage. Symptoms can take as long as 20 years to develop. Through ancient times, leprosy was regarded by the community as a contagious, mutilating and incurable disease. Today, leprosy is treatable and curable, and we now know it is difficult to transmit.91,92

While leprosy is most common in temperate, subtropical and tropical climates, approximately 100 cases are diagnosed each year in the United States. Children are more susceptible than adults to contracting the disease.93

Erythema nodosum leprosum (ENL) is a serious inflammatory complication of leprosy that can include severe skin lesions, nerve pain, loss of nerve function, joint swelling and high fever.94

PHARMACEUTICAL ADVANCES

- **Ancient, “Incurable” Disease Now Treated with “Second Chance” Drug**

Nearly 40 years after thalidomide was first found to produce severe birth defects when used as a treatment for morning sickness associated with pregnancy in countries around the world, it was approved for the first time by the FDA in 1998. With tight restrictions, it is now used to treat debilitating skin sores that result from ENL.91 In clinical trials, treatment with thalidomide caused improvement in at least 70 to 80 percent of patients with ENL, compared to approximately 25 percent of patients given placebo.96

Since the Orphan Drug Act, over 1,450 drugs in development have been designated as orphan products.97

Leprosy—Reason for Exile in the Old World

Tales of leprosy date back to biblical times. During those times, leprosy was thought to be transmitted by contact with infected people. To decrease the possibility of catching the disease, leprosy sufferers were often shunned. “...[I]n Europe during the Middle Ages, leprosy sufferers had to wear special clothing, ring bells to warn others that they were close, and even walk on a particular side of the road, depending on the direction of the wind. Even in modern times, leprosy treatment has often occurred in separate hospitals and live-in colonies called leprosariums because of the stigma of the disease.”90 However, new medicines continue to combat leprosy infections, and the number of known cases is falling.
Poractant alfa, approved in 1999, treats RDS in premature babies by reducing the amount of air trapped in the lining of the lungs. A natural porcine-derived surfactant, poractant alfa increases lubrication within the lung’s air sacs thus improving expansion and ventilation.  

Children with the genetic, metabolic disorder tyrosinemia gradually develop liver failure and liver cancer, but a new drug, nitisinone, approved in 2002, can extend their lives. These children lack the enzyme that breaks down the amino acid tyrosine. Normally, the liver is where tyrosine is broken down; when it accumulates in the blood, it can lead to progressive liver failure and, often, cancer. Tyrosinemia may also cause damage to the kidneys, eyes, skin, and nervous system.

Of the 250,000 infants born prematurely each year, up to 50,000 will suffer from infant RDS, and 5,000 will die from it. RDS usually occurs right after birth.

Three new medicines have been approved in the last decade for this one rare condition, advancing the way that neonates with immature lungs are treated. With these medicines, premature infants have a better chance of surviving this life-threatening disorder.

PHARMACEUTICAL ADVANCES

Rescuing the Tiniest Lungs

Calfactant, approved in 1997, is used to treat babies with RDS, and also to prevent premature babies from developing RDS. A natural bovine-derived surfactant, calfactant attaches rapidly to the surface of the air-to-liquid interface within the lung’s air sacs and modifies surface tension similarly to natural lung surfactant, thereby allowing the air sacs to expand and improving newborns’ breathing ability.

Nitric oxide, approved in 1999, reduces the common complications of lung hypertension in newborns by expanding blood vessels in the lungs. Nitric oxide reduces the need for ventilator support and helps regulate the muscle tone in the arteries of the lungs.

Tyrosinemia

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The most common and severe form of the disease is acute tyrosinemia, with which children are born or develop soon after birth. Infants with acute tyrosinemia exhibit rapid onset of symptoms, and they often fail to gain weight and grow. Infants with the less prevalent chronic tyrosinemia have a more gradual and less severe onset of symptoms.

Children who experience liver failure or are diagnosed with liver cancer as a result of tyrosinemia rarely make it into their twenties without a liver transplant. According to the FDA, this disorder affects 2,500 children in the United States.
Hope is in the Pipeline for Children with Progeria

Medical researchers are racing to beat the clock in search of a cure for progeria, a premature aging condition that afflicts just 14 children in the United States and usually leads to death near age 13. In 2003, scientists were able to isolate the gene mutation that causes this rare disease. In 2004, researchers were able to explain how the gene mutation works. Now, NIH scientists and others are testing a group of cancer drugs donated by pharmaceutical companies. These drugs appear to repair cells damaged due to the disease. By halting the rapid aging process associated with the disease and restoring damaged cells, medical research gives children living with progeria hope that their time will not run out before they reach adulthood.

