BIOTECHNOLOGY'S IMPACT ON DISEASES OF THE ELDERLY: A WHITE PAPER

September 2000

PREPARED FOR BIO
BY

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EXECUTIVE SUMMARY

As people age they walk a minefield of life-threatening and debilitating diseases. Coronary heart disease, stroke, cancer, Alzheimer's and Parkinson's diseases, chronic renal failure, diabetes mellitus and osteoporosis are among the most destructive.

"Biotechnology's Impact on Diseases of the Elderly: A White Paper" describes the costs of these eight age-related illnesses in human and economic terms. It also examines some of the biotech medicines on the market and in development to treat the diseases and details their impact on patients' quality of life and health-care expenditures.

The report demonstrates not only that biotech medicines on the market have the most impact on treating elderly patients, but also that biotech drugs and vaccines in development represent even greater promise for improving the health and quality of life of senior citizens.

The study highlights 20 marketed drugs and 57 of the more than 350 drugs and vaccines in late-stage clinical trials. All these biotech medicines reduce the need for expensive hospitalization and nursing home care and are far less invasive than most traditional therapies. In some instances, the report documents actual per patient cost savings achieved by biotech drugs.

For example, Epogen®, a protein drug used to treat anemia associated with chronic renal failure and cancer chemotherapy, reduces the need for blood transfusions to replenish red blood cells, resulting in a 23 percent per patient cost savings. Leukine® and Neupogen®, protein drugs used to restore white blood cells destroyed by cancer chemotherapy, reduce the need for bone marrow transplants, saving tens of thousands of dollars per patient. Another drug, the phosphate binder RenaGel® for chronic renal failure, saves $1,500 per patient by reducing hospitalizations.

The human cost of these illnesses on tens of millions of patients and their families is not quantifiable. The economic cost is $451 billion a year in the United States, the majority expended for hospital and nursing home care.

Biotechnology, the study demonstrates, offers the best hope for improving seniors' health and reducing health-care costs because it uncovers the molecular causes of disease and develops diagnostics that help prevent illnesses and therapies that treat the causes, not just symptoms.

"Biotechnology's Impact on Diseases of the Elderly" was prepared by PAREXEL International Medical Marketing Services Inc. for the Biotechnology Industry Organization (BIO).

Alzheimer's disease, cancer (breast, colorectal, lung and prostate), chronic renal failure, coronary heart disease (angina and acute myocardial infarction), diabetes mellitus, osteoporosis, Parkinson's disease and stroke were selected because they represent the most intractable and life-threatening age-related diseases.

The report presents a disease digest for each, including an overview of the disease; summary of the impact of current biotechnology products on the disease; summary of the promise of future biotechnology products for treating the disease; list of references; and tables detailing the information described in the digest.

Among the eight disease areas reviewed, they have the greatest impact on the elderly based on the following specific criteria:

- **Prevalence —**osteoporosis, coronary heart disease, and diabetes.
- **Mortality —**coronary heart disease, cancer (all types), stroke, and diabetes.
- **Cost —**coronary heart disease, cancer (all types), Alzheimer's disease, and diabetes.
- **QoL —** less comparative information is available here , but all eight diseases substantially affect QoL. Topping the list, however, would certainly be the late stages of Alzheimer's disease, cancer and diabetes, and severe cases of stroke and coronary heart disease.
- **Overall —**diseases with the greatest unmet need, those that appear on more than one of the above lists, are coronary heart disease, cancer, stroke, Alzheimer's disease, and diabetes.

The report discusses the following marketed biotechnology products:

- Epogen®, Procrit®, Renagel®, Orthoclone OK®T3, Simulect®, and Zenapax® for chronic renal failure.
- Epogen®, Procrit®, Herceptin®, Leukine®, and Neupogen® for the various cancers.
- ReoPro®, Retavase®, Activase®, and Integrelin® for coronary heart disease.
- Prandin®, Humalog®, Humulin®, and Novolin® for diabetes mellitus.
- Activase® for stroke.

Of the biotechnology products in the pipeline, the report looks at 57 across the eight disease areas as follows:

- **Cancer,** 11 products.
- **Parkinson's disease,** 11 products.
- **Alzheimer's disease,** 10 products.
- **Coronary heart disease,** 7 products.
- **Diabetes mellitus,** 7 products.
- **Chronic renal failure,** 4 products.
- **Osteoporosis,** 4 products.
- **Stroke,** 3 products.

Conclusion

Over the past 25 years many new biotechnology products have been developed to treat the growing health-care needs of senior citizens. This research report demonstrates that biotechnology products have had a substantial impact on treating elderly patients in the eight major disease categories examined. The data also present examples of the numerous new products under development that hold even greater promise for improving the health and quality of life of seniors.

This study represents a snapshot of biotechnology's contributions and promise after a quarter century of research and development. The future is even more exciting based on the rapid rate of progress in genetic research and the completion in June 2000 of a rough draft of the human genome sequence, which will accelerate the search for disease causes and cures.

BIO represents more than 900 biotech companies, academic institutions and state biotech centers in all 50 U.S. states and in 26 other nations. BIO members are involved in the research and development of health-care, agricultural, industrial and environmental biotechnology products.

This report is available on BIO's Web site at www.bio.org. For more information contact Dan Eramian, Charles Craig or Lisa Dry at (202) 857-0244.

I. INTRODUCTION

Background

The proportion of seniors in the population is increasing. Americans are living longer, and the number of seniors is growing as a proportion of the population. It will become increasingly important to Americans to treat and cure the diseases of aging that cost millions of lives and dollars and decrease the quality of life (QoL) for senior citizens.

The burden of illness in the elderly will increase. At present, the diseases of aging — heart disease, cancer, stroke, Alzheimer's disease, diabetes and others — take a devastating toll on seniors and society overall. For example, in the United States in 2000, the cost of cardiovascular diseases and stroke is an estimated $326.6 billion. This includes the cost of physicians and other professionals, hospital and nursing home services, medications, home health care, and other medical costs (e.g., durable equipment) and productivity lost because of morbidity and mortality (American Heart Association [AHA], 2000). The burden of illness can be expected to grow as the number of seniors and their life spans increase.

Biotechnology will play an important role in curing and treating the diseases of aging. As the burden of illness among the elderly increases, treatment with biotechnology drugs and other new products is expected to improve the health and overall QoL of seniors (Pharmaceutical Research and Manufacturers of America [PhRMA], 1999). Potentially, these treatments will lead to cost savings to seniors and to the health-care community and society as a whole through a reduction in expensive hospitalization or other health-care services.

The promise of biotechnology:

- New therapeutic classes. The real promise of biotechnology may be its potential to reshape the drug development process and to redefine the way in which illnesses are treated. There are several hundred biotechnology products in the pipeline, and many of them work in entirely new ways (PhRMA, 2000).

- Targeting drugs for the individual patient. Equally important is the potential of biotechnology to allow drugs to be targeted for the individual patient. Increasingly, biotechnology companies have identified the genes responsible for certain conditions through single-nucleotide polymorphisms (SNPs), which open up the possibility of tailoring drugs to the specific variation of a disease as it occurs in a given individual.

II. STUDY OBJECTIVES

The Biotechnology Industry Organization (BIO) asked PAREXEL International Medical Marketing Services, Inc. (PAREXEL), to prepare a white paper designed to: 1) identify the major diseases of the elderly; 2) identify biotechnology products currently on the market for these diseases; and 3) identify biotechnology products currently in the pipeline. Each of these objectives is discussed in further detail below.

1. Identify the major diseases of the elderly

PAREXEL identified the major diseases of U.S. seniors (the major population covered by Medicare) that are the focus of biotechnology products, either currently marketed or in development. Criteria for identifying the diseases were the following:

- High incidence and prevalence among the elderly;
- High probability of causing death, hospitalization or reduced levels of functioning or QoL among the elderly; and
- High total costs associated with the disease, including both direct costs of treating the disease and indirect costs because of lost productivity.

2. Identify biotechnology products currently on the market

PAREXEL then identified biotechnology products that have had a substantial impact on the diseases.

3. Identify biotechnology products currently in the pipeline

Next, PAREXEL identified a sample of biotechnology products currently in the pipeline that target the major diseases.

For the identified diseases and drugs, information regarding QoL impacts was generally less complete and more difficult to obtain than was information regarding clinical and cost impacts.

III. METHODOLOGY

To obtain the information for this white paper, PAREXEL reviewed readily available information identified through Internet sources such as Lexis-Nexis, PubMed (Medline) and general search engines (e.g., AltaVista). The type of information reviewed included:

- The popular press (e.g., *The Wall Street Journal*);
- Publications of FDC Reports, Inc. (e.g., *The Pink Sheet*);
- Medical and health journal articles;
- Medical conference abstracts;
- Product package inserts;
- Corporate Web sites;
- Association Web sites (e.g., American Heart Association);
- Other Web sites such as www.recap.com ("Clinicals" section);
- *R&D Directions: What's in the Pipeline;* and
- Pharmaceutical Research and Manufacturers of America (PhRMA), *New Medicines in Development for Older Americans* (1999) and *New Medicines in Development: Biotechnology* (2000).

Limitations

Although an extensive search and review was performed for each of the major diseases of the elderly and the current and pipeline biotechnology products targeting those diseases, in some areas only incomplete or limited information was readily available. It should be noted that the information in this report is intended to provide an overview of the selected diseases and products and to serve as a basis for additional research. It is not intended to serve as guidance to medical practitioners regarding the use of the products discussed.

IV. MAJOR DISEASES OF THE ELDERLY

PAREXEL and BIO jointly identified eight major diseases affecting senior citizens, as highlighted below.

Major Diseases of the Elderly

A. Alzheimer's Disease
B. Cancer (Breast, Colorectal, Lung and Prostate)
C. Chronic Renal Failure
D. Coronary Heart Disease (Angina and Acute Myocardial Infarction)
E. Diabetes
F. Osteoporosis
G. Parkinson's Disease
H. Stroke

Eight "disease digests" are presented on the following pages. Each digest includes an overview of the disease, the impact of current biotechnology products on the disease, and the promise of biotechnology pipeline products for treating the disease. Following each disease section are references and tables detailing information described in the digest.

A. Alzheimer's Disease

Overview

Alzheimer's disease (AD) is a progressive neurodegenerative disease characterized by brain lesions, loss of neurons and profound impairment of memory. Over the span of a few years, seemingly benign forgetfulness becomes a pervasive destruction of an individual's ability to remember, reason and function. Depression, anxiety, paranoia and agitation make many AD patients unmanageable, with the risks of stove burners left on, medications forgotten and nocturnal wanderings ultimately leading to costly placement in supervised apartments or nursing homes. In its later stages, the patient's personality itself seems to evaporate. AD patients cease to recognize loved ones or to be aware of themselves, except at the most basic level (*NeuroInvestment,* 2000).

Age itself is a risk factor for AD. The prevalence of AD in the population doubles from age 65 to 75, and again from 75 to 85. The scale of the problem is increasing as the elderly segment of the population continues to grow. There are 4 million people with AD in the United States today (Alzheimer's Disease and Related Disorders Association, Inc. [ADRDA], 2000), and that figure is projected to reach 6 million in the next decade, with proportionate increases in social and fiscal burdens (Rice, 1993). Overall mortality for AD patients averages eight years, but ranges up to 20 years, from the onset of symptoms (ADRDA, 2000).

AD is rapidly becoming the most widespread and costly age-related disorder in the United States. The total cost of illness of AD is estimated at $100 billion per year; per-year home-care costs are estimated at $12,500 per patient; and per-year hospital/nursing home costs are estimated at $42,000 per patient per year. The total annual per-patient cost (including home care, hospital care, drugs, physician care, etc.) is estimated at $174,000 (ADRDA, 2000).

There are several QoL/functional status indicators developed for AD. Most instruments track memory, thinking and behavior, such as the Alzheimer's Disease Assessment Scale (ADAS-cog), the Neuropsychiatric Inventory (NPI) and the Alzheimer's Disease Cooperative Study Inventory (ADCS-ADL), which includes activities of daily living (ADL).

Impact of Current Biotechnology Products

To date, no biotechnology products for AD have reached the market in the United States. Indeed, only two pharmaceutical compounds have been approved for the treatment of AD in the United States: the cholinesterase inhibitors Cognex® (tacrine) and Aricept® (donepexil), both of which prevent the breakdown of acetylcholine, a chemical important in memory.

While there has been ample popular press coverage regarding the roles that such substances as anti-inflammatory drugs, estrogen, herbal ginkgo and vitamin E may play in slowing the progression of AD, there has been no dramatic breakthrough in the treatment of the disorder itself, in spite of the myriad research programs targeting it. Progress has been made, but it has become clear that AD is a complex, multifactorial process.

The Promise of Future Biotechnology Products

Clinically, AD is increasingly viewed as a cerebral amyloidosis, that is, a progressive accumulation of amyloid-beta (Aß) protein (amyloid plaques) in the brain. Amyloid plaques are surrounded by portions of degenerating neurons as well as astrocytes and microglial cells (both of which are parts of the supporting structure of nerve tissue) and contain evidence of an inflammatory reaction. Amyloid protein injures brain cells through oxidative processes and generation of free radicals.

Recent AD research has focused on the relationship between accumulation of amyloid and the production of neurofibrillary tangles (knots or clumps in the connections among nerve cells). Inhibition of two enzymes (β-secretase and γ-secretase) is thought to reduce the generation of amyloid, interrupt the formation of neuriticplaques (associated with nerve inflammation) and prevent neuron death. Scientists recently announced identification of the β-secretase enzyme; further characterizing this enzyme is a critical step in developing an inhibitor with potential therapeutic value. Companies exploring amyloid inhibitors include Scios Inc., Amgen Inc., Alteon Inc., Elan Corporation and Axonyx Inc.

Scientists are also exploring other treatment pathways for AD. American Biogenetic Sciences, Inc. is investigating the potential of a molecule to promote new nerve growth that accumulates in regions of brain tissue known to be affected by AD. Guilford Pharmaceuticals Inc. and Amgen are investigating the potential of neuroimmunophilins to promote the regrowth and repair of damaged nerves.

Promising biotechnology treatments for AD, however, are a few years away. Only one product (CX516, one type of AMPAKINEs®, by Cortex Pharmaceuticals, Inc.) is in Phase II trials, and most are in the preclinical phase or Phase I. These new products are discussed below.

AN-1792

A new vaccine in development by Elan and American Home Products Corporation has the potential to revolutionize treatment for AD patients. Known as AN-1792, the vaccine is designed to stop the production of plaques in the brain. Because plaque is a brain intruder, immunization with the rogue protein may prime the body's immune system to signal the creation of antibodies that will fight the protein and prevent the formation of plaques. Tests on mice that had been given the human AD gene suggest the viability of this approach. Not only did the vaccine prevent the formation of plaques; it significantly reduced pre-existing ones. Forthcoming human trials will involve patients with early-stage AD. They will receive four injections of the vaccine to see if it is possible to safely trigger an immune response (Dobson, 2000).

Even if it works perfectly in humans, AN-1792 will need at least four years of testing before it could be on the market (LaMendola,2000).

Phenserine

Phenserine is in development at Axonyx as a potential treatment for AD. Phenserine is a highly selective, reversible acetylcholinesterase inhibitor. (Acetylcholinesterase is an enzyme that interferes with normal nerve impulse transmission.) Its rapid disappearance from the blood is expected to reduce the possibility of toxicity. Results from a Phase I trial in the United States show that phenserine inhibits acetylcholinesterase activity in healthy volunteers, confirming previous preclinical data. The trial evaluated the therapeutic range for a single dose of the drug. An additional trial to evaluate multiple doses of the drug is planned. The company expects to start a Phase II efficacy study in patients with AD during 2000 (Axonyx, 2000).

AMPAKINEs®

Research conducted at the University of California–Irvine demonstrates that AMPAKINEs, developed by Cortex, can increase the production of the important neurotrophic factors BDNF (brain-derived neurotrophic factor) and NGF (neuronal growth factor) in critical areas of the brain involved in memory. Experiments were conducted on slices of brain tissue maintained in culture and in aged rats and mice. Increases in the expression of BDNF were observed in both species.

As part of the normal aging process, there is a decline in the production of neurotrophins, particularly BDNF. This decrease results in less healthy neurons, which are characteristically smaller than young nerve cells. A number of researchers have demonstrated that infusion of neurotrophins may restore the size and function of aged neurons. In pill form, AMPAKINEs should be far less invasive than administering neurotrophic factors directly by injecting protein- or neurotrophin-producing cells into the brain. It should also overcome the problems associated with direct administration, which may lead to aberrant nerve cell growth and connections (*PR Newswire,* 1999).

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Table 1: Disease Overview for the Elderly — Alzheimer's Disease

Disease Category	Alzheimer's Disease
Epidemiology	**Prevalence:** 4 million; 1 in 10 persons aged 65+; 50% of persons aged 85+ **Mortality:** Average of 8 years (and as many as 20+ years) from the onset of symptoms
Total Cost of Illness	**Total cost:** $100+ billion per year
Direct / Indirect Costs	**Caregiver:** $33 billion per year due to work absenteeism **Home care:** $12,500 per patient per year **Hospital/nursing home care:** $42,000 per patient per year **Drugs:** $200 million per year ($10 billion projected by 2005) **Total per-patient cost:** $174,000 per year
QoL / Functional Status	Results in impaired memory, thinking and behavior. Alzheimer's patients become totally incapable of caring for themselves. Major QoL instruments: ▪ ADAS-cog (measures patient's memory, language and orientation) ▪ ADCS-ADL ▪ NPI (evaluates the frequency and severity of 10 types of behavioral symptoms, such as anxiety, apathy and loss of inhibition)
Comments	**Source:** ADRDA, 2000

ADAS-cog: Alzheimer's Disease Assessment Scale
ADCS-ADL: Alzheimer's Disease Cooperative Study Inventory (includes activities of daily living)
ADRDA: Alzheimer's Disease and Related Disorders Association, Inc.
NPI: Neuropsychiatric Inventory

Table 2: Biotechnology Pipeline Products for the Elderly — Alzheimer's Disease

Pipeline Product	Phase / Date Submitted	Company	Therapeutic Area	Class	Indication	Mechanism of Action	Route of Admin. / Dosing
Γ-secretase inhibitor	Research	Scios / Lilly	CNS	β-amyloid modulator	Treatment of Alzheimer's disease	Inhibits β-amyloid formation	
β-secretase inhibitor	Preclinical	Amgen	CNS	β-amyloid protease inhibitor; peptide genotype	Treatment of Alzheimer's disease	Reduces accumulation of amyloid by inhibiting production of β-secretase	
ABS-205	Preclinical	American Biogenetic Sciences	CNS	Nerve growth factor (NGF)	Treatment of Alzheimer's disease	Small organic molecule with neurotrophic-like properties similar to those of NGF and plays a key role in promoting new nerve growth; crosses blood-brain barrier into brain tissue, shown to accumulate in the hippocampus and cortex; brain regions often affected by Alzheimer's and other forms of neurodegeneration	Oral
AN-1792	Phase I	Elan / AHP	CNS	42 amino acid form of the beta-amyloid peptide ($Aß_{42}$)	Treatment of Alzheimer's disease	Alters amyloid plaque deposition by accelerating the clearance of amyloid plaque	Injection
CEP-1347	Phase I	Cephalon	CNS	Signal transduction modulators	Treatment of Parkinson's disease and Alzheimer's disease	Signals transduction modulators may suppress or override neuronal survival mechanisms and thereby elicit neuronal death	Oral
CEP-3265	Preclinical	Cephalon	CNS	Gene transcription regulators	Treatment of Alzheimer's disease	Enhances the endogenous expression of NGF (nerve growth factor) and promotes neuronal survival in regions of the brain known to be affected by Alzheimer's disease	Oral
CX516	Phase II	Cortex	CNS	AMPA receptor modulator (AMPAKINEs®)	Treatment of Alzheimer's disease	Enhances the functioning of the AMPA type glutamate receptor by increasing the amount of current flow that takes place when glutamate binds to the receptor	Oral

Table 2: Biotechnology Pipeline Products for the Elderly — Alzheimer's Disease (continued)

Pipeline Product	Phase / Date Submitted	Company	Therapeutic Area	Class	Indication	Mechanism of Action	Route of Admin. / Dosing
FKBP	Preclinical	Guilford Pharma-ceuticals / Amgen	CNS	FKBP-neuroimmuno-philin ligands	Treatment of Alzheimer's disease	Neuroimmunophilin ligands gain access to the central nervous system and promote the regrowth and repair of damaged nerves	Oral
Phenserine	Phase I	Axonyx	CNS	Reversible acetylcholines-terase inhibitor	Treatment of Alzheimer's disease	Reduces production of beta-amyloid precursor protein and beta-amyloid peptide	

Pipeline Product	Impact on Mortality and Morbidity	Impact on Costs	Impact on QoL (Patient / Caregiver)	Comments
Γ-secretase inhibitor				
β-secretase Inhibitor				
ABS-205				
AN-1792	Elan researchers reported in the scientific journal *Nature* that immunization with AN-1792 significantly reduced pre-existing amyloid plaque and inhibited further plaque formation in the brains of Elan's transgenic (PDAPP) mouse model of Alzheimer's disease			Dobson, 2000
CEP-1347	CEP-1347 has been shown to prevent neuronal death *in vitro* and in several models of neuronal death *in vivo*			Cephalon, 1999
CEP-3265				
CX516	Published studies demonstrate that AMPAKINEs® (of which CX516 is only one) can cause a statistically significant increase in the memory of elderly animals and humans			*PR Newswire,* 1999
FKBP				
Phenserine	Preclinical studies showed dramatic improvement in animal memory and cognitive performance			Axonyx, 2000

CNS: Central nervous system
NGF: Nerve growth factor

B. Cancer

Overview

Cancer is described as the uncontrolled growth and spread of abnormal cells, which can ultimately result in death. More than 8.2 million Americans have cancer today, and it is expected that more than 1.2 million new cases will be diagnosed in 1999. Cancer is the second leading cause of death, after heart disease; about 563,000 Americans are expected to die of cancer this year. The lifetime risk of developing cancer is one in two among men and one in three among women (Ries, 2000).

The costs of cancer are tremendous: According to the National Institutes of Health (NIH), more than $107 billion is spent each year, of which $37 billion is spent on direct medical care. Even more dramatic is the $59 billion in mortality costs resulting from premature death (ACS, *Cancer: Basic Facts,* 1999).

Many types of cancers affect Americans today; however, the elderly specifically are at greatest risk for developing breast, colorectal, lung and prostate cancers. Each of these cancers is discussed below.

BREAST CANCER

Breast cancer is the most common type of cancer among women after skin cancer; it rarely occurs in men. It is characterized by malignant tumors that are either *in situ* (meaning that the cancer is confined to a specific area, namely breast ducts [stage 0]) or *invasive* (meaning that the cancer has invaded the fatty tissue of the breast and can spread to other parts of the body [stages 1 through 4]) (ACS, *Breast Cancer Overview,* 1999).

One in eight women will be diagnosed with breast cancer during her lifetime. Today, more than 1.2 million women aged 65 and older are living with the disease. Although the overall mortality rate has decreased, an estimated 120.2 per 100,000 women aged 65 and older continue to die from breast cancer each year (ACS, *Breast Cancer Overview,* 1999; Ries, 2000). With the increasing use of mammography (X-ray of the breast), tumors are being detected at earlier stages, further decreasing the mortality rate. In fact, studies show that mammography has decreased mortality by more than 30 percent (Rimer, 1997).

Treatment for breast cancer varies according to stage and rate of growth of the cancer, as well as age and other factors. Most women will have some type of surgery (e.g., lumpectomy, partial/total mastectomy, axillary dissection) in addition to other types of therapy (e.g., chemotherapy, radiation therapy, bone marrow transplants, hormone therapy [tamoxifen]).

Breast cancer has been estimated to cost more than $6.6 billion each year, more than 60 percent of which is spent caring for patients 65 and older (Schrag, 1999; Berkowitz, 2000). On average, Medicare spends approximately $17,000 to $20,000 each year per breast cancer patient (Berkowitz, 2000).

Breast cancer is not only an economic burden to society; it also results in reduced QoL in its victims. Some of the key QoL domains affecting women with breast cancer are breast pain, fear of disease recurrence, sexual dysfuction, anxiety and mood impairment (Gotay, 1998).

COLORECTAL CANCER

Colon and rectum cancers have similar features and thus are referred to together as "colorectal cancer." Cancer can occur in any of the four sections of the colon (ascending, transverse, descending and sigmoid colons) or the anus (rectum). Generally, the cancer develops slowly over a period of years and may develop from polyps (protruding growths of tissue in the lining of the colon or rectum) or dysplasia (abnormal tissue development). More than 95 percent of colorectal cancers are adenocarcinomas, which are cancer cells that line the inside of the colon and rectum (ACS, *Colon and Rectum Cancer Overview,* 1999).

Colorectal cancer affects both men and women. In the elderly population (those aged 65 and over), an estimated 287.8 per 100,000 persons will be diagnosed with the disease each year. Today, about 1 million elderly persons are living with colorectal cancer. The five-year survival rate is 60.9 percent. Although 121.5 per 100,000 persons aged 65 and over die each year of colorectal cancer, screening for the disease (e.g., fecal occult blood tests, colonoscopy) has resulted in increased detection of early-stage colorectal cancer and an associated decrease in mortality (Ries, 2000; Midgley, 1999).

Surgery (e.g., resection) and chemotherapy are the primary treatments used in patients with colorectal cancer. However, although 80 percent of patients have complete macroscopic clearance of their disease by resection, the disease recurs in 50 percent of these patients. Adjuvant chemotherapy can decrease the risk of recurrence and improve survival, but there is continuing controversy about the overall effectiveness of adjuvant chemotherapy for treating colorectal cancer (Midgley, 1999). Other therapies such as immunotherapy, gene therapy and biological agents are currently under investigation for treating colorectal patients and show promising results.

Colorectal cancer costs society an estimated $6.5 billion each year. In 1990, more than $8,000 was spent on each patient with colorectal cancer, and the disease costs an estimated $51,000 from date of diagnosis to death (Riley, 1995). In addition to costs, colorectal cancer also diminishes a person's QoL, primarily causing pain, constipation and psychological distress (Ulander, 1997).

LUNG CANCER

Lung cancer is the leading cause of death among the elderly and has resulted in one of the highest costs to our society, at more than $10 billion annually (ACS, *Lung Cancer Overview,* 1999). An estimated 346.8 per 100,000 persons aged 65 and over are diagnosed with the deadly disease each year. The five-year survival rate is only 12.3 percent for this population, resulting in 312.7 deaths per 100,000 each year (1993-97) (Ries, 2000).

The majority (80 percent) of lung cancer victims have non-small cell lung cancer (NSCLC); the other 20 percent have small cell lung cancer (SCLC). Lung cancer typically begins in the lining

of the bronchi[1] (ACS, *Lung Cancer Overview,* 1999). It often takes years to develop and is usually a result of smoking, which is associated with about 80 percent of all lung cancer cases. Other risk factors include exposure to asbestos or other cancer-causing agents in the workplace and lung scarring from some types of pneumonia. Since most lung cancer patients do not exhibit any symptoms, the majority of tumors are detected when the cancer is in advanced stages.

Treating lung cancer is more complicated than other cancers. Surgery to remove the tumor or some of the lung can be performed if the lungs are in good condition, and chemotherapy and/or radiation can kill cancer cells. As a result of poor survival in lung cancer patients, the focus of treatment is typically on palliative care; thus, improving the patient's QoL is often one of the goals of treatment. Pain, dyspnea and anorexia are the major symptoms and QoL scales typically focus on measuring these symptoms (Montazeri, 1998). Current treatment options, namely for those with advanced disease (e.g., chemotherapy), have not regularly alleviated symptoms without causing unpleasant and/or life-threatening toxic effects. Additional research is recommended to better understand the interaction of treatment with the patient's QoL and survival (Montazeri, 1998).

PROSTATE CANCER

Prostate cancer begins in a man's prostate gland, a small gland (the size of a walnut) located just below the bladder and in front of the rectum. If the cancer goes undetected or becomes uncontrolled, it can spread to the lymph nodes and then to other organs of the body. Typically, however, the cancer is likely to grow more slowly, and in many cases, men will likely die of other diseases before prostate cancer. The five-year survival rate is 93.6 percent (ACS, *Prostate Cancer Overview,* 1999; Ries, 2000).

The incidence of prostate cancer is very high. Approximately 1,025 in 100,000 men aged 65 and over will develop the disease each year, equal to approximately 145,000 men. Today, more than 880,000 elderly men have the disease, and one in six will develop the disease in his lifetime (Ries, 2000). There is no known cause for prostate cancer, although the following are risk factors: age (prostate cancer risk increases with age), race (more frequent in African-American men), diet (more frequent in men with high-fat diets) and heredity (family members) (ACS, *Prostate Cancer Overview,* 1999).

Surgery, radiation and hormone therapy are the most common types of treatment for prostate cancer, although chemotherapy and "watchful waiting" are also options if the cancer has spread outside of the prostate gland or if the cancer is in a very early stage, respectively. Since prostate cancer and associated surgery can damage nerves found next to the prostate, urinary incontinence, erectile dysfunction and bowel dysfunction are common functional problems in these patients. As a result, functional status is one of the key domains of QoL in these patients (McCammon, 1999; Shrader-Bogen, 1997; Herr, 1997).

Prostate cancer costs have been estimated to reach more than $5 billion annually (Potosky, 1999). Approximately $11,000 is spent over a two-year period in treating a prostate cancer patient, the majority (86 percent) of which is spent on inpatient care (Beemsterboer, 1999).

[1] The windpipe (trachea) brings air down into the lungs, which are then divided into tubes (bronchi), and further divided into smaller branches (bronchioles). At the end of each bronchiole are tiny air sacs (alveoli).

Impact of Current Biotechnology Products

Biotechnology products have had a significant impact on the overall morbidity and mortality of cancer patients. There are some 20 products already on the market for detection, treatment and follow-up of various cancers. Products with considerable impact are discussed below.

EPOGEN®/PROCRIT® (RECOMBINANT HUMAN ERYTHROPOIETIN [RHUEPO])

Recombinant human erythropoietin (rHuEPO) is a glycoprotein produced in the kidneys that stimulates red blood cell division. Its primary indication is for the treatment of anemia in chronic renal failure patients (CRF),[2] although rHuEPO is also indicated for red blood cell stimulation in cancer-related anemia. rHuEPO is marketed as Epogen (Amgen Inc.) and Procrit (Ortho Biotech Inc.). Specific highlights of rHuEPO are as follows:

- **Significantly greater hematocrit response and reduction in number of blood transfusions.** Clinical trial results demonstrate that rHuEPO administered to cancer patients with anemia resulted in a significant increase in hematocrit (red blood cells as a percentage of total blood volume) compared with placebo. Additionally, results show a significant decrease in the number of patients requiring blood transfusions (22 percent) compared with placebo (43 percent) (Amgen, *Epogen package insert,* 1999).

- **Increase in QoL compared with standard of care.** Cancer-related anemia patients treated with rHuEPO demonstrated an 8.3-point increase in QoL, as measured by the linear analogue scale assessment (LASA), compared with a 1-point decrease in QoL for patients treated with standard of care, such as blood transfusions. (Cremieux, 1999).

- **More cost-effective than standard of care.** A study by Cremieux (1999) showed that rHuEPO is 23 percent more cost-effective than the standard of care (e.g., blood transfusions) when maintaining the hemoglobin level is the goal (Cremieux, 1999).

HERCEPTIN® (TRASTUZUMAB)

Herceptin, developed by Genentech, Inc., was approved for the treatment of metastatic breast cancer in September 1998. Since then, it has been used to treat more than 41,000 women, or 25 to 30 percent of women who have tumors that overexpress the human epidermal growth factor receptor protein known as HER2 protein (*The Pink Sheet*, "Roche developing," 2000). By binding to the HER2 protein, Herceptin inhibits the proliferation of tumor cells. Specific benefits of Herceptin include:

- **Longer time to disease progression and higher survival rate.** Clinical trial results showed that Herceptin in conjunction with chemotherapy (paclitaxel) produced a one-year survival rate of 79 percent, compared with 68 percent in patients treated with chemotherapy alone. Results also showed a significantly longer time to disease progression (7.2 months) compared with 4.5 months for the chemotherapy-only group.

[2] See "Chronic Renal Failure" section for additional information.

LEUKINE® (SARGRAMOSTIM)

Leukine is a recombinant human granulocyte colony-stimulating factor (rhuGM-CSF) that is widely used as adjuvant support in cancer patients who have neutropenia, a condition characterized by an abnormally small number of infection-fighting white blood cells called neutrophils. Leukine, produced by Immunex Corporation, has been on the market since 1991. Leukine has had a significant impact on morbidity and mortality of cancer patients and has also demonstrated potential cost savings in bone marrow transplant (BMT) candidates. Highlights of Leukine include:

- **Significant improvement in various clinical endpoints and improvement in survival.** Several clinical trials involving patients with cancer (e.g., prostate cancer, acute myelogenous leukemia) have shown that Leukine significantly improves duration of hospitalization, incidence of infections, antibacterial usage and other clinical indicators. Additionally, in at least one study, improvement in 100-day survival and median survival was demonstrated in patients after graft failure following bone marrow transplants (Immunex, *Leukine package insert*, 1999).

- **Cost savings in bone marrow transplant candidates.** In a cost study of cancer patients receiving bone marrow transplants, patients given Leukine had shorter hospital stays and fewer infectious complications than patients treated with the standard of care, resulting in an average cost savings of $14,500 (Desch, 1997).

NEUPOGEN® (FILGRASTIM)

Amgen's product, Neupogen, received its first approved indication in 1991 for cancer patients with chemotherapy-induced neutropenia. Neupogen is a form of granulocyte colony stimulating factors (G-CSF), a naturally occurring substance that produces neutrophils (infection-fighting white blood cells). The product has reduced the incidence of infection associated with a number of cancer treatments, such as BMT and peripheral blood progenitor cell (PBPC) transplantation. Neupogen has demonstrated the following benefits:

- **Reduced incidence, duration and severity of neutropenia.** In patients with small cell lung cancer, Neupogen reduced the incidence, duration and severity of grade IV neutropenia. In addition, reductions in the number of days of treatment with intravenous antibiotics and reductions in the number of days of hospitalization were also demonstrated.