Primary IGF-1 Deficiency

Kids labeled as having “short stature” are shorter than 97.5 percent of other children their same age and gender. Short stature can be caused by several factors, including family genetics, hormone problems, or various diseases.

Recently, it has been found that short stature can also be the result of low insulin-like growth factor-1 (IGF-1) levels. This condition is called Primary IGF-1 Deficiency (Primary IGFD). If left untreated, Primary IGFD can lead to other complications such as lipid disorders, obesity, diabetes, or decreased bone density.

PHARMACEUTICAL ADVANCES

First Medicine to Treat Primary IGFD

In 2005, the FDA approved mecasermin, the first treatment for approximately 6,000 children in the United States with severe Primary IGFD. Mecasermin is a manufactured protein that functions like the natural human protein as a growth catalyst. This protein must be present for children’s bones, cartilage, and organs to grow properly. An eight-year clinical trial demonstrated that, on average, children grew one inch per year for each year of therapy using this new medicine.

The number of orphan drugs is expected to rise in the coming years as more new medicines are developed that target specific genetic disorders.
Currently, there is no medicine available that allows narcolepsy patients to maintain a normal level of awareness consistently, but some of the most severe symptoms, such as EDS and cataplexy, can usually be controlled with medications. The cause of narcolepsy remains unknown, but genetic factors may play a role.

**PHARMACEUTICAL ADVANCES**

**Easing Worst Symptoms of Sleep Disorder**

*Modafinil* was approved in 1998 for the treatment of narcolepsy and is the first new stimulant for treatment in the last 20 years. Modafinil promotes wakefulness without affecting memory, concentration, or learning. It also has a lower habituation potential than other stimulants that are often used for treatment of narcolepsy. In clinical trials, modafinil proved to be effective in alleviating EDS while producing fewer, less serious side effects than other medications.

*Sodium oxybate* is the first approved treatment for cataplexy. Available since 2002, it reduces the number of cataplexy attacks, which can cause a patient’s muscles to feel weak or paralyzed.

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**Narcolepsy**

In people with *narcolepsy* the brain does not properly regulate sleep and wake cycles, so they experience episodes of frequent, uncontrollable daytime sleeping. It is estimated that narcolepsy, which is generally a lifelong condition, affects 135,000 people in the United States. For these patients, falling asleep in unlikely situations is much more than an inconvenience; it can jeopardize their education, ruin relationships, or endanger their lives when driving.

**Excessive Daytime Sleepiness (EDS)** is the most common symptom of narcolepsy patients, but they can also have *cataplexy* (sudden loss of muscle tone), sleep paralysis (temporary inability to use muscles), and hallucinations before and/or after sleep episodes. A cataplexy episode is often triggered by emotions such as surprise or anger, causing a range of effects, from a simple slumping of the head or a more dramatic collapse of the body. An estimated 20,000 to 50,000 narcolepsy patients experience cataplexy.

**ALS/Lou Gehrig’s Disease**

*Amyotrophic lateral sclerosis (ALS)*, also known as *Lou Gehrig’s Disease*, is a progressive disease that affects motor nerve cells in the brain and spinal cord. Motor neurons degenerate and eventually die, causing the brain to lose its ability to control muscle movement. The progressive loss of muscle strength and coordination eventually interfere with the ability to perform routine activities, such as going up steps, swallowing, or rolling over. Eventually it leads to death, often because it affects the muscles needed for breathing. ALS, however, has no effect on a person’s ability to think or reason. It is usually fatal within five years of diagnosis.
Symptoms usually do not develop until after age 50. In about 10 percent of cases, ALS is caused by a genetic defect. In other cases, the cause of the nerve deterioration is unknown. ALS affects approximately 30,000 people in the United States, and about 5,000 new cases are diagnosed each year.

**PHARMACEUTICAL ADVANCES**

**Breakthrough Treatment a First After 126 Years**

ALS was first identified in 1869, but the first drug, riluzole, was not approved for treatment until 1995. It is the first drug to show any increase in survival for ALS patients. The increase is a modest three months on average, but it offers hope. The drug is based on a theory that the disease is caused by toxic levels of glutamate in the brain. Neurons in the central nervous system use glutamate to communicate with one another. The brain normally regulates glutamate levels, but glutamate has been found at abnormally high levels in the cerebrospinal fluid of some ALS patients. Scientists theorize that glutamate toxicity might be killing motor neurons, leading to progressive muscle degeneration in people with ALS. Riluzole, however, inhibits the release of glutamate in the brain.