- **Potential cost advantage over bone marrow transplants.** Patients administered Neupogen to support PBPC transplantation compared with patients receiving bone marrow transplants demonstrated reduced resource use, including a reduction in hospital length of stay and in the number of transplantation days. Additionally, time to neutrophil restoration and platelet recovery was significantly shorter. Overall cost savings were estimated to be 29 percent (or $13,600) per transplant (Henderson, "Whole blood," 1999; Henderson, 1996; Schmitz, 1996).

The Promise of Future Biotechnology Products

More than 175 biotechnology products are in preclinical or clinical phases of development for cancer and cancer-related conditions. The potential for these drugs reaches beyond new modes of treatment. In fact, these products have and will continue to provide new insights into the behavior of cancer cells (Crewdson, 2000). According to Dr. Paul Bunn, a veteran cancer researcher and chief of the University of Colorado Cancer Center in Denver:

> *"What is happening in cancer research is similar to the advent of antibiotics to treat infectious disease. All these things are more exciting than anything we ever had."*

Furthermore, Dr. Marc Lippman, director of the Lombardi Cancer Center at Georgetown University, called these new drugs:

> *"The tip of the iceberg. I'm not suggesting that every cancer patient is now assured a cure, but I do think if you can say, 'What is the thought process behind these agents versus the process behind those agents we were using in the clinic five years ago,' there's no comparison."*

Although in many cases new agents fail in the clinical phases of development and hence, reach the U.S. market, new products will be discovered. Eleven of the most promising products are discussed in detail below.

AVICINE™

AVI Biopharmaceuticals has developed a vaccine called Avicine that will potentially treat patients with colorectal, prostate and pancreatic cancers. Studies have demonstrated that Avicine extends the survival rate of patients in latter stages of colorectal cancer and may be able to slow the advance of prostate and pancreatic cancer (Brenneman, 1999).

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Avicine is an essentially nontoxic therapeutic cancer vaccine that elicits a highly specific immune response to the human hormone and growth factor chorionic gonadotropin (hCG), a cancer-associated oncofetal protein. The vaccine blocks hCG from encouraging tumor growth, angiogenesis (formation of new blood vessels), invasion and immunosuppression. In the clinical trials to date, patients who responded to the two epitopes (sites on an antigen molecule to which antibody molecules bind) in the vaccine lived longer than patients treated with chemotherapy alone. Avincine is in Phase II trials for pancreatic cancer and will soon enter a Phase III pivotal trial in colorectal cancer and a Phase II trial in prostate cancer (*Biotech Business,* 2000).

BEC2

ImClone Systems Inc., in collaboration with Merck and Company, has developed a monoclonal antibody, currently called BEC2, for the treatment of small cell lung cancer. Phase II studies have shown that the compound significantly increases survival for these patients (Grant, 1999). BEC2 is currently in a Phase III trial to evalute the effects of the product in approximately 800 patients with small cell lung carcinoma (*Cancer Weekly Plus*, "BEC2 enters Phase III," 1998).

CEAVAC™

CeaVac is in Phase III trials for the treatment of advanced colorectal cancer. The product, developed by Titan Pharmaceuticals, Inc. has shown evidence of slowing the disease in patients with surgically removed colon cancer in Phase II trials (*Business Wire,* 1999). The current Phase III study, which has enrolled 260 patients to date, is comparing the safety and efficacy of standard therapy (5-FU and Leucovorin) with standard therapy plus CeaVac. The study is being performed at 45 clinical centers in the United States and United Kingdom. Dr. Louis R. Bucalo, president and CEO of Titan Pharmaceuticals, said:

> *"We are pleased to be able to meet our initial accrual goals and further expand this clinical study. CeaVac is among the most advanced, standardized products in development for the active immunotherapy of colorectal cancer, and we look forward to the further progress of this study."*

GVAX®

Cell Genesys, Inc. has initiated a multicenter Phase I/II clinical trial of GVAX lung cancer vaccine. This clinical trial follows an initial pilot study that demonstrated preliminary evidence of antitumor activity in advanced lung cancer patients who had failed chemotherapy (*Cancer Weekly Plus,* 2000). Dale G. Ando, MD, of Cell Genesys, said:

> *"We are encouraged by the combination of safety and indications of antitumor activity we observed in our initial GVAX lung cancer vaccine trial, particularly in view of the fact that lung cancer has been largely unresponsive to other immunotherapies to date. GVAX cancer vaccines have now been reported to show evidence of immunologic and antitumor activity in all four types of cancer tested to date — prostate cancer, lung cancer, melanoma and kidney cancer — indicating that GVAX may be applicable to multiple types of cancer."*

The initial pilot study of GVAX lung cancer vaccine was conducted in patients with advanced lung cancer, the majority of whom had failed treatment with surgery, radiation, chemotherapy or some combination. Recently updated findings indicate that, of the 22 patients who could be evaluated, three showed significant disease stabilization (in two cases continuing after 18 months), and one patient's tumors shrank by more than 50 percent at two of three disease sites. In all cases, GVAX therapy was shown to be safe and well tolerated in the outpatient setting. In addition to the clinical evidence of antitumor activity described above, the vaccine has demonstrated potent antitumor immunity, as evidenced by the microscopic examination of vaccination site and metastatic tumor site biopsies (*Cancer Weekly Plus,* "BEC Enters Phase II," 1999).

HERCEPTIN® (TRASTUZUMAB)

Genentech, in collaboration with Hoffmann-La Roche, Inc., has developed an antibody that received approval in 1998 for treating metastatic breast cancer patients whose bodies overexpress the HER2 protein. Currently, Herceptin is in clinical trials for early-stage breast cancer. It is expected that the compound will more easily find and destroy its target inside smaller, less-developed tumors (Matus, 1999). According to Francisco J. Esteva, MD, assistant professor of Medicine at the University of Texas M. D. Anderson Cancer Center in Houston,

> *"Breast cancer experts say Herceptin (trastuzumab), one of the first 'smart drugs' that attack tiny genetic targets, shows promise for effectively treating early stages of HER2-positive breast cancer. In 25 to 30 percent of breast cancers, the HER2 gene makes the disease extremely aggressive and hard to treat. Along with chemotherapy, Herceptin has already been shown to moderately slow the development of late-stage breast cancer."*

NEOVASTAT

Neovastat is a liquid cartilage extract developed by AEterna Laboratories, Inc., that is in Phase III studies for the treatment of breast, lung and prostate cancers. The product is classified as an angiogenesis inhibitor with multiple mechanisms of action, blocking the two main pathways of angiogenesis: matrix metalloproteinases (MMPs) and vascular endothelial growth factor (VEGF). Additionally, Neovastat regulates the VEGF-induced proliferation of endothelial cells necessary in the growth of new blood vessels (*Cancer Weekly Plus*, "Anti-angiobenic shark," 1998; *Canada NewsWire,* "AEterna Presents," 2000).

NOVEL ERYTHROPOIESIS STIMULATING PROTEIN (NESP)

Amgen has developed a drug similar to Epogen® (rHuEPO) — novel erythropoiesis stimulating protein (NESP) — that is in Phase II trials for treating patients with cancer-related anemia (*Pharmaceutical Approvals Monthly,* 1999). Amgen has already submitted a new drug application to the Food and Drug Administration (FDA) for NESP in December 1999 for chronic renal failure and chronic renal insufficiency.[3] The primary difference between rHuEPO and NESP is the formulation: NESP has a longer half-life than rHuEPO and will likely allow for less frequent dosing in cancer patients treated for anemia. Analysts have reported that Amgen could reap more than $1 billion in sales of NESP over the next few years (*Biotechnology Newswatch,* "Amgen," 1999).

[3] Additional information regarding NESP in chronic renal failure is located in the "Chronic Renal Failure" section.

ONCONASE®

Developed by Alfacell Corporation, Onconase is in Phase III trials for the treatment of various cancers. Onconase is a novel cytotoxic ribonuclease (RNase) that has demonstrated antitumor effects (*Business Wire,* "Onconase," 2000). According to Dr. Stan Mikulski of Alfacell Corporation (*Cancer Weekly Plus,* "Cancer Therapies," 1998),

> *"We believe Onconase, in combination with proteasome inhibitors, could constitute a therapeutic approach to cancer treatment. This combination may also allow for more effective treatment of otherwise resistant tumors. In fact, Alfacell is currently testing such combinations* in vivo *in collaboration with the National Cancer Institute."*

PANOREX® (EDRECOLOMAB)

Centocor, Inc., in collaboration with Glaxo Wellcome Inc., has developed a monoclonal antibody against the 17-1A epithelial antigen, which has demonstrated abilities as an adjuvant therapy in colorectal cancer (Martin, 1999). Panorex has been approved in Germany to treat advanced colon cancer, but not yet approved in the United States (currently in Phase II trials). However, results show that Panorex has reduced deaths in test patients by a third (30 percent) after seven years (Crewdson, 2000).

PRINOMASTAT (AG3340)

Prinomastat, developed by Agouron Pharmaceuticals, Inc., is in Phase III trials for treatment of prostate cancer in conjunction with mitoxantrone/prednisone as well as for treatment of non-small cell lung cancer in combination with paclitaxel/carboplatin chemotherapy regimens. According to University of California–San Francisco researcher J. O'Leary and colleagues, Prinomastat has been shown to potently inhibit angiogenesis, tumor invasion and metastasis (*Cancer Weekly Plus,* "Oral anti-angiogenesis," 1999; *American Society of Clinical Oncology,* "Identification," 1999).

SU5416

SU5416, developed by Sugen, Inc., is an angiogenesis inhibitor that has demonstrated that it can control tumor growth in certain tumors. In a Phase I trial, SU5416 showed significant inhibition of a variety of tumors.

> *"SU5416 is a promising new agent aimed at controlling tumor growth via a novel mechanism of action: Inhibition of Flk-1 signaling. Phase II studies in multiple tumor types are planned for early 1999" (Cancer Weekly Plus, "*Phase I," 1999*).*

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Table 1a: Disease Overview for the Elderly — Breast Cancer

Disease Category	Breast Cancer (Female Only)
Epidemiology	**Incidence:** 441.2 per 100,000 aged 65+ (1993–97) **Point prevalence:** 1,198,939 aged 65+ (1999) **Lifetime prevalence:** 1 in 8 women **Mortality:** 120.2 per 100,000 aged 65+ (1993–97) **5-year relative survival:** 86.6% aged 65+ (1989–96)
Total Cost of Illness	**Total cost:** $4.2 billion–$6.6 billion annually with those aged 60+ accounting for 60% of total costs
Direct / Indirect Costs	**Average annual per-patient costs:** Medicare payments (1998$): $17,430 (aged 60-69), $18,473 (aged 70–79), $20,560 (aged 80+) **Total per-patient costs from diagnosis to death:** Medicare payments (1998$): $57,401 (aged 60–69), $52,035 (aged 70–79), $43,143 (aged 80+); $35,000 HMO payments (1991$)
QoL / Functional Status	Women aged < 50 experience higher levels of depression; older women have higher emotional well-being scores In survivors, key symptoms include breast pain, fear of disease recurrence, sexual dysfunction/dissatisfaction, anxiety and mood impairment
Comments	**Sources:** ACS, *Cancer: Basic Facts,* 1999; Berkowitz, 2000; Fireman, 1997; Gotay, 1998; NCI, 1999; Ries, 2000; Riley, 1995; Schrag, 1999; Wenzel, 1999

Note: Point prevalence based on 1994 Connecticut rates and U.S. population estimates

ACS: American Cancer Society
HMO: Health maintainance organization
NCI: National Cancer Institute

Table 1b: Disease Overview for the Elderly — Colon and Rectum Cancers

Disease Category	Colon and Rectum Cancers
Epidemiology	**Incidence:** 287.8 per 100,000 aged 65+ (1993–97) **Point prevalence:** 984,895 aged 65+ (1999) **Lifetime prevalence:** 1 in 18 persons **Mortality:** 121.5 per 100,000 aged 65+ (1993–97) **5-year relative survival:** 60.9% aged 65+ (1989–96)
Total Cost of Illness	**Total cost:** $6.5 billion annually
Direct / Indirect Costs	**Average annual per-patient costs:** $8,016 Medicare payments (1990$) **Total per-patient costs from diagnosis to death:** $51,865 Medicare payments (1990$); HMO payments (1991$): $42,000 (colon), $51,000 (rectum)
QoL / Functional Status	ADLs decreased from 70% to 57% postoperatively; key endpoints include pain, constipation, psychological distress
Comments	**Sources:** ACS, *Colon and Rectum Cancer Overview,* 1999; Fireman, 1997; NCI, 1999; Ries, 2000; Riley, 1995; Schrag, 1999; Ulander, 1997

Note: Point prevalence based on 1994 Connecticut rates and U.S. population estimates

ACS: American Cancer Society
ADL: Activities of daily living
NCI: National Cancer Institute

Table 1c: Disease Overview for the Elderly — Lung and Bronchus Cancers

Disease Category	Lung and Bronchus Cancers*
Epidemiology	**Incidence**: 346.8 per 100,000 aged 65+ (1993–97); 80% of lung cancers are non-small cell lung cancer (NSCLC); 20% are small cell lung cancers (SCLC) **Point prevalence:** 255,582 aged 65+ **Lifetime prevalence:** 1 in 13 persons **Mortality:** 312.7 per 100,000 aged 65+ (1993–97) **5-year relative survival:** 12.3% aged 65+ (1989–96)
Total Cost of Illness	**Total cost:** $10 billion annually
Direct / Indirect Costs	**Average annual per-patient costs:** $17,371 Medicare payments (1990$) **Total per-patient costs from diagnosis to death:** $29,184 Medicare payments (1990$); $33,000 HMO payments (1991$)
QoL / Functional Status	Focus on palliative care due to poor survival; key instruments include EORTC QLQ-LC13 and QLQ-C30; major symptoms include pain, dyspnea and anorexia In a cost-utility analysis using the TTO method (1=full health; 0=death), results demonstrate that QoL may not be improved with combination chemotherapy: TTO = 0.61 (best supportive care) vs. TTO = 0.34 (polychemotherapy) ($p<0.03$)
Comments	**Sources:** ACS, *Lung Cancer Overview,* 1999; Desch, 1996; Fireman, 1997; Montazeri, 1998; NCI, 1999; Ries, 2000; Riley, 1995

Note: Point prevalence based on 1994 Connecticut rates and U.S. population estimates

*Includes small cell and non-small cell lung cancers

ACS: American Cancer Society
ADL: Activities of daily living
EORTC: European Organization for Research and Treatment of Cancer
EORTIC QLQ-C30: EORTC-Quality of Life Questionnaire Version 3.0
EORTC QLQ-LC13: EORTC-Quality of Life Questionnaire Lung Cancer Module
HMO: Health maintenance organization
NCI: National Cancer Institute
TTO: Time trade-off

Table 1d: Disease Overview for the Elderly — Prostate Cancer

Disease Category	Prostate Cancer
Epidemiology	**Incidence:** 1,025 per 100,000 aged 65+ (1993–97); 180,400 new cases - 80% aged 65+ (2000) **Point prevalence**: 881,088 aged 65+ (1999) **Lifetime prevalence:** 1 in 6 persons **Mortality:** 226.2 per 100,000 aged 65+ (1993–97) **5-year relative survival:** 93.6% aged 65+ (1989–96)
Total Cost of Illness	**Total cost:** $5 billion annually
Direct / Indirect Costs	**Per-patient costs:** Total (2-year): $11,182; inpatient cost: $9,635 (86%); outpatient cost: $1,547 (14%) **Average annual per-patient costs:** $7,005 Medicare payments (1990$) **Total per-patient costs from diagnosis to death:** $48,684 Medicare payments (1990$); $29,000 HMO payments (1991$)
QoL / Functional Status	Endpoints vary by stage and treatment; key functional endpoints include urinary incontinence, erectile dysfunction and bowel dysfunction; QoL measures typically based on functional status
Comments	**Sources:** ACS, *Prostate Cancer Overview*, 1999; Beemsterboer, 1999; Herr 1997; Fireman, 1997; McCammon, 1999; NCI, 1999; Potosky, 1999; Ries, 2000; Riley, 1995; Shrader-Bogen, 1997

Note: Point prevalence based on 1994 Connecticut rates and U.S. population estimates

ACS: American Cancer Society
HMO: Health maintenance organization
NCI: National Cancer Institute
QoL: Quality of life

Table 2: Current Biotechnology Products for the Elderly — Breast, Colon and Rectum, Lung and Bronchus and Prostate Cancers

Product on Market	Relevant Indication(s)	Company	Approval Dates	Class	Mechanism of Action	Route of Administration	Dosing
Epogen® (epoetin alfa)	Anemia in cancer patients on chemotherapy	Amgen	July 1999	Glycoprotein	Stimulates red blood cell production; produced in the kidney and stimulates the division of committed erythroid progenitors in the bone marrow	IV, SC	150 units/kg SC TIW up to 300 units/kg TIW
Herceptin® (trastuzumab)	Metastatic breast cancer	Genentech	September 1998	Monoclonal antibody	Selectively binds with high affinity to the human epidermal growth factor receptor 2 protein (HER2)	IV	Weekly maintenance dose: 2 mg/kg over 30-minute infusion if initial dose was tolerated (4 mg/kg over 90 minutes)
Leukine® (sargramostim)	Mobilization and following transplantation of autologous PBPC; myeloid reconstitution after BMT; BMT failure / engraftment delay	Immunex	March 1991; November 1996	rHuGM-CSF	Stimulates proliferation and differentiation of hematopoietic progenitor cells	Injection	Varies by indication: 250 mcg/m^2/day administered IV or SC over a 2- to 24-hour period
Neupogen® (filgrastim)	Reduce incidence of infection in chemotherapy-induced neutropenia	Amgen	February 1991; June 1994;	rHuG-CSF	Selectively stimulates the production of a certain type of infection-fighting WBC (neutrophil) and is used to decrease the incidence of infection in certain cancer treatments	SC bolus injection, by short IV infusion (15 to 30 minutes), or by continuous SC or IV infusion	Single daily injection of 5 mcg/kg/day
Procrit® (epoetin alfa)	See Epogen	J&J / Ortho Biotech	April 1993	See Epogen	See Epogen	See Epogen	See Epogen

Table 2: Current Biotechnology Products for the Elderly — Breast, Colon and Rectum, Lung and Bronchus and Prostate Cancers (continued)

Product on Market	Impact on Mortality and Morbidity	Impact on Costs	Impact on QoL (Patient / Caregiver)	Comments
Epogen® (epoetin alfa)	Significantly greater hematocrit response compared with placebo ($p < 0.008$); significant decrease in number of patients with blood transfusions compared with placebo (22% vs. 43%, $p<0.03$)	In cancer-related anemia patients, $0.81 spent on epoetin yields the same effectiveness as $1 spent on SOC; epoetin is considered 23% more cost-effective than SOC using hemoglobin level as the end point	Cancer-related anemia patients treated with epoetin demonstrated an 8.3-point increase in QoL as measured by the LASA compared with 1-point decrease in patients treated with SOC	Amgen, *Epogen package insert*, 1999; *Drug Topics*®, 1999; Adams, 2000; Cremieux, 1999
Herceptin® (trastuzumab)	1-year survival rate of 79% for Herceptin + all chemo group compared with 68% for all chemo-only group; significantly longer time to disease progression (7.2 months) for Herceptin + all chemo group compared with the all chemo group only (4.5 months)		Phase II and Phase III trials demonstrated that Herceptin + chemotherapy does not adversely affect QoL compared with chemotherapy alone	Genentech, 1998; Osoba, 1999; *The Pink Sheet,* "Roche reopens," 2000; *The Pink Sheet,* "Herceptin label," 1998
Leukine® (sargramostim)	Improvement in 100-day survival and median survival in graft failure patients; significant improvement in various clinical endpoints including time to neutrophil / myeloid engraftment, duration of hospitalization, incidence of infections and antibacterial usage	In a cost-minimization study, recipients of BMT demonstrated cost savings of $14,500 compared with SOC		Immunex, 1998; *The Pink Sheet,* "Immunex Leukine," 1998; *The Pink Sheet,* "From the interim," 1998; *The Pink Sheet,* "Lilly Gemzar," 1998; Desch, 1997

Table 2: Current Biotechnology Products for the Elderly — Breast, Colon and Rectum, Lung and Bronchus and Prostate Cancers (continued)

Product on Market	Impact on Mortality and Morbidity	Impact on Costs	Impact on QoL (Patient / Caregiver)	Comments
Neupogen® (filgrastim)	In patients with small cell lung cancer, G-CSF reduced the incidence of fever with neutropenia and culture-confirmed infections; reduced incidence, duration and severity of grade IV neutropenia, number of days of treatment with IV antibiotics and days of hospitalization	Potential cost advantage over BMT due to reduced hospital LOS, transfusion days and other reductions in resource use; potential cost savings of 29%, $13,600 per BMT compared with SOC	In non-Hodgkin's lymphoma patients, use of G-CSF along with combination chemotherapy resulted in significant improvement in QoL	Amgen, *Neupogen package insert,* 1998; Adams, 2000; *The Pink Sheet,* "Immunex Leukine," 1998; Henderson, "Whole blood," 1999; Henderson, 1996; Mastroianni, 1998; Schmitz, 1996
Procrit® (epoetin alfa)	See Epogen	See Epogen	See Epogen	Ortho Biotech, 1990

AML: Acute myelogenous leukemia
AWP: Average wholesale price
BMT: Bone marrow transplant
G-CSF: Granulocyte-colony stimulating factor
HER2: Human epidermal growth factor receptor 2
IV: Intravenous
LASA: Linear analogue scale assessment
LOS: Length of stay
NIH: National Institutes of Health
PBPC: Peripheral blood progenitor cells
QALYs: Quality-adjusted life years
QoL: Quality of life
rHuG-CSF: Recombinant granulocyte colony-stimulating factor
SC: Subcutaneous injection
SOC: Standard of care
TIW: Three times a week
WBC: White blood cells

Table 3: Biotechnology Pipeline Products for the Elderly — Breast, Colon and Rectum, Lung and Bronchus and Prostate Cancers

Pipeline Product	Phase / Date Submitted	Company	Therapeutic Area	Class	Indication	Mechanism of Action	Route of Admin. / Dosing
Avicine™	Phase II; March 2000	AVI Biopharm.	Cancer	Vaccine	Treatment of colorectal, prostate, pancreatic cancers	Elicits a highly specific immune response to hCG, a cancer-associated oncofetal protein	Injection
BEC2	Phase III; 1999	ImClone Systems / Merck	Cancer	Monoclonal antibody	Adjuvant treatment of SCLC	Mimics the ganglioside GD3 expressed on the surface of most tumors	Intradermal
CeaVac™	Phase III; 1999	Titan	Cancer	Monoclonal antibody vaccine	Treatment of advanced colorectal cancer	Generates immune responses to carcinoembryonic antigen	Injection
GVAX®	Phase I/II	Cell Genesys	Cancer	Vaccine	Treatment of advanced lung cancer	Antitumor activity	Injection
Herceptin® (trasluzumab)	Phase III (breast); Phase II (NSCLC)	Genentech / Hoffman-La Roche	Cancer	Monoclonal antibody	Adjuvant treatment of early-stage breast cancer in patients who overexpress HER2 protein	Selectively binds with high affinity to the HER2 protein	IV
Neovastat	Phase III; 1999	Aeterna Laboratories	Cancer	Angiogenesis inhibitor	Treatment of breast, lung and prostate cancers	Liquid cartilage extract — blocks the VEGF receptors, stops the proliferation of endothelial cells — the building blocks of new blood vessels	
NESP	Phase III; 1999	Amgen	Cancer	NESP	Treatment of cancer-related anemia (various cancers)	Stimulates red blood cell production	IV; SC
Onconase®	Phase III; 1999	Alfacell	Cancer	Novel cytotoxic ribonuclease (Rnase)	Treatment of various cancers	Inhibits protein synthesis	
Panorex® (edrecolomab)	Phase III; 1999	Centocor / Glaxo Wellcome	Cancer	Monoclonal antibody	Adjuvant therapy in the treatment of colorectal cancer	Binds with 17-1A epithelial antigen	

Table 3: Biotechnology Pipeline Products for the Elderly — Breast, Colon and Rectum, Lung and Bronchus and Prostate Cancers (continued)

Pipeline Product	Phase / Date Submitted	Company	Therapeutic Area	Class	Indication	Mechanism of Action	Route of Admin. / Dosing
Prinomastat (AG3340)	Phase III; 1999	Agouron	Cancer	Angiogenesis inhibitor	Treatment of prostate and NSCLC in combination with chemotherapy	Inhibits MT-MMP-1	
SU5416	Phase II/III	Sugen	Cancer	Angiogenesis inhibitor	Treatment of colorectal cancer	Block VEGF-mediated Flk-1 receptor signaling	

Table 3: Biotechnology Pipeline Products for the Elderly — Breast, Colon and Rectum, Lung and Bronchus and Prostate Cancers (continued)

Pipeline Product	Impact on Mortality and Morbidity	Impact on Costs	Impact on QoL (Patient / Caregiver)	Comments
Avicine™	Potentially extends the survival rate; evidence of objective antitumor responses and stabilization of tumor growth		Evidence of QoL benefits	Brenneman, 1999; *Cancer Weekly Plus,* "Phase II," 1998
BEC2	In SCLC patients, survival and relapse-free survival was substantially better in patients treated w/ BEC2 combined with Bacillus Calmette-Guerin (BCG)			Grant, 1999; *Cancer Weekly Plus*, "BEC2 enters," 1998
CeaVac™	Evidence of reduced disease progression in patients with surgically resected colon cancer			*Business Wire*, 1999
GVAX®	Preliminary evidence demonstrates antitumor activity in multiple types of cancer			*Cancer Weekly Plus,* "GVAX cancer," 2000; *Cancer Weekly Plus,* "Trial results," 1999
Herceptin® (trasluzumab)	Expected to find and destroy HER2 protein in less-developed tumors quicker than in late stages		In late-stage breast cancer, Phase II/III trials demonstrated that Herceptin + chemo do not adversely affect compared with chemotherapy alone	Genentech, 2000; Osoba, 1999; Matus, 1999
Neovastat	Demonstrates ability to stop proliferation of endothelial cells, formation of new blood vessels			*Cancer Weekly Plus,* "Anti-angiogenic," 1998; *Canada NewsWire,* 2000
NESP	Expected to significantly increase hematocrit response and decrease need for blood transfusions			www.amgen.com; *Biotechnology Newsletter,* Jan. 4 1999; *Pharm Approvals Monthly,* Dec. 1, 19/1/99
Onconase®				*Business Wire,* 2000; *Cancer Weekly Plus,* "Cancer therapies," 1998
Panorex® (edrecolomab)	Colorectal cancer studies indicate reduction in mortality rate by 30% and 27% relapse rate			*Chicago Tribune,* Feb. 27, 2000

Table 3: Biotechnology Pipeline Products for the Elderly — Breast, Colon and Rectum, Lung and Bronchus and Prostate Cancers (continued)

Pipeline Product	Impact on Mortality and Morbidity	Impact on Costs	Impact on QoL (Patient / Caregiver)	Comments
Prinomastat (AG3340)	Reduction in tumor cell invasion and angiogenesis in prostate cancer			ASCO, 1999
SU5416	Demonstrates control of tumor growth in angiogeneisis-dependent neuroblastoma tumors			*Cancer Weekly Plus*, "Phase I," 1999

ADL: Activities of daily living
ASCO: American Society for Clinical Oncology
HER2: Human epidermal growth factor receptor 2
HCG: Human hormone and growth factor chorionic gonadotropin (hCG)
IV: Intravenous
MT-MMP: Membrane-type matrix metalloproteinase
NESP: Novel erythropoiesis stimulating protein
NSCLC: Non-small cell lung cancer
QoL: Quality of life
SC: Subcutaneous
SCLC: Small cell lung cancer
VEGF: Vascular endothelial growth factor

C. Chronic Renal Failure

Overview

More than 3 million people in the United States suffer from one or more kidney conditions such as renal failure — the deterioration of kidney function (National Institute of Diabetes and Digestive and Kidney Diseases [NIDDK], "End-Stage," 2000). Chronic renal failure (CRF) affects more than 250,000 people in the United States each year. In older Americans, the primary causes of CRF are diabetes and hypertension, two of the leading chronic conditions affecting the elderly. Its course is irreversible and eventually leads to end-stage renal disease (ESRD) (Ford-Martin, 1999).

According to the U.S. Renal Data System (USRDS), the elderly represent the fastest growing age group suffering from ESRD. There were 40,000 new cases of ESRD in 1997, and the median age of new cases is 65 years. From 1992 to 1996, the prevalence of treated elderly ESRD patients increased approximately 9 percent, and in 1997 more than 105,000 people were living with the disease. Mortality rates during the first year of ESRD dialysis treatment were 30 percent among people aged 65 to 74 and 46 percent among those aged 75 and over. Average survival time for ESRD patients aged 65 and over ranges from two to four years, although overall survival time has increased in the past decade because of changes in treatment methods and new products (USRDS, 1999; NIDDK, "End-Stage," 2000).

The vast majority of elderly patients with ESRD receive treatment via hemodialysis, a procedure that cleans and filters the blood, typically performed at a dialysis center three times a week for two to four hours (USRDS, 1999; NIDDK, "End-Stage," 2000). Although dialysis has helped patients live longer with ESRD, problems such as bone disease, high blood pressure, nerve damage and anemia can occur. Most patients undergoing dialysis develop anemia as a result of insufficient levels of erythropoietin (EPO), a glycoprotein needed to stimulate production of red blood cells. This deficiency contributes to illness and death among ESRD patients (Adamson, 1998).

QoL varies widely among ESRD patients. Based on studies using the Medical Outcomes Study Standard Form Health Survey (SF-36), overall QoL is substantially lower in the ESRD population than in the general population, namely in terms of physical functioning and well-being. In addition, perceptions of QoL differ considerably among patients, caregivers and physicians (Beusterien, 1996; Molzahn, 1997; Parsons, 1997; USRDS, 1999).

ESRD is estimated to cost $16 billion per year in direct medical costs (including predialysis, dialysis and transplantation patients). Medicare alone spent more than $12 billion (USRDS, 1999). The annual per-patient cost to treat an elderly ESRD patient is estimated at $52,000 to $57,000, the majority of which is spent on institutional services such as hospitalization and nursing home and hospice care (USRDS, 1999).

Impact of Current Biotechnology Products

EPOGEN®/PROCRIT® (RECOMBINANT HUMAN ERYTHROPOIETIN [RHUEPO])

Since 1989, rHuEPO (also called epoetin alfa), a landmark biotech product, has been used in the treatment of anemia in CRF patients (including predialysis and dialysis patients). Erythropoietin is a glycoprotein produced in the kidney that stimulates red blood cell division. Marketed by Amgen Inc. as Epogen and by Ortho Biotech Inc. as Procrit. Key points regarding rHuEPO are as follows:

- **Significant increase in hematocrit contributes to improvement in patient survival:** According to the USRDS, mean hematocrit (red blood cells as a percentage of total blood volume) for rHuEPO-treated patients with ESRD increased from 30.1 percent in 1993 to 32.4 percent by the end of 1997. (Treatment guidelines recommend a hematocrit target range of 33 to 36 percent.) Associated benefits of increased hematocrit include avoidance of transfusions and improvements in cardiovascular functioning, QoL and patient survival (USRDS, 1999; NKF-DOQI, 1997). A study conducted by Harnett et al. (1995) demonstrated a direct link between higher hematocrit and improvements in patient survival, in that a one-unit decrease in hemoglobin increased the relative risk of mortality by 18 percent (Cohen, 1997).

- **Improvement in QoL:** A common morbidity associated with ESRD is impaired cognitive function. Cognitive impairment can hinder a patient's ability to live well or to work well with his or her medical management team. A combination of adequate dialysis with the correction of anemia with rHuEPO can mitigate the neurobehavioral syndrome associated with ESRD, leading to improved cognition. The patient is then more apt to receive *and* apply ongoing, positive reinforcement techniques of treatment goals and outcomes to improve overall quality of life. Clinical trials with rHuEPO therapy have demonstrated not only significant improvements in hematocrit levels and thus survival, but also overall improvements in QoL (Trenkle, 1998; Beusterien, 1996). Using the SF-36, significant improvements in assessments of energy, physical functioning, social functioning, mental health and other domains were found in patients treated with rHuEPO (Beusterien, 1996; Revicki, 1995).

- **Reduced need for blood transfusions and associated costs:** rHuEPO reduces the need for blood transfusions, thus avoiding the costs of transfusion and potential complications (e.g., hepatitis B) and contributing to overall reductions in hospitalization rates and improved productivity (Harris, 1994; Shih, 1999).

RENAGEL® CAPSULES (SEVELAMER HYDROCHLORIDE)

Renagel, developed by GelTex Pharmaceuticals, Inc. and approved in November 1998, is a phosphate binder used to decrease serum phosphorus concentrations in ESRD patients, ultimately to prevent bone disease. Key aspects of Renagel include:

- **Reduced hospitalization and associated costs.** Preliminary studies show that Renagel results in an overall reduction in the number of hospitalizations and in overall cost savings. Hospitalization costs for Renagel-treated patients were approximately $4,400 compared with an estimated $5,900 for the standard of care (*The Pink Sheet*, "Pathogenesis tobi," 2000).

ORTHOCLONE OKT®3 (MUROMONAB-CD3)

Orthoclone OKT3, developed by Ortho Biotech, was approved in June 1986 for reversal of acute kidney transplant rejection. A typical course of this therapy costs approximately $3,000 to $7,200 (*Patient Care,* 1999). Key results for OKT3 are as follows:

- **Reduced number of kidney rejection episodes and associated costs.** Studies show that the cost is offset by a reduction in the number of kidney rejection episodes, thereby reducing the overall cost of treating rejection episodes. Five-year follow-up costs of graft survival are estimated to be $30,474 in the OKT3-treated group vs. $32,687 in the conventionally treated group (Shield, 1996; Woodle, 1996).