According to Dr. Jeffrey Rothstein of Johns Hopkins University School of Medicine, this medicine offers great hope despite the fact that the improvement is not dramatic: "This is against the background of decades when no drug ever did anything for the disease. Initial therapies for many diseases, like leukemia and other cancers, had the same kind of effect... a modest increase in survival. But they were followed by better therapies that, over time, increased patients’ survival.... It’s a daunting task, but I envision that someday it will be possible to develop drugs that will not only stop motor neurons from dying but replace them and reverse the course of ALS."

**A Pitch for ALS**

Sixty-five years after baseball legend Lou Gehrig announced his battle with ALS to the world, Red Sox pitcher Curt Schilling brought the disease back to international attention. During game two of the 2004 World Series, Schilling, pitching with an injured ankle, wrote “K ALS,” meaning strikeout ALS, on his shoe, just below his blood-stained sock. Photographers looking to capture images of an athlete persevering through pain instead told the story of a man fighting for the 30,000 Americans living with ALS.

Curt Schilling is the pitcher for the 2004 World Series Champion Boston Red Sox. He and his wife, Shonda, became involved in the fight against ALS after meeting Dick Bergeron, an ALS patient, in 1992.
Finding treatments for rare cancers at specific stages for patients unresponsive to existing treatment might be the toughest—and most gratifying—work a scientist could ever attempt.

Cancer

Cancer is a group of diseases in which abnormal cells develop and spread through parts of the body. Anyone can develop cancer. The National Cancer Institute estimates that 9.8 million Americans with a history of cancer were alive in 2001. Some were cancer-free; others were continuing to undergo treatment.134

PHARMACEUTICAL ADVANCES

Disrupting DNA Adds Months for Severe Brain Cancer Patients

In the two most aggressive forms of astrocytoma, brain tumors grow rapidly and spread to other parts of the body. Astrocytoma is classified into four grades (Grade I being the least aggressive and IV most aggressive). Grade III is anaplastic astrocytoma, which affects 2,000–3,000 people a year with an average survival of two to three years. Grade IV is glioblastoma multiforme, which affects 8,000–10,000 people each year and is usually fatal within one year.135

Temozolomide can add an average of two and a half additional months—an enormous amount of time in the world of cancer treatment—for patients with glioblastoma multiforme.134,135 “It doesn’t sound like much... but if you can demonstrate that you can extend life for two or three months for the average patient, that’s a significant advance,” says Dr. Warren Mason, the co-author of a New England Journal of Medicine study about the drug.136 Patients taking temozolomide for treatment of anaplastic astrocytoma experienced an average survival time of nearly 16 months.137

Approved in 1999, temozolomide is the first major new treatment for anaplastic astrocytoma in 20 years, and with a second indication approved in 2005, it is the first in over 30 years for glioblastoma.138,139 It works by disrupting DNA to prevent cancer cells from multiplying and prolongs survival when combined with standard radiation.140 Additionally, it is a more convenient therapy for patients; it is an oral treatment allowing patients to take their medication in the comfort of their own homes rather than having to receive intravenous treatments at a physician’s office or hospital.

Dual-Action Therapy Initiates Immune Response and Attacks Tumor Cells Directly

Non-Hodgkin’s lymphoma is a cancer of lymphatic tissues, such as lymph nodes, spleen, and other immune system organs. There are several different types of non-Hodgkin’s lymphomas. One of those types, follicular lymphoma, makes up 22 percent of all non-Hodgkin’s lymphomas. Follicular lymphoma is not curable, but due to its slow growth, 60 to 70 percent of patients live at least five years; it occurs mainly in adults, with an average age of 60.141 People with follicular non-Hodgkin’s lymphoma usually have lymphoma in many parts of the body. According to the FDA Office of Orphan Products, the condition affects 193,500 people in the United States.

With the 2003 approval of tositumomab and Iodine-131 tositumomab, patients with a subset of follicular non-Hodgkin’s lymphoma—CD20 positive follicular non-Hodgkin’s lymphoma—gained a new treatment option with an innovative therapeutic twist. The drug is made up of an immune system protein, called an antibody, attached to radioactive Iodine-131. Combined, they form a “radiolabeled” monoclonal antibody that is able to bind to a protein found only on the cancer cells, thus targeting the radioactivity directly to the cancer cell, killing it.142,143

This new medicine is used for patients with CD20 positive follicular non-Hodgkin’s lymphoma who have not responded to other treatments or whose cancer has returned after chemotherapy.144 For more than two years,
There are approximately 6,000–7,000 rare diseases.\textsuperscript{149}

First Ray of Hope for Asbestos-Related Lung Cancer

When someone first experiences symptoms and is diagnosed with \textit{malignant pleural mesothelioma}, the fatal cancer is often already in advanced stages, and doctors expect them to live just nine to 13 months.\textsuperscript{146} Malignant pleural mesothelioma is a cancer of the lining of the lung and chest cavity, called the pleura. This is a very rare type of cancer affecting only 2,000 new people each year, and it is associated with exposure to asbestos.