SIMULECT® (BASILIXIMAB)

Simulect, developed by Novartis Pharmaceuticals Corp., is indicated for the prevention of acute rejection episodes in kidney transplant recipients. Approved in May 1998, Simulect has demonstrated that it significantly decreases the incidence of transplant rejection episodes, based on clinical trial data. Specific highlights of Simulect are as follows:

- **Reduction in number of kidney rejection episodes and associated costs.** According to a Novartis/Lewin Group economic analysis, Simulect would lead to an overall first-year medical cost savings of $5,762 (not including drug acquisition costs). Rejection treatment costs would be reduced by $1,080 (*The Pink Sheet,* 1998).

ZENAPAX® (DACLIZUMAB)

Zenapax, developed by Hoffmann-La Roche Inc., was approved by the FDA in December 1997 for the prevention of acute rejection in renal transplant recipients. Results from a Phase III clinical trial demonstrated that Zenapax reduced the incidence of rejection following kidney transplantation and was associated with better survival:

- **Reduced incidence of kidney transplant rejection and improved survival.** The American Society of Nephrology (ASN) presented new findings for Zenapax based on Phase III clinical trials. Results from two of these trials demonstrated that the incidence of kidney transplant rejection was reduced and the overall survival rate among patients treated with Zenapax® was higher (94 percent and 96 percent, respectively) compared with non-Zenapax treated patients (91 percent and 88 percent, respectively) (*Transplant Weekly,* 1999).

The Promise of Future Biotechnology Products

NOVEL ERYTHROPOIESIS STIMULATING PROTEIN (NESP)

In December 1999, Amgen filed for FDA approval of a new drug called NESP for anemia in CRF and other diseases. Based on clinical trial evidence, NESP has a longer half-life than EPO and will likely allow for less frequent dosing in patients treated for anemia (Macdougall, 1999). A Phase III clinical trial compared NESP with rHuEPO in 522 patients receiving hemodialysis and peritoneal dialysis (in Europe and Australia). The results demonstrated that NESP was as effective as rHuEPO when administered one to three times per week (97 percent and 95 percent were successfully managed with once weekly and once every two week dosing with NESP, respectively) (*R&D Focus Drug News,* 1999). According to Amgen, NESP would be indicated for CRF patients on dialysis as well as patients with chronic renal insufficiency (CRI, or pre-dialysis CRF). The company is conducting Phase II trials of NESP in oncology (*Pharmaceutical Approvals Monthly*, "Clinical trial," 1999).

> *"The results are very significant.… They basically show that one can manage hemoglobin levels of people with chronic renal failure at the same level as they do with EPO or epoetin alfa, but then can do so by dosing NESP once every week and, in some cases, once every two weeks, as opposed to three times a week of EPO"* (Pihl-Carey, 1999).

OSTEOGENIC PROTEIN-1 (OP-1)

Creative BioMolecules, Inc., has provided the FDA with preclinical data that indicates that the administration of OP-1 offers clinical advantages over the current standard of care for patients with CRI. OP-1 is a multifunctional protein that regulates the development of several tissues, including bone, eye and kidney tissue. The study indicated that OP-1 reduced scar tissue formation, reduced tubular damage to the kidneys and preserved renal function. The study has recently been presented at the Annual Meeting of the American Society of Nephrology (*BioSpace News,* 1999).

ADVANCED DIALYSIS TECHNOLOGY

Vasca, Inc., has demonstrated to the FDA the features of its novel dialysis treatment LifeSite®. This technology represents the first major advance in dialysis treatment in nearly a decade. The two currently available dialysis methods, hemodialysis and peritoneal dialysis, can be problematic due to high infection rates (which results from the obtrusive nature of the procedures), clotting problems and eventual site and vein access limitations. The LifeSite Dialysis Access System, which is implanted just beneath the patient's skin, has been designed to minimize access problems and reduce the risk of infection. The LifeSite® System is available throughout Europe and Canada and currently investigational in the United States (Vasca, 2000). Gerald Beathard, MD, PhD, clinical professor, Louisiana State University Medical Center and the University of Texas Health Sciences Center, said:

> *"We can now contribute to better dialysis with LifeSite. Our patients feel better, experience fewer complications and have an improved quality of life."*

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Table 1: Disease Overview for the Elderly — Chronic Renal Failure

Disease Category	Chronic Renal Failure
Epidemiology	**Incidence:** ESRD: 39,980 (aged 65+) (1997) **Prevalence:** CRF: 250,000 (all ages) ESRD: 104,720 (aged 65+) (1997) **Mortality:** ESRD: 57,793 (aged 65+) (1997); 30–46% in first year and overall 3- to 5-year survival (aged 65+) (1997)
Total Cost of Illness	**Total cost (ESRD):** $16 billion (all payers); $12 billion (Medicare only) (1997)
Direct / Indirect Costs	**Total per-patient ESRD:** $52,000–$57,000 (aged 65+, Medicare payments, 1997)
QoL / Functional Status	Lower functional status and well-being (SF-36) (Beusterien, 1999); SASS rating: 6.37 (6.6 general population); IWB rating: 10.03 (11.77 general population); TTO rating: 0.61 (scale of 0 to 1, 0=death) (Molzahn, 1997)
Comments	**Sources:** Beusterien, 1999; Molzahn, 1997; NIDDK, "Kidney," 2000; USRDS, 1999

CRF: Chronic renal failure
ESRD: End-stage renal disease
IWB: Index of well-being
NIDDK: National Institute of Diabetes and Digestive and Kidney Diseases
SASS: Self-Anchoring Striving Scale
SF-36: Short form health survey
TTO: Time trade-off
USRDS: U.S. Renal Data System

Table 2: Current Biotechnology Products for the Elderly — Chronic Renal Failure

Product on Market	Relevant Indication(s)	Company	Approval Dates	Class	Mechanism of Action	Route of Administration	Dosing
Epogen® (epoetin alfa)	Anemia in CRF; anemia in cancer patients on chemotherapy; anemia in HIV+ patients	Amgen	June 1989; July 1999	rDNA	Stimulates red blood cell production; produced in the kidney and stimulates the division and differentiation of committed erythroid progenitors in the bone marrow	IV; SC	Based on body weight; 50–100 units/kg TIW; average dose is 5,383 units (1997)
Procrit® (epoetin alfa)	See Epogen	J&J / Ortho Biotech	December 1990; April 1993; December 1996	See Epogen	See Epogen	See Epogen	See Epogen
Renagel® Capsules (sevelamer hydrochloride)	ESRD	GelTex Pharmaceuticals / Genzyme	November 1998	Phosphate binder	Inhibits intestinal phosphate absorption	Oral	2 to 4 capsules, TID; 403 mg/capsule
Orthoclone OKT®3 (Muromonab-CD3)	Acute allograft rejection in renal transplant patients	Ortho Biotech	June 1986	Monoclonal antibody	Blocks the CD3 molecule in the membrane of T cells	Bolus IV	5 mg in 5 mL bolus per day for 10–14 days (adults)
Simulect® (basiliximab)	Kidney transplant rejection	Novartis / Ligand	May 1998	IL-2 receptor antagonist	IL-2 receptor antagonist binds with high affinity to the alpha chain of the high affinity IL-2 receptor complex, inhibiting IL-2 binding	IV	20 mg, two doses (adults) over 4 days
Zenapax® (Daclizumab)	Prophylaxis of acute organ rejection in patients receiving renal transplants	Hoffmann-La Roche	December 1997	IL-2 receptor antagonist	IL-2 receptor antagonist binds with high affinity to the alpha chain of the high affinity IL-2 receptor complex, inhibiting IL-2 binding	IV	1 mg/kg, five doses over 14-day intervals

Table 2: Current Biotechnology Products for the Elderly — Chronic Renal Failure (continued)

Product on Market	Impact on Mortality and Morbidity	Impact on Costs	Impact on QoL (Patient / Caregiver)	Comments
Epogen® (epoetin alfa)	Trials have indicated that a higher hematocrit was correlated with improved patient survival; significant increase in hematocrit in 95% of patients with CRF, reduction in mean number of blood transfusions in CRF and cancer patients undergoing chemotherapy; results vary by patient status (dialysis vs. nondialysis patients)	$20,314 for epoetin vs. $14,142 for transfusion therapy in hemodialysis patient with ESRD	Significant improvement in QoL domains of the SF-36: energy, physical function, activity level, functional ability, disease symptoms, social activity, health status	Amgen, *1999 Annual Report,* Amgen, *Epogen package insert,* 1999; *Drug Topics Red Book,* 1999; Greer, 1999; Revicki, 1995; Shih, 1999
Procrit® (epoetin alfa)	See Epogen	$20,314 for epoetin vs. $14,142 for transfusion therapy in hemodialysis patient with ESRD	See Epogen	*Drug Topics Red Book,* 1999; Johnson and Johnson, 1999; Ortho Biotech, 1990; Shih, 1999
Renagel® Capsules (sevelamer hydrochloride)	Reduction in phosphorus levels, parathyroid hormone levels; lower calcium x phosphorus levels; lower total- and LDL-cholesterol levels; no impact on HDL-cholesterol and triglyceride levels	Overall reduction in number of hospitalizations; hospitalization costs were $4,432 vs. $5,866 for SOC		Genzyme, 1998; *Pharmaceutical Approvals Monthly*, "GelTex," 1999; *The Pink Sheet,* "Pathogenesis tobi," 2000
Orthoclone OKT®3 (Muromonab-CD3)	Patient survival was not significantly different between groups; reversed 94% of rejections compared with 75% with steroid treatment; graft survival rates were 62% and 45% for OKT3 and steroid-treated patients, respectively	OKT3 adds $8,219 to transplant hospitalization costs, but is offset by a reduction in the cost of treating rejection episodes; 5-year follow-up cost of $30,474 with OKT3 vs. $32,687 with SOC		*Patient Care,* 1999; Shield, 1996

Table 2: Current Biotechnology Products for the Elderly — Chronic Renal Failure (continued)

Product on Market	Impact on Mortality and Morbidity	Impact on Costs	Impact on QoL (Patient / Caregiver)	Comments
Simulect® (basiliximab)	No difference in patient survival; significantly lower incidence of rejections at 6- and 12-month post-transplantation	Anticipated overall first-year medical cost savings of $5,762 (not including cost of drug); anticipated reduction in rejection treatment costs of $1,080		*The Pink Sheet,* 1998
Zenapax® (Daclizumab)	Survival rates for Zenapax vs. SOC in two trials were 94% vs. 91% and 96% vs. 88%, respectively; incidence of acute rejection at 6 months and 1 year reduced vs. placebo (p=0.001)			*Patient Care,* 1999*; The Pink Sheet,* 1998; *The Pink Sheet*, "Protein design labs," 2000; *Transplant Weekly*, 1999

CRF: Chronic renal failure
EPO: Epogen
ESRD: End-stage renal disease
HDL: High-density lipoprotein
HIV(+): Human immunodeficiency virus (positive)
IL-2: Interleukine-2
IV: Intravenous
LDL: Low-density lipoprotein
QoL: Quality of life
rDNA: Recombinant deoxyribonucleic acid
rHuEPO: Recombinant human erythropoietin
SF-36: Short form health survey
SC: Subcutaneous
SOC: Standard of care
TID: Two times a day
TIW: Three times a week
U: Units

Table 3: Biotechnology Pipeline Products for the Elderly — Chronic Renal Failure

Pipeline Product	Phase / Date Submitted	Company	Therapeutic Area	Class	Indication	Mechanism of Action	Route of Admin. / Dosing
LifeSite®	Investigational	Vasca	Genitourinary	Novel dialysis treatment (implant)	Dialysis		Implant (just beneath patient skin)
NESP	NDA submitted December 1999	Amgen / Kirin Brewery	Genitourinary	NESP	Anemia in CRF patients on dialysis / predialysis patients	Stimulates red blood cell production	IV; SC
NESP	Phase II January 2000	Amgen	Cancer	NESP	Miscellaneous cancers	Stimulates red blood cell production	IV; SC
Osteogenic Protein-1 (OP1)	Phase I	Creative BioMolecules	Genitourinary	Multifunctional protein	Chronic renal insufficiency		

Pipeline Product	Impact on Mortality and Morbidity	Impact on Costs	Impact on QoL (Patient / Caregiver)	Comments
LifeSite®				
NESP	Mean hemoglobin level was -0.03 g/dL for NESP vs. -0.06 g/dL for rHuEPO; 97% and 95% of NESP patients treated once weekly and once every other week were successfully managed			*BioWorld Today,* 1999; *Pharmaceutical Approvals Monthly*, "Clinical trial," 1999
NESP				*R&D Focus Drug News,* 1999; *The Pink Sheet*, "Amgen", 2000
Osteogenic Protein-1 (OP1)	Reduced scar tissue formation and tubular damage to the kidneys and preserved renal function			*BioSpace News,* 1999

CRF: Chronic renal failure
IV: Intravenous
NESP: Novel erythropoiesis stimulating protein
rHuEPO: Recombinant human erythropoietin
SC: Subcutaneous

D. Coronary Heart Disease

Overview

Coronary heart disease (CHD) is a collective term that encompasses the clinical syndromes associated with acute myocardial infarction (heart attack, or MI), ischemic heart disease (atherosclerosis), angina pectoris (chest pain associated with those conditions) and acute coronary syndrome (ACS — unstable angina or non-Q-wave MI). In 1997, CHD accounted for approximately 466,000 of the more than 2 million deaths in the United States, representing one of every five deaths (all causes). According to the Atherosclerosis Risk in Communities (ARIC) study conducted by the National Heart, Lung and Blood Institute (NHLBI), an American suffers a coronary event about every 29 seconds, and about every minute someone dies from one. An estimated 1.1 million Americans will suffer a new or recurrent coronary event this year, and of these, more than 40 percent will be fatal (AHA, 2000).

While the death rate and the actual number of deaths from CHD are declining (27.7 percent and 9 percent, respectively, from 1987 to 1997), 84.9 percent of people who die from CHD are aged 65 or older. The estimated lifetime risk for developing CHD is high: Even at age 70, one of every three men and one of every four women will develop CHD in their remaining years of life (Lloyd-Jones, 1999). Age is one of the most important nonmodifiable risk factors for developing CHD (others include heredity and male gender). Additionally, hypertension — the most prevalent chronic medical condition affecting the adult population — is a well-established risk factor for the development of CHD. The incidence of hypertension increases with advancing age: 57.3 percent of men and 60.8 percent of women aged 65–74, and 64.2 percent of men and 77.3 percent of women aged 75 and older have high blood pressure, according to the National Health and Nutrition Examination Study III (NHANES III, 1988-94) (AHA, 2000). Hypertension generally doubles the risk of cardiovascular disease (AHA, 2000), which includes blood vessels in other parts of the body as well as the heart.

It is estimated that direct and indirect costs to treat CHD will total $118.2 billion this year. More than $10 billion was paid to Medicare beneficiaries alone in 1996 (AHA, 2000). Nearly 70 percent of all patients who suffer a coronary event will fail medical therapy and require revascularization procedures in order to survive. These procedures include coronary artery bypass graft (CABG) for patients who have suffered cardiac arrest and percutaneous transluminal coronary angioplasty (PTCA) for patients with uncontrolled and unstable angina (AHA, 2000). These expensive surgical interventions are the primary drivers of the high cost of treating CHD. Currently, researchers in the biotechnology field are developing products that can be used to replace or reduce the need for these high-cost procedures, or to refine current intervention technologies to decrease the risk of bleeding, the occurrence of re-infarction and the need for repeat surgeries.

Impact of Current Biotechnology Products

REOPRO® (ABCIXIMAB)

ReoPro, developed by Eli Lilly and Company and Centocor, Inc., is a genetically engineered fragment of a monoclonal immunoglobulin antibody. The drug selectively binds to glycoprotein platelet (GP IIb/IIIa) receptors and inhibits platelet aggregation; it is used with heparin and aspirin as an adjunct to PTCA. Clinical trial data have demonstrated:

- **A reduction in mortality, myocardial infarction and the need for urgent intervention.** In the Evaluation of c7E3 to Prevent Ischemic Complications (EPIC) trial, patients undergoing PTCA who were considered at high risk for abrupt closure of the treated coronary vessel were randomized to receive ReoPro or placebo. The results of the study demonstrated a 4.5 percent lower incidence of the primary endpoints studied (death, MI and emergency intervention) in patients treated with ReoPro (Lefkovits, 1996).

- **Improvement in long-term outcomes.** In the EPILOG trial (Evaluation in PTCA to Improve Long-Term Outcome with Abciximab GP IIb/IIIa Blockade), a broad population of patients undergoing PTCA were randomized to receive placebo or ReoPro plus standard-dose or low-dose weight-adjusted heparin. The incidence of death or MI within 30 days was lower in both ReoPro groups (4.2 percent and 3.8 percent in the standard- and low-dose heparin groups, respectively) versus 9.1 percent in the placebo group, who had received either low-dose or standard-dose heparin only (Roe, 1998).

- **A reduction in mortality in patients with unstable angina.** Data from the CAPTURE trial (C7E3 Anti-Platelet Therapy in Unstable Refractory Angina) indicated that the incidence of primary coronary events was reduced when ReoPro was used in this patient population (11.3 percent versus 15.9 percent in the placebo group). Results from the trial also demonstrated a lower incidence of major bleeding in patients treated with ReoPro. These results could contribute to a reduction in overall treatment costs by lowering costs for treating complications (Ellis, 1998).