Now the first drug approved for this rare cancer, \textit{pemetrexed}, combined with other treatments, gives patients 40 percent longer survival time compared with current treatment alone. “Before [pemetrexed] was available, patients suffering from mesothelioma had no hope—rarely living a year after diagnosis,” said Nicholas J. Vogelzang, MD, Director of the Nevada Cancer Institute in Las Vegas. “At 18 months, there is still a statistically significant difference in survival, which demonstrates patients are living longer when treated with this [pemetrexed] combination,” Volgelzang said.\textsuperscript{147}

Approved in 2004, pemetrexed is a novel antifolate, a class of drugs that targets the folic acid metabolic pathway, which affects availability of certain B complex vitamins.\textsuperscript{148} It is indicated for patients with the advanced form of the disease who have already had chemotherapy. Pemetrexed was found in clinical trials to be as effective as other cancer drugs, but with fewer side effects, such as hair loss and subsequent infections.

Karl, like many people, was not one to visit his doctor often, even if he was feeling under the weather. However, after days and days of feeling tired and eventually having difficulty just getting in and out of the car, Karl decided it was time to see a doctor. After an x-ray and other tests, he was diagnosed with mesothelioma. Karl’s daughter, who works in a hospital, was familiar with the disease and understood the prognosis was poor. Fortunately, after several chemotherapy treatments with pemetrexed, Karl’s condition began to improve. Karl’s wife is thankful, noting, “Every day, we are both thankful for our lives. And, he is improving every day and he is doing more and more: He is in the yard, or we are going shopping together, or we can drive in town together. He could not drive before. Now, little by little, it’s getting better and better and we are very grateful for that.”\textsuperscript{150}
In leukemia, the bone marrow produces abnormal white blood cells—the leukemia cells, which in time may crowd out normal white blood cells, red blood cells, and platelets. Types of leukemia vary according to which type of blood cells are affected, how developed the cancer cells are at the time of diagnosis, and how different they are from normal cells. According to the National Cancer Institute, there were 30,600 new cases of leukemia in the United States in 2003.

PHARMACEUTICAL ADVANCES

■ Ancient Medicinal Offers New Hope to Young Adults

Contrary to images people may conjure up when hearing “arsenic,” it actually has given new hope to patients with acute promyelocytic leukemia (APL), which is most common in young adults and causes fatigue and tendency to bleed. Arsenic-containing preparations, dating back more than 2,000 years, were used more than 100 years ago for leukemia therapy but were replaced by modern chemotherapy. Because some Chinese arsenic-containing treatments showed effectiveness against leukemia, attention again turned to arsenic.

Arsenic trioxide was approved in 2000 to treat APL patients whose disease has recurred or failed to respond to standard treatment (about 400 of the 1,500 diagnosed cases per year). About 75 percent of APL patients can be cured with other combination therapies, but those who do not achieve remission or who relapse can now be treated with arsenic trioxide.

■ From Texas Soil to New Class of Anticancer Therapy

The story of gemtuzumab began with a soil sample gathered in Kerrville, Texas, in 1981 and finally burst to the forefront of oncology in 2000 as the first in a new class of drugs, “antibody-targeted chemotherapy.” Scientists studying the soil discovered a powerful cancer-fighting substance, calicheamicin, which destroyed the DNA of cancer cells and proved to be stronger than any anticancer drugs at the time. But it was up to 10,000 times more toxic to normal cells than other anticancer drugs. Researchers discovered that by attaching calicheamicin to an antibody (immune system protein), they could safely bring it directly to the tumor, bypassing most normal cells. In May 2000, the FDA approved the first antibody-targeted chemotherapy, gemtuzumab, for use in patients over age 60 with relapsed acute myeloid leukemia (AML).