RETAVASE® (RETEPLASE) AND ACTIVASE® (ALTEPLASE)

Produced by Boehringer Mannheim, Inc. and Centocor, Inc. using recombinant DNA technology, Retavase is a tissue plasminogen activator (tPA) that catalyzes plasminogen to generate plasmin. Plasmin in turn degrades the fibrin matrix of a thrombus (blood clot), thereby exerting its thrombolytic ("clot-busting") action. Retavase is indicated for management of acute MI (AMI), improvement of ventricular function following AMI, reduction of the incidence of congestive heart failure and reduction of mortality associated with AMI (*Health News Daily*, 1996).

Activase, developed by Genentech, Inc., is also a tPA of recombinant DNA origin that exerts its thrombolytic activity much like that of ReoPro. Activase is currently FDA-approved for MI, the prevention of reocclusion after thrombolysis for AMI, for acute pulmonary embolism and for acute ischemic stroke (McEvoy, 2000).

INTEGRILIN® (EPTIFIBATIDE)

Developed by Schering Plough Corporation and COR Therapeutics, Inc. as another antagonist of the glycoprotein platelet (GP IIb/IIIa) receptor, Integrilin prevents fibrinogen and other adhesion ligands from binding to the glycoprotein receptor, thereby inhibiting platelet aggregation. Inhibition persists as long as the drug is being administered and is reversible after infusion stops (thereby permitting platelet aggregation to resume). Integrilin is indicated for the treatment of patients with ACS, including patients who are medically managed and those undergoing PTCA. In this setting, Integrilin decreased the rate at which patients died, suffered a new MI or needed urgent care (*The Pink Sheet*, "Schering/Cor," 1998; *The Pink Sheet*, "Schering/Cor's Integrilin," 1999; *Biotechnology Newswatch*, 2000).

The Promise of Future Biotechnology Products

ANGIOMAX™ (BIVALIRUDIN)

Angiomax, developed by The Medicines Company, is a new intravenous anticoagulant drug that will be useful in coronary intervention procedures. Produced by recombinant technology, this exclusive drug is a potent and direct inhibitor of thrombin, a key component in blood clot formation. The only available alternative, heparin, affects clot formation through several clotting factors (thereby increasing the risk of bleeding) and lacks binding affinity and specificity for thrombin. This advantage gives Angiomax a variety of potential uses as an alternative to heparin in the management of cardiovascular disease and surgical procedures.

- **Potential reduction in hemorrhage, infarction and mortality.** A Phase III trial involving 5,674 patients either undergoing elective coronary revascularization procedures or experiencing ACS has shown that Angiomax was associated with a significant reduction in the risk of hemorrhage (58 fewer events per 1,000 patients treated) and in death or infarction (14 fewer deaths per 1,000 patients treated) (*Blood Weekly,* 2000).

The Medicines Company has recently initiated a Phase II trial using Angiomax in patients who experienced heparin-induced thrombocytopenia (HIT) and heparin-induced thrombocytopenia and thrombosis syndrome (HITTS) after undergoing angioplasty. HIT and HITTS are two severe adverse reactions to heparin involving a decrease in the number of platelets. Successful completion of this study would make Angiomax the only approved anticoagulant for this patient population and would give the drug its third clinical indication (*Blood Weekly,* 1999).

CROMAFIBAN

Cromafiban is an oral glycoprotein IIb/IIIa inhibitor under development by COR Therapeutics. Phase II clinical studies have shown that cromafiban achieved predictable and consistent levels of platelet aggregation inhibition (PAI), potentially providing clinical usefulness in the prevention of MI and ischemic events (*R&D Focus Drug News*, 1999). Little variability between peak and trough levels of PAI, coupled with the possibility of once-daily dosing, remarkably distinguishes cromafiban from other currently available, shorter-acting compounds with PAI activity. Multiple Phase II clinical studies of cromafiban are under way, and the Phase III program is slated to begin in the second half of 2000 (*Business Wire,* 1999).

TNKase™ (Tenecteplase) and Lanoteplase (nPA)

Genentech is working to put a new formulation of its tPA Activase® on the drug market. Its new drug, TNKase, represents the first thrombolytic agent that can be administered as a single injection, enhancing its potential usefulness in emergency and transport situations and in other scenarios outside of the hospital setting. Results from the ASSENT-2 (Assessment of the Safety and Efficacy of a New Thrombolytic) study in which 16,950 heart attack patients received tPA or the modified form TNK are promising: "The primary outcome was 30-day mortality. The mortality rates at 30 days were almost identical — at about 6.2 percent — in the two groups" (Wysong, 1999).

Additional advantages of single-bolus dosing include the ease of storage, reconstitution and administration of the drug for health-care providers who work in intense and emergent patient environments. These benefits improve access to therapy for heart attack patients.

A similar genetically engineered thrombolytic agent is being developed by Bristol Myers Squibb Inc. Lanoteplase, a third-generation plasminogen activator (nPA), is also being designed to have a prolonged half-life, an increased specificity for fibrin (the primary component in intracoronary clots) and increased resistance to proteins that can interfere with clot-dissolving effects. Results from a Phase III trial called TIME-II (Intravenous nPA for Treatment of Infarcting Myocardium Early) were comparable to the results of the ASSENT-2 study. Preliminary results comparing 15,000 patients randomized to receive either lanoteplase or tPA showed that all-cause mortality rates at 30 days were similar between the two groups. The possibility of single-bolus thrombolytic therapy not only facilitates better access to therapy for AMI patients, but should also result in fewer dosing errors (McCann, 1999).

Other Potential Advanced Therapies in the Treatment of CHD

While most therapeutic treatments now under investigation for treating CHD are directed toward improving coronary blood flow with antiplatelet and clot-dissolving agents, increasingly prominent findings support the research and development of drugs that treat the disease through alternative biological mechanisms. Clinical literature demonstrates that the effects of ACS may be partly attributed to severe and injurious inflammatory response. Alexion Pharmaceuticals, Inc., has developed two humanized monoclonal antibodies, 5G1.1 and 5G1.1-SC (fragmented antibody), that specifically block the production of harmful proteins that trigger inflammatory response. This breakthrough may provide a significant therapeutic alternative to, or a synergistic relationship with, existing CHD therapies (Kinlay, 1998).

Researchers have found that arterial stiffening with advancing age plays a major role in cardiovascular disease. Alteon Inc. has initiated a Phase IIa clinical trial involving its novel therapeutic agent ALT-711. This compound has demonstrated the potential to reverse aging of the cardiovascular system by cleaving pathological protein-glucose structures called Advanced Glycosylation End-product (A.G.E.) Cross-links. The aging process has been attributed in part to these cross-links. A safe drug with the ability to prevent or reduce arterial stiffening in humans would likely have substantial implications for the morbidity and mortality of heart disease (Sebastian, 1999).

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Table 1: Disease Overview for the Elderly — Coronary Heart Disease

Disease Category	Coronary Heart Disease
Epidemiology	**Incidence:** CHD: 1 coronary event every 29 seconds and 1 fatal event every minute; MI: AMI occurs in about 2 in 1,000 people per year; Angina: 350,000 per year **Prevalence:** CHD: 12.2 million; MI: 7.2 million; Angina: 6.3 million **Mortality:** CHD: 466,101 deaths (1997), causes 1 of every 5 deaths (1997), 84.9% aged 65+; AMI is the most common cause of death in the U.S., 1.1 million new and recurrent cases of coronary attack per year, 25% of men and 38% of women die within 1 year; Angina: Very low mortality rate (rate included in CHD)
Total Cost of Illness	**Total cost (CHD):** $118.2 billion (2000) **Medicare:** $10.5 billion (1996) **Per patient (average for coronary event):** $22,720 (1996) (patients under 65 years of age)
Direct / Indirect Costs	**Direct:** $55.2 billion **Indirect:** $63 billion **Hospital/nursing home:** $42 billion **Physicians:** $8.1 billion **Drugs:** $3.5 billion **Home health / durables:** $1.6 billion
QoL / Functional Status	CHD is the leading cause of premature, permanent disability in the U.S. labor force
Comments	**Source:** AHA, 2000

AHA: American Heart Association
AMI: Acute myocardial infarction
CHD: Coronary heart disease, including acute myocardial infarction, other acute and subacute forms of ischemic (coronary) heart disease, old MI, angina pectoris and other forms of chronic, ischemic heart disease
MI: Myocardial infarction

Table 2: Current Biotechnology Products for the Elderly — Coronary Heart Disease

Product on Market	Relevant Indication(s)	Company	Approval Dates	Class	Mechanism of Action	Route of Administration	Dosing
ReoPro® (abciximab)	Clotting complications of coronary disease; PCI; UA	Centocor / Eli Lilly	December 1994; December 1997	GP IIb/IIIa inhibitor	Inhibits platelet aggregation	IV	Adult dosage is a 0.25 mg/kg IV bolus administered 10–60 minutes before the start of PCI, followed by continuous IV infusion (0.125 mg/kg/min up to 10 mg/min for 12 hours).
Retavase® (reteplase)	AMI	Boehringer Mannheim / Centocor	October 1996	Reteplase recombinant plasminogen activator	Thrombolytic; converts plasminogen to plasmin	IV Bolus	Double bolus dosing (within 30 minutes)
Activase® (alteplase)	AMI; pulmonary embolism; acute ischemic stroke	Genentech	November 1987; June 1990; June 1996	Recombinant tissue plasminogen activator	Dissolves blood clots	IV	0.9 mg/kg infused over 60 minutes, with 10% administered as IV bolus over 1 minute
Integrilin® (eptifibatide)	ACS; Angioplasty	COR Therapeutics / Schering-Plough	May 1998; September 1999	GP IIb/IIIa inhibitor	Blocks receptors, known as GP IIb/IIIa, on platelets that are responsible for thrombus development	IV	ACS: 180 mcg/kg IV bolus followed by 2 mcg/kg/min (72 hrs); PCI patients (no ACS): 135 mcg/kg bolus before PCI followed by 0.5 mcg/kg/min for 20–24 hrs

Table 2: Current Biotechnology Products for the Elderly — Coronary Heart Disease (continued)

Product on Market	Impact on Mortality and Morbidity	Impact on Costs	Impact on QoL (Patient / Caregiver)	Comments
ReoPro® (abciximab)	Prevented 1 death per MI per 23 treated patients, compared with 1 death per MI per 38 treated patients for tirofiban and 1 death per MI per 67 treated patients for eptifibatide; ReoPro with J&J's Palmaz-Schatz stent reduced mortality by 58% (EPISTENT); AMI patients receiving PTCA, stent and ReoPro experienced a 47% reduction in risk for death, repeat MI or urgent revascularization compared with PTCA and stents alone (30 days) (ADMIRAL)	Shown to be cost-effective in patients receiving the drug along with coronary stents and in certain patients at high risk of ischemic complications (AMI and UA)		Dunn, 1999; *The Gray Sheet,* 1999; *The Pink Sheet,* "GP IIb/IIIa," 1999
Retavase® (reteplase)	Selected outcomes of 35-day mortality, 6-month mortality and combined outcome of 35-day mortality or nonfatal stroke was less with reteplase patients when compared with streptokinase; significantly less congestive heart failure, atrial fibrillation, asystole, cardiogenic shock and hypotension than streptokinase (INJECT); complete patency compared with alteplase (60% vs. 45%) in RAPID II	Cost per year of life saved estimated at $14,438; shown to be effective when compared with other benchmark cost data such as CABG ($26,000); cholesterol-lowering treatment ($154,000)		*Health News Daily,* 1996

Table 2: Current Biotechnology Products for the Elderly — Coronary Heart Disease (continued)

Product on Market	Impact on Mortality and Morbidity	Impact on Costs	Impact on QoL (Patient / Caregiver)	Comments
Activase® (alteplase)	26% reduction in mortality (9.8% placebo vs. 7.2% alteplase) (ASSET); significant increase in survival in post-AMI patients undergoing coronary artery angiography (4.4% vs. 8.9% 30-day mortality) (GUSTO-I); decreased overall incidence of bleeding complications, alteplase vs. streptokinase and heparin	Cost per year of life saved estimated at $32,768 for tPA		Genentech, 1999; Genentech, 2000
Integrilin® (eptifibatide)	In ACS, cut incidence of death per MI from 15.7% to 14.2% (30 days) compared with placebo (PURSUIT); death from any cause or new MI reduced from 13.6% with placebo to 12.1% with etifibatide in patients followed for 165+ days; reduced need for urgent intervention (IMPACT II); in PCI, reduced composite endpoint of death per MI per urgent repeat intervention from 11.6% to 9.1% (30 days) (IMPACT II)			*The Pink Sheet,* "Schering/Cor," 1998; *The Pink Sheet,* "Schering/Cor's Integrilin," 1999; *Biotechnology Newswatch*, 2000

ACS: Acute coronary syndrome
ADMIRAL: Abciximab Before Direct Angioplasty and Stenting in Myocardial Infarction Regarding Acute and Long-Term Follow-up trial
AMI: Acute myocardial infarction
ASSET: Anglo-Scandinavian Study of Early Thrombolysis
CABG: Coronary artery bypass graft
EPISTENT: Evaluation of IIb/IIIa Platelet Inhibitor for Stenting
GP IIb-IIIa: Glycoprotein protein IIb-IIIa inhibitor
HND: FDC Reports, *Health News Daily*
IMPACT: Integrilin to Manage Platelet Aggregation to Combat Thrombosis
INJECT: International Joint Efficacy Comparison of Thrombolytics trial
IV: Intravenous
MI: Myocardial infarction
PCI: Percutaneous coronary intervention
PTCA: Percutaneous transluminal coronary angioplasty
PURSUIT: Platelet IIb/IIIa Underpinning the Receptor for Suppression of Unstable Ischemia Trial
RAPID II: Reteplase and Alteplase Patency Investigation during Myocardial Infarction trial
TGS: FDC Reports, *The Gray Sheet*
tPA: Tissue plasminogen activator
UA: Unstable angina

Table 3: Biotechnology Pipeline Products for the Elderly — Coronary Heart Disease

Pipeline Product	Phase / Date Submitted	Company	Therapeutic Area	Class	Indication	Mechanism of Action	Route of Admin. / Dosing
TNKase™ (tenecteplase)	Phase III (ASSENT-II)	Genentech / Boeringer Ingelheim	CHD	tPA	ACS; AMI	Thrombolytic ("clot-buster")	IV
Integrilin® (eptifibatide)	Phase II (INTEGRETI)	COR Therapeutics / Genentech	CHD	PAI	AMI	GP IIb/IIIa inhibitor	IV bolus followed by continuous infusion
5G1.1-SC	Phase IIb	Alexion Pharmaceuticals	Circulatory	Monoclonal antibody anti-inflammatory	ACS	Blocks inflammatory responses that occur during ACS	IV
ALT-711	Phase II	Alteon	Circulatory	A.G.E. cross-link breaker / alpha dione cleaving agent	Cardiovascular disease	Reverses glucose-protein cross-links after they have formed	Oral
Angiomax™ (bivalirudin) (formerly Hirulog)	Phase II (HIT/HITTS); Phase III (AMI and PTCA)	Biogen / The Medicines Company, Inc.	Circulatory	Anticoagulant	HIT/HITTS; PTCA	Direct thrombin inhibition	IV; weight-based dosing
Lanoteplase	Phase III (TIME-II)	BMS	Circulatory	3rd-generation plasminogen activator	AMI	Thrombolytic ("clot-buster")	IV
Cromafiban	Phase II	COR Therapeutics / Lilly	Circulatory	GP IIb-IIIa PAI	UA, angioplasty, AMI and stroke	PAI	Oral; once-daily dosing

Table 3: Biotechnology Pipeline Products for the Elderly — Coronary Heart Disease (continued)

Pipeline Product	Impact on Mortality and Morbidity	Impact On Costs	Impact on QoL (Patient / Caregiver)	Comments
TNKase™ (tenecteplase	TPA vs. TNK: 30-day mortality identical in each group — 6.2% of 16,950 heart attack patients (ASSENT-II); formulation enhances usefulness in emergency and transport situations; increases patient access to treatment			Single bolus affords ease of storage and administration; additional benefit to health-care workers (Wysong, 1999)
Integrilin® (eptifibatide)	INTEGRETI study is ongoing			
5G1.1-SC	Research in preclinical stage			Kinlay, 1998
ALT-711	Phase II trial demonstrated potential to reverse aging of the cardiovasculature, resulting in substantial potential implications in morbidity and mortality			Sebastian, 1999
Angiomax™ (bivalirudin)	Fewer deaths and re-infarctions demonstrated in Phase III trials (14 fewer per 1,000 patients treated); significant reduction in the risk of hemorrhage shown in Phase III trials (58 fewer per 1,000 patients treated)			Developer seeking indication for heparin-induced thrombocytopenia; if successful, drug would represent the only available treatment for this patient population (*Blood Weekly,* 1999)

Table 3: Biotechnology Pipeline Products for the Elderly — Coronary Heart Disease (continued)

Pipeline Product	Impact on Mortality / Survival	Impact on Costs	Impact on QoL (Patient / Caregiver)	Comments
Lanoteplase	Preliminary study results show 30-day mortality rates similar to that of tPA; formulation enhances usefulness in emergency and transport situations; increases patient access to treatment			Single bolus affords ease of storage and administration; additional benefit to health-care workers (McCann, 1999)
Cromafiban	Morbidity and mortality trials slated to begin after 2nd-quarter 2000	Oral dosing form availability has great cost advantage over IV therapy	Contributes to patient compliance, success rates	*R&D Focus Drug News*, 1999; *Business Wire,* 1999

ACS: Acute coronary syndrome
AMI: Acute myocardial infarction
CHD: Coronary heart disease
GP IIb-IIIa: Glycoprotein protein IIb-IIIa inhibitor
HIT: Heparin-induced thrombocytopenia
HITTS: Heparin-induced thrombocytopenia with thrombosis syndrome
INTEGRETI: Integrilin and Tenecteplase in acute myocardial infarction
IV: Intravenous
PAI: Platelet aggregation inhibition
PTCA: Percutaneous transluminal coronary angioplasty
tPA: Tissue plaseminogen activator
UA: Unstable angina

E. Diabetes Mellitus

Overview

Diabetes mellitus is a group of diseases characterized by high levels of blood glucose resulting from defects in insulin secretion and/or action. Insulin helps metabolize carbohydrates, fats and proteins; store glycogen in the liver; and convert glucose to fat. Diabetes affects an estimated 15.7 million people in the United States (5.9 percent of the population). This includes an estimated 10.3 million people who have been diagnosed, and 5.4 million people who are not aware that they have the disease (American Diabetes Association [ADA], 2000). The number of diabetes cases increases daily — approximately 2,200 people are diagnosed with the disorder each day (Albright, 2000).

The U.S. Centers for Disease Control and Prevention (CDC) estimates that the number of diabetes cases will double by the year 2020 (CDC, "Health," 1999). This is due partly to the aging population and partly to a recent increase in the number of child and adolescent cases of diabetes.

The two major types of diabetes are type I (insulin is not produced by the pancreas) and type 2 (insulin is produced, but the body cannot use it effectively). Type 1 diabetes, often called insulin-dependent diabetes mellitus (IDDM), affects 5 to 10 percent of the diagnosed U.S. diabetic population and most frequently develops during childhood or adolescence. Type 2 diabetes affects 90 to 95 percent of U.S. diabetic population and most frequent develops in people over the age of 40. Two other types of diabetes are known as "gestational" and what is known as "other types." Gestational diabetes affects women during pregnancy; it develops in 2 to 5 percent of all pregnancies and disappears after pregnancy. **"**Other types**"** refers to diabetes resulting from specific genetic syndromes, surgery, certain drugs, malnutrition, infections and other illnesses.

The cause of diabetes is generally unknown, although the major risk factors associated with the disease (NIDDK, 2000) are:

- Having a family history of diabetes
- Being over the age of 40
- Being overweight
- Having low HDL cholesterol
- Having a history of gestational diabetes
- Giving birth to a baby weighing 9 pounds or more
- Being in certain racial and ethnic groups, including African Americans, Hispanics/Latinos, Asian and Pacific Islanders and Native Americans

The elderly represent the largest population group with diabetes. Age impairs the body's ability to produce insulin, which is why approximately 50 percent of all diabetes cases occur in people older than 55 years of age. Approximately 18.4 percent of the U.S. population (6.3 million people) aged 65 and older have diabetes. It is also suspected that half of the elderly population with diabetes is undiagnosed. Diabetics also represent 18 percent of all nursing home residents; diabetics in nursing homes tend be younger than nondiabetic residents (Morley, 1998).

At present, diabetes is an incurable and chronic disease requiring ongoing treatment. Diabetes treatment focuses on stabilizing blood-glucose levels through insulin, diet, exercise and glucose monitoring. The treatment of type 1 diabetes always includes multiple daily insulin injections;

however, other forms of insulin delivery are under study and may come to fruition soon. Human insulin (rDNA) was introduced in 1982 and is the most widely form of insulin used today. It is purer and causes fewer side effects than the animal counterpart. A strict diet, exercise and glucose monitoring are necessary components of treatment for all types of diabetes.

Forty percent of people with type 2 diabetes also require insulin injections and/or oral medication(s). The recent introduction of oral agents that control glucose levels has greatly improved and simplified the management and treatment of type 2 diabetes. The recently completed United Kingdom Prospective Diabetes Study (UKPDS), a 20-year study of 5,000 people with type 2 diabetes, established the effectiveness of oral agents for that disease (DeFronzo, 1999). The remaining 60 percent of people with type 2 diabetes control their blood glucose levels with diet, exercise and monitoring alone, without medication.

Transplantation of a human pancreas is also a treatment option, although it is mostly used for patients with both diabetes and end-stage renal disease. Data show that a pancreatic transplant is far more successful if a kidney transplant is performed at the same time. Even with duel transplants, 50 percent of recipients remain dependent on insulin after five years following the transplant. There are also far more people who need pancreatic transplants than organs available.

Diabetes is associated with serious complications and can result in premature death. Diabetes is the major cause of heart disease, stroke, end-stage renal disease, adult blindness and lower-limb amputations (Albright, 2000). Other complications resulting from diabetes include complications with pregnancy, birth defects, diabetic ketoacidosis (accumulation of acids and ketones in body tissues and fluids), , gum disease and death. Patients with diabetes are hospitalized twice as often as patients without diabetes, and their hospitalizations are 30 percent longer (Geiss, 1993).

However, most of these side effects are slowed down and/or prevented through early detection and treatment. A major clinical study conducted from 1983 to 1993 by the National Institute of Diabetes and Digestive and Kidney Diseases (NIDDK) showed that maintaining blood sugar levels in diabetics as close to normal as possible slows the onset and progression of eye disease (76 percent reduced risk), kidney disease (50 percent reduced risk) and nerve disease (60 percent reduced risk) (NIDDK, 1994). The CDC believes that 90 percent of adult blindness associated with diabetes is preventable (Geiss, 1993).

Diabetes is the seventh leading cause of death in the United States, taking 193,000 lives a year (ADA, 2000). Overall, the life expectancy for people with diabetes is 10–15 years shorter than the general population. Research shows that the death rate of middle-aged diabetics is twice that of middle-aged nondiabetics (Brenneman, 1999).

Studies show that people with diabetes have worse QoL than people without diabetes, but better QoL than people with most other serious chronic diseases. Several studies assert that people with type 1 diabetes have a poorer QoL than people with type 2 diabetes (Rubin, 1999). Maintaining glycemic control is often associated with better QoL. Complications of diabetes are the most important disease-specific determinant of QoL for those with the disease. Interestingly, intensive treatment regimens for type 1 diabetes do not impair QoL. These regimens consist of three to four insulin injections daily, frequent glucose monitoring, diet and exercise (Grant, 1999).

A 1999 study of glucose tolerance and QoL among non-institutionalized elderly people (73 years or older) in Finland concluded that subjects with previously diagnosed diabetes had a poorer QoL compared with those with undiagnosed diabetes, impaired glucose tolerance, or normal glucose tolerance. Using the Nottingham Health Profile (NHP) instrument, the study found that a greater number of diabetic patients reported problems on all three energy item indicators, nearly all physical mobility indicators and half of the pain indicators (Hiltunen, 1999).

The total cost of diabetes in the United States was estimated at $98.2 billion in 1998. This includes direct medical costs of approximately $44 billion for medical care, hospitalizations and treatment supplies, and indirect costs of approximately $54 billion for disability payments, time lost from work and premature death. A 1994–96 study found that per capita expenditure among diabetic Medicare beneficiaries was 1.7 times greater than among Medicare beneficiaries without diabetes (Krop, 1999).

In 1997, per capita health-care costs for people with diabetes was $10,071, compared with $2,699 for nondiabetics. A reported 74,927 persons were permanently disabled by diabetes. On average, people with diabetes aged 18–64 lost 8.3 days from work in 1997, while the same group of people without diabetes lost 1.7 days from work (NIDDK, 2000).

A 1997 study on the direct cost of diabetes for the elderly (age 65 and over) found that $4.11 billion was spent on hospital care, $255 million on physician visits and $306 million on nursing home visits (Weinberger, 1997). However, the full economic and societal cost of diabetes is difficult to measure because mortality records fail to assess the impact of the disease on the proximate cause of death and costs associated with undiagnosed patients are not quantifiable (CDC, *Diabetes*, 1999).

Impact of Current Biotechnology Products

Biotechnology is changing the composition of pharmaceuticals used in the treatment diabetes. Recombinant DNA (rDNA) uses insulin engineered from human cells rather than animal cells, the previous treatment option, and is associated with better health outcomes. Studies indicate that problems with immunogenicity (provoking an immune response) are less likely with rDNA than with insulin derived from animals (Eli Lilly and Company, *Humulin package insert,* 1994).

PRANDIN™ (REPAGLINIDE)

Prandin, an oral blood glucose-lowering drug (benzoic acid derivative) used to treat type 2 diabetes, was introduced by Novo Nordisk, Inc. in December 1997. Taken two to four times a day, the tablet stimulates the production of insulin in the pancreas.

Prandin reduces the incidence and severity of hypoglycemic side effects compared with other oral hypoglycemic agents. The FDA advisory committee called for additional postmarketing surveillance for adverse cardiovascular events. Labeling advises that increases in dosage be made carefully in patients with impaired renal function or renal failure necessitating dialysis (Vinson, 1998).

In one-year clinical trials, Prandin was not associated with excess mortality rates compared with other oral hypoglycemic agents. Reported adverse side effects included upper respiratory

infection,16 percent (placebo, 8 percent); sinusitis, 6 percent (placebo, 2 percent); and arthralgia, 6 percent (placebo, 3 percent) (*The Pink Sheet*, "Novo Nordisk," 1998). Prandin™ is used frequently in combination therapy with (Glucophage® (metformin). However, Glucophage treatment should be avoided in patients over 80 years of age because of declining kidney function (Morley, 1998).

Prandin enables patients to reach ideal glucose levels and reduce the subsequent risk of complications. In patients with type 2 diabetes, complications from the disease affect QoL (U.K. Prospective Diabetes Study Group, 1999). The QoL of people with type 2 diabetes taking insulin has been reported to be poorer than those taking oral agents or diet alone (Jacobson, 1997; Diabetes Control and Complications Trial Research Group, 1996). New diabetes guidelines recommend using oral agents (such as Prandin) to achieve glycemic control and to prevent cardiovascular complications (Garber, 1999). Studies also show that the medication is cost-effective (Riddle, 1999).

HUMALOG® (INSULIN LISPRO RDNA ORIGIN)

Humalog, introduced by Eli Lilly and Company in June 1996, is a rapid-acting parenteral blood glucose-lowering agent with a short-acting duration that is used to treat type 1 diabetes (Eli Lilly and Company, 1999). It is primarily used subcutaneously through a prefilled pen device and must be used with longer-acting insulin. It was the first insulin analog to closely parallel the way the body itself makes insulin. The dosage varies from patient to patient depending on their needs, disease state, diet, other medications and activity. Humalog can also be used intravenously for a longer-acting effect.

Humalog is an effective insulin for achieving short-acting hypoglycemic control. A 1997 randomized crossover study of IDDM patients found that Humalog is associated with lower risk of severe hypoglycemia and coma (Benelux-UK Study Group, 1997). An article reviewing 22 controlled trials provided ample documentation that Humalog is effective in achieving metabolic control and further correlated these results with improved QoL. Episodes of mild hypoglycemia were reduced in 22 percent of the studies, although no change in the frequency of severe hypoglycemia was observed. However, there was a lower incidence of episodes of severe hypoglycemia at nighttime (Heinmann, 1999).

A multinational 1997 QoL study comparing Humalog with Humulin® showed a statistically significant higher satisfaction rate for those using Humalog. The QoL domains studied included energy/fatigue, health distress, treatment satisfaction and treatment flexibility (Kotsanos, 1997).

HUMULIN® (HUMAN INSULIN, RDNA ORIGIN)

Humulin, introduced by Eli Lilly and Company in October 1982, is a polypeptide hormone found to be chemically, physically, biologically and immunologically equivalent to pancreatic human insulin. Humulin is a synthesized, non-disease-producing, special laboratory strain of *Escherichia coli* bacteria that is purer than insulin from animal origins.

Humulin is intermediate-acting insulin combined with the more rapid onset of action of regular insulin. Humulin comes in seven formulations of human insulin, isophane suspension and zinc suspension that have different durations of action. The dosage varies from patient to patient

depending on their needs, disease state, diet, other medications and activity. The reported side effects are local and systemic allergic reactions (Eli Lilly and Company, *Humulin® package insert*, 1994). The only recent literature on Humulin is a short-term comparison that found Humulin to be better tolerated than Humalog. Glycemic control and incidence of hypoglycemia and adverse effects were similar in both products (Daniels, 1997).

NOVOLIN® (HUMAN INSULIN, RDNA ORIGIN)

Novolin, introduced in 1982 by Novo Nordisk, Inc., was the first human insulin (rDNA origin) approved. It is available in eight formulations and several delivery mechanisms, although it is delivered primarily through the NovoPen®, a disposable, prefilled insulin pen.

According to a manufacturer's survey, 86 percent of Novolin insulin users found the delivery mechanism to be easier to use than syringes. The survey also found that patients were 100 percent compliant with their insulin regimen when using the NovoPen. Respondents also stated that the product improved their QoL (Novo Nordisk, *Novolin package insert*, 1982).

The Promise of Future Biotechnology Products

In 1997 the NIH convened a team of experts to analyze diabetes and future research prospects. Their findings identified biotechnology as the primary area of impact on diabetes advances. This includes genetics autoimmunity and the beta cell, cell signaling and cell regulation (Albright, 1999). In addition to the biotechnology product trials listed below, two major studies sponsored by NIH will be conducted on the molecular genetics of insulin secretion and action (NIDDK, 1994). Recruitment is now under way. The long-term goal of this research is diabetes immunization/prevention.

INHALED INSULIN (RDNA)

Inhaled Therapeutics Systems Inc., in collaboration with Pfizer Inc., is in Phase III testing of a new insulin that is inhaled, making possible reproducible delivery of a rapid-acting insulin into the lungs. A dry powder is delivered through the mouth to the deep lung through a portable aerosol system. The aerosolized insulin is transported through the lung tissue to the bloodstream for systemic distribution. Thus far, the product has tested favorably, and the company expects FDA approval in three to five years (Roller, 1998).

Results from a Phase II study found that the inhaled product was as effective as injected insulin in treating both type 1 and type 2 diabetes. In addition, a 56-patient Phase II study found that patients unresponsive to an oral insulin product responded satisfactorily to the inhaled version (*The Pink Sheet*, "Pfizer/Hoechst," 1998).

AI-401 (RDNA)

Eli Lilly and AutoImmune Inc. are currently testing AI-401, an oral tolerance product for stopping the progression of diabetes. AI-401 is an oral form of rDNAthat the manufacturers believe will modify the immune system to stop the destruction of insulin-producing cells (*The Pink Sheet*, "In Brief," 1994).

INSULINOTROPIN

Insulinotropin, developed by Scios, Inc. and licensed by Norvo Nordisk, Inc., is being developed for treatment of type 2 diabetes. This product is a naturally occurring peptide hormone that stimulates the release of insulin in response to higher blood sugar levels (*Health Daily News*, 1996).

SOMATOKINE® (IGF-I/BP3)

SomatoKine, being developed by Celtrix Pharmaceuticals Inc., is an insulin-like growth factor/BP3 complex that specifically treats debilitating and degenerative conditions associated with diabetes and osteoporosis. The product is delivered through Elan Corporation's Medipad®, a disposable microinfusion pump. It is currently in Phase II trials.

Phase II trial results have already shown that severely osteoporotic hip fracture patients treated with subcutaneous infusions of SomatoKine lost about 2 percent of hip-bone mineral density at six months compared with a 6 to 7 percent loss for placebo (*The Pink Sheet*, "Elan," 1999).

ALTERED PEPTIDE LIGANDS (APL)

APL's are peptides corresponding to T-cell epitopes with one altered amino acid. Trials using APL-based insulin have focused on the body's immune system (Smets, 1998). Several manufacturers are testing variations of this ligand for diabetes.

SYMLIN™ (PRAMLINTIDE)

Amylin Pharmaceuticals, Inc. is conducting Phase III trials with SYMLIN, an orally administered synthetic analog of human amylin (a peptide that is normally co-secreted with insulin by pancreatic beta cells but may be deficient in diabetic patients). The agent appears to display efficacy in both type 1 and type 2 diabetes. Early results from Phase III trials indicate that the agent improved glycated hemoglobin levels after six months when added to insulin regimens of type 1 patients (Portyansky, 1999; *Medical Industry Today,* "Study," 1999).

AC2993 (EXENDIN-4)

AC2993 (exendin-4), also from Amylin Pharmaceuticals, is in Phase I testing as an investigational drug for type 2 diabetes. The product was originally isolated from the salivary secretions of the Gila monster. A synthetic version of the peptide is being tested in subcutaneous form (Roller, 2000).

BIOARTIFICIAL PANCREAS

The development of a bioartificial pancreas is a promising treatment option for type 1 diabetes. Experiments are being conducted with a tissue-engineered pancreatic construct based on immunoisolated, insulin-secreting cells (Pappas, 1999).

The QoL for patients with type 1 diabetes can be significantly improved through pancreas transplantation. Implanting an artificial pancreas would eliminate the need for insulin injections, frequent self-monitoring of blood glucose levels and dietary restrictions. It would also be more cost-effective than authentic pancreatic transplantation, and would eliminate the wait for a transplant. Increasing evidence also suggests that an artificial pancreas may slow the progression of long-term diabetic complications. However, patients would risk the adverse effects of lifelong immunosuppression (Mayes, 2000).