In patients with AML, unhealthy white and red blood cells and platelets build up in the bone marrow, blood, and other parts of the body leading to infections, easy bleeding, and anemia. AML quickly worsens if not treated. It is estimated that in 2005, 11,960 cases of AML will be diagnosed and will cause 9,000 deaths. Gemtuzumab was found to cause remission in about 30 percent of AML sufferers and produces fewer side effects than traditional chemotherapies.

■ A Powerful Attack and a True Trailblazer

The approval of imatinib mesylate in 2001 proved that a targeted therapy—one that directly turns off the signal of a protein known to cause cancer—could powerfully attack cancer with few side effects. Imatinib not only benefits patients with chronic myeloid leukemia (CML), but its success proves that the targeted therapies scientists dreamed of do work. With this proof-of-concept, scientists may be able to create strong, effective targeted therapies.
A new generation of precise and powerful drugs known as “targeted therapies” may represent a better way to treat many cancers, bringing hope for patients with rare cancers. Leukemia treatments are blazing the trail.

“Slowly, many scientists believe, the drugs are transforming cancer treatment. But for now, the drugs are still only a whisper of hope. They are not a miracle cure and not fully understood. Many are still in clinical trials. Those that work often help patients in subsets of disease—one kind of leukemia, one type of breast cancer...

“Yet for all they are not, it is what the drugs achieve for the lucky few that captures the imagination: the stories that patients tell of teetering near death, only to see a stunning comeback, at least for a while. They can mean an extra three months or five months or a year—another Christmas with the family, another season to plant a garden, another passage in the life of a child. Side effects, the bane of cancer treatment, are comparatively few.”

— Donna St. George, The Washington Post
Looking back over the last decade, we have clearly made much progress and because of these new treatments many lives have changed. These facts offer hope to the many patients with rare diseases who are still waiting for treatments. Looking forward, the future holds great promise.

Just as the number of new orphan drugs being approved has grown, the number currently being studied continues to rise. According to the FDA’s Office of Orphan Products Development, in 2004 there were a record 160 applications for orphan status among drugs in development. That number represented a 30 percent increase over the average of 124 per year in the previous four years.

Pharmaceutical discovery is entering a new era. Our new understanding of the genome and powerful scientific research tools are opening new doors to discovery of breakthrough medicines. The number of orphan drugs is expected to rise in the coming years as more new medicines are developed that target specific genetic disorders.

Progress has been made in the last decade, but the work continues. Biopharmaceutical companies are working tirelessly so that more patients with rare diseases will have new treatments one day soon.
LOOKING BACK...
In the past year alone, nine new orphan drugs were approved. These new medicines that provide additional treatment options for a variety of diseases include:

- **Nelarabine**—For patients with T-cell acute lymphoblastic leukemia and T-cell lymphoblastic lymphoma, this new treatment resulted in complete disappearance of cancer cells in some patients during clinical trials.170

- **Deferasirox**—The first oral therapy for chronic iron overload, it allows patients to drink their medicine rather than endure multi-hour nightly infusions to remove excess iron.171

- **Sorafenib tosylate**—The first new treatment for kidney cancer in 12 years, it extended time until tumor progression and until death in patients with this rare cancer.172

- **Lenalidomide**—This is an oral treatment for patients requiring blood transfusions as a result of anemia caused by myelodysplastic syndrome, which causes low red blood cell counts. Patients who received this medicine during clinical trials no longer needed blood transfusions.173

LOOKING AHEAD...
Every day researchers continue to search for and develop new medicines for rare diseases. Here are examples of the many potential orphan drugs that scientists currently are working on:

- **Dasatinib**—This new compound, currently in review with the FDA, builds on the success of the first targeted cancer treatment, imatinib. Dasatinib is being tested as an alternative to treat patients with chronic myeloid leukemia. One clinical study found 95 percent of patients had progression-free survival in the first six months.175

- **Anti-GDF-8 antibody/MYO-029**—Currently in early clinical trials, this recombinant human antibody (immune system protein) is being tested to treat muscular dystrophy (MD) and other muscle-wasting diseases.176 It is designed to inhibit the protein myostatin, which limits muscle growth,177 and it would be the first treatment to halt the breakdown of muscle in MD.178

- **FK778**—The first in a new class of drugs to help prevent acute rejection after kidney, heart and liver transplants. FK778 is now in Phase II clinical trials,179 and to this point, tests indicate that it may treat both short- and long-term problems that accompany organ transplantation.180

## Medicines in Development for Selected Rare Diseases174

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Much has been done...

...but the work continues.
The number of orphan drugs being developed is going up: In 2004, there were a record 160 applications for orphan status, representing a 30 percent increase over the average (124 per year) of the prior four years.