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Table 1: Disease Overview for the Elderly — Diabetes

Disease Category	Diabetes
Epidemiology	**Incidence:** Approximately 2,200 people are diagnosed with diabetes every day, equal to 803,000 new cases a year **Prevalence:** Currently an estimated 15.7 million people, or approximately 5.9% in the United States have diabetes **The elderly:** Approximately 50% of all diabetes cases occur in people older than 55 years of age. Approximately 18.4% of the U.S. population (6.3 million) aged 65 or older have diabetes **Mortality / survival:** Diabetes is the 7th leading cause of death in the U.S.; yearly deaths are estimated at 193,000; life expectancy for diabetics is 10–15 years less than for the general nondiabetic population **Cause of other diseases:** Diabetes is the major cause of heart disease, stroke, end stage renal disease, adult blindness and lower limb amputations
Total Cost of Illness	**Total cost:** $98.2 billion (1998) **Per capita health cost:** $10,071 (1997)
Direct / Indirect Costs	**Direct cost:** $44 billion (1998) **Indirect cost:** $54 billion (1998) **Direct costs for the elderly (aged 65+):** $4.1 billion in hospital costs, $255 million in physician costs and $306 million in physician costs for nursing home visits **Medicare:** Payments are 1.7 times higher for patients with diabetes compared with nondiabetics
QoL / Functional Status	Diabetics have lower QoL than healthy patients and patients with other chronic diseases; people with type 2 diabetes have higher QoL than people with type 1 diabetes; using the NHP, the diabetic non-institutionalized elderly (age 73+) have a poorer QoL than the nondiabetic non-institutionalized elderly
Comments	**Sources:** ADA, 2000; Krop, 1996; NIDDK, *Diabetes Overview*, 2000; CDC, *Diabetes,* 1999; Rubin 1999; Weinberger, 1997

ADA: American Diabetes Association
CDC: Centers for Disease Control and Prevention
NHP: Nottingham Health Profile
NIDDK: National Institute of Diabetes and Digestive and Kidney Diseases
QoL: Quality of life

Table 2: Current Biotechnology Products for the Elderly — Diabetes

Product on Market	Relevant Indication(s)	Company	Approval Dates	Class	Mechanism of Action	Route of Administration	Dosing
Prandin™ (repaglinide)	Type 2 diabetes	Novo Nordisk	December 1997	Meglinide	Stimulates insulin secretion from the beta cells of the pancreas by binding to sites on the beta cell, where it acts through calcium channels; it produces insulin and provides glycemic control	Oral tablet taken 30 minutes before meals	0.5 to 4 mg TID; dependent upon weight, diet, exercise and disease state
Humalog® (insulin lispro rDNA origin)	Type 1 diabetes	Eli Lilly	June 1996	Human insulin, rDNA	Blood glucose lowering agent	SC; taken 15 minutes before meals	Dependent upon weight, diet, exercise and disease state
Humulin® (human insulin rDNA origin)	Type 1 diabetes	Eli Lilly	October 1982	Human insulin, rDNA	Maintains glycemic control	SC	Dependent upon weight, diet, exercise and disease state
Novolin® (rDNA origin)	Type 1 diabetes	Novo Nordisk	October 1982	Human insulin, rDNA	Blood glucose–lowering agent	SC	Dependent upon weight, diet, exercise and disease state

Table 2: Current Biotechnology Products for the Elderly — Diabetes (continued)

Product on Market	Impact on Mortality and Morbidity	Impact on Costs	Impact on QoL (Patient / Caregiver)	Comments
Prandin™ (repaglinide)	No association with excess mortality rates compared with other oral hypoglycemic agents in one-year clinical trials; strengthens the ability to control hypoglycemia / controls side effects; greater compliance due to oral form; contraindicated in patients with diabetic ketoacidosis and patients with type 1 diabetes who have renal functioning impairment or renal functioning requiring hemodialysis; provides strong management of type 2 diabetes; achieves glycemic control and helps to prevent cardiovascular complications; causes average weight gain of 3.3%; adverse side effects reported: upper respiratory infection, 16% (placebo: 8%); sinusitis, 6% (placebo: 2%); arthralgia, 6% (placebo: 3%)	Maintaining glycemic control greatly reduced risk of complications; cost-effective for treating type 2 diabetes	Using oral agents leads to improved QoL	*The Pink Sheet,* 1998; Garber, 1999; Riddle, 1999
Humalog® (insulin lispro rDNA origin)	Pens have high accuracy of dosage, prevent accidental overdose; associated with lower risk of severe hypoglycemia and coma; lower incidence of episodes of severe hypoglycemia at nighttime; well-documented outcomes on the safety and efficacy of insulin lispro for the treatment of type 1 diabetes	Costs 20% more than regular insulin	In a 1997 study comparing Humalog to Humulin R, patients undergoing Humalog therapy reported a higher QoL than those receiving Humulin R; domains measured were energy / fatigue, health distress, treatment satisfaction and treatment flexibility; convenience of delivery mechanism leads to greater compliance, higher QoL; improved glycemic control has been correlated to higher QoL	Eli Lilly & Company, 1999; Heinmann, 1999; Kotsanos, 1997
Humulin® (human insulin rDNA origin)	Some allergies associated with Humulin; maintains glycemic control	Same as above	See Humalog	Eli Lilly and Company, 1994
Novolin® (rDNA origin)	Maintains glycemic control	Same as above	Convenience of delivery mechanism leads to greater compliance, higher QoL; improved glycemic control has been correlated to higher QoL	Novo Nordisk, 1982

IV: Intravenous
QoL: Quality of life
rDNA: recombinant DNA
SC: Subcutaneous
TID: Three times a day

Table 3: Biotechnology Pipeline Products for the Elderly — Diabetes

Pipeline Product	Phase / Date Submitted	Company	Therapeutic Area	Class	Indication	Mechanism of Action	Route of Admin. / Dosing
rDNA (inhaled insulin)	Phase III	Inhaled Therapeutic Systems	Diabetes	rDNA inhaled insulin	Types 1 and 2 diabetes	Permits reproductive delivery of rapid-acting insulin in the lungs; pulmonary-delivered insulin	Inhaled
rDNA AI-401	Phase II	AutoImmune	Diabetes	rDNA oral insulin	Type 2 diabetes	Modify the immune system to prevent the destruction of insulin-producing cells	Oral
Insulinotropin	Phase I	Scios / Norvo Nordisk	Diabetes	Peptide hormone stimulation	Osteoporosis and type 2 diabetes	Stimulates the release of insulin in response to high blood sugar	
SomatoKine® (IGF-I/BP3)	Phase II	Celtrix Pharmaceuticals	Diabetes	Insulin-like growth factor / BP3 complex	Growth factor	Maintains bone density	Microinfusion pump
Altered peptide ligands (APL)	Phase I		Type 2 diabetes	APL-based insulin		Insulin that works on the body's immune system	
SYMLIN™ (pramlintide)	Phase III	Amylin Pharmaceuticals	Types 1 and 2 diabetes	Hormone stimulation	Insulin supplement		
AC2993 (exendin-4)	Phase I	Amylin Pharmaceuticals	Type 2 diabetes	Peptide			Subcutaneous injection

Table 3: Biotechnology Pipeline Products for the Elderly — Diabetes (Continued)

Pipeline Product	Impact on Morbidity	Impact on Costs	Impact on QoL (Patient / Caregiver)	Comments
rDNA (inhaled insulin)	When inhaled insulin is combined with oral therapies, glucose levels met or exceeded ADA targets for effective control		Phase II trials showed significantly improved nerve conduction velocity	Roller, 1998; *The Pink Sheet,* 1994
rDNA AI-401				*The Pink Sheet,* 1994
Altered peptide ligands (APL)				*Lancet,* 1998
Insulinotropin				*Health News Daily,* 1996
SomatoKine® (IGF-I/BP3)	Improves bone density in patients with osteoporosis			*The Pink Sheet,* 1999
SYMLIN™ (pramlintide)				Roller, 1998
AC2993 (exendin-4)				Roller, 1998

ADA: American Diabetes Association
APL: Altered peptide ligands
rDNA: recombinant DNA
SC: Subcutaneous injection

F. Osteoporosis

Overview

Osteoporosis is a major public health threat for more than 28 million Americans, 80 percent of whom are women. In the United States today, 10 million individuals already have the disease and 18 million more have low bone mass, placing them at increased risk for osteoporosis. Osteoporosis is responsible for more than 1.5 million fractures annually, including 300,000 hip fractures, approximately 700,000 vertebral fractures, 250,000 wrist fractures and 300,000 fractures at other sites (Ray, 1997).

Osteoporosis is characterized by progressive loss of bone architecture and mineralization, leading to the loss of bone strength and an increased risk of fracture. The skeleton is constantly being remodeled by cells that lay down new bone (osteoblasts) and those that resorb bone (osteoclasts). A prolonged imbalance of resorption over formation can occur in post-menopausal women and in men and women with certain disorders such as renal failure. This imbalance leads to weaker bone structure and a higher risk of fractures. These fractures often heal poorly and result in substantial costs to the health-care system (NPS Pharmceuticals, 2000). Estimated national direct expenditures (hospitals and nursing homes) for osteoporotic and associated fractures were $13.8 billion in 1995 ($38 million each day), and this cost is rising (National Osteoporosis Foundation [NOF], 2000).

Certain people are more likely to develop osteoporosis than others, namely those with certain risk factors. Some of the most important of these risk factors include being female, having a thin and/or small frame, advanced age, a family history of osteoporosis, being postmenopausal, abnormal absence of menstrual periods (amenorrhea), anorexia nervosa or bulimia, a diet low in calcium, use of certain medications such as corticosteroids and anticonvulsants, low testosterone levels in men, an inactive lifestyle, cigarette smoking, excessive use of alcohol and being Caucasian or Asian, although African Americans and Hispanic Americans are at significant risk as well (NOF, 2000).

Specialized tests can measure bone density in various sites of the body to detect osteoporosis before a fracture occurs. These tests can be used to predict a person's chances of fracturing in the future, determine the rate of bone loss and/or monitor the effects of treatment (if the test is conducted at intervals of a year or more) (NOF, 2000).

The most typical sites of osteoporosis-related fractures are the hip, spine, wrist and ribs, although the disease can affect any bone in the body. The rate of hip fractures is two to three times higher in women than men; however, one-year mortality following a hip fracture is nearly twice as high for men as for women. A woman's risk of hip fracture is equal to her combined risk of breast, uterine and ovarian cancer (NOF, 2000).

Although there is no cure for osteoporosis, the following medications are approved by the FDA for postmenopausal women to prevent or treat osteoporosis: estrogens (e.g., Premarin®, Estrace®), calcitonin (Miacalcin®), alendronate (Fosamax®), raloxifene (Evista®) and risedronate (Actonel®) (NOF, 2000).

Osteoporosis has been described as a primary factor contributing to a deterioration of QoL for older women (Birge, 1993). Osteoporosis can cause acute and chronic pain, impairments in functional status and a perception of poor health. Several groups of researchers have developed health-related QoL instruments for use in osteoporosis clinical trials and therapeutic management. The Osteoporosis Quality of Life Questionnaire (OQLQ) was designed to measure the QoL of elderly women with spinal fractures owing to osteoporosis. The questionnaire was developed specifically for this group because spinal fractures are the most prevalent and potentially the most debilitating of osteoporotic fractures (Cook, 1993). Additional QoL instruments include the Quality of Life Questionnaire of the European Foundation for Osteoporosis (Qualeffo), developed by the European Foundation for Osteoporosis as a disease-specific questionnaire for patients with established vertebral osteoporosis, and the Osteoporosis-Targeted Quality of Life Survey Instrument (OPTQol), a cross-sectional survey instrument developed to assess the impact of osteoporosis on QoL in peri- and postmenopausal women (Lips, 1997; Lydick, 1997).

Impact of Current Biotechnology Products

Currently there are no biotechnology treatments for osteoporosis. Although many available osteoporosis therapies can slow bone resorption, most cannot stimulate bone formation.

The Promise of Future Biotechnology Products

The biotechnology-related treatments under investigation focus on stimulating bone growth, inhibiting bone resorption and improving the delivery mechanisms for current osteoporosis treatments. These include synthetic analogues of the active component of parathyroid hormone and insulin-like growth factors. Preliminary studies suggest that these agents hold significant promise. Alone, or more likely in combination with other drugs mentioned below, novel regimens will become available to substantially maintain, or where indicated, increase bone mass and reduce fractures.

ALX1-11

An emerging therapy, parathyroid hormone, has been shown to increase bone mass. NPS Pharmaceuticals, Inc. (formerly Allelix Biopharmaceuticals) is currently developing ALX1-11, an injectable version of human parathyroid hormone, a naturally occurring protein involved in the regulation of bone metabolism. ALX1-11 is in Phase III clinical trials for postmenopausal osteoporosis. The study involves 80 to 100 sites in North America and approximately 2,000 women (NPS Pharmaceuticals, 2000).

- **Potential significant increase in bone mineral density.** In a Phase II clinical trial of 217 osteoporotic, postmenopausal women, ALX1-11 was shown to safely produce significant increases in bone mineral density. In addition to studies done with ALX1-11, a number of independent investigators have established the usefulness of parathyroid hormone analogs in replacing bone lost to osteoporosis. Currently available therapies such as estrogen replacement and bisphosphonates halt bone loss stemming from the disease, while parathyroid hormone may offer the opportunity to rapidly reverse the course of this devastating illness. This could be especially important for osteoporosis sufferers who have

lost significant amounts of bone and who have either had a disease-related fracture or who are at high risk of experiencing a fracture (Bourque, 1999). Dr. Hunter Jackson, president and CEO of NPS Pharmaceuticals (formerly Allelix Biopharmaceuticals), said:

> *"The Phase III trial for ALX1-11 is a very important part of our strategy to add value to advanced drug development programs in areas where new therapies are desperately needed. We believe that ALX1-11 will provide an effective weapon for patients and their physicians in the battle against a disease that is increasingly important in our society. ALX-11 should work well as a stand-alone product, and we think it also has promise as an effective therapy in combination with other osteoporosis products currently in use. We look forward to continued clinical explorations of the effects of ALX1-11 and and to its ultimate use by osteoporosis patients."*

OSTEOPROTEGERIN (OPG)

Injections of Amgen Inc.'s osteoprotegerin (OPG), one of the body's natural protectors against bone loss, reportedly reduced bone loss significantly in a study of postmenopausal women. In earlier Studies, OPG had been shown effective in earlier animal studies to prevent the formation of osteoclasts, the cells responsible for bone degradation or resorption.

- **Significant reduction in bone loss.** Researchers conducted a randomized, placebo-controlled, dose-ranging study with 52 postmenopausal women, a population particularly at risk for developing osteoporosis. The goal of the investigation was to determine if giving recombinant (synthetically produced using genetic techniques) OPG to patients with osteoporosis would restore bone mass and prevent fractures. Scientists found that a single injection of OPG has a potent and rapid onset of action to prevent bone resorption by osteoclasts. A decrease of bone resorption of approximately 80 percent was reached three to four days following dosing. At higher doses, bone resorption was suppressed for at least 28 days following a single injection of OPG. This indicates that OPG could be given at infrequent intervals to protect against bone loss (*Immunotherpay Weekly,* "Bone Protection," 1999).

Researchers reported their findings at the 21st Annual Meeting of the American Society for Bone and Mineral Research (ASBMR) held in St. Louis, Missouri, last year.

PROTEINOID ORAL DRUG DELIVERY SYSTEM (PODDS) CALCITONIN

Emisphere Technologies, Inc. is developing (with Novartis Pharmaceuticals Corporatoin) an oral version of calcitonin. Calcitonin is a naturally occurring non-sex hormone involved in calcium regulation and bone metabolism. In women who are at least five years beyond menopause, calcitonin slows bone loss, increases spinal bone density and — according to anecdotal reports — relieves the pain associated with bone fractures. Calcitonin reduces the risk of spinal fractures and may reduce hip fracture risk as well. Calcitonin is currently available as an injection or nasal spray, although a proteinoid oral drug delivery system (PODDS) is in development (Emisphere, 2000).

SOMATOKINE® (IGF-I/BP3)

SomatoKine is the recombinant equivalent of insulin-like growth factor-1 and its major binding protein, BP-3. The product, developed by Insmed Pharmaceuticals Inc., is currently in Phase II trials to treat patients with osteoporosis. BP-3, Elan's Medipad system, a patch-like microinfusion pump device that delivers through subcutaneous infusion, will be used to deliver SomatoKine in development (Paul, 1999).

- **In clinical trials, SomatoKine has shown that it can help rebuild bone and muscle in osteoporotic patients who undergo hip surgery.** In clinical trials, patients who took SomatoKine lost only 2 percent of bone density in the eight weeks following hip surgery; patients who did not receive the drug lost up to 7 percent of bone density. In a completed Phase IIa study involving 24 severely osteoporotic hip-fracture surgery patients who were given one or two doses of SomatoKine or placebo, the results showed benefit among treated patients on several measurements, including hip bone mass and functional ability (Shrine, 1999).

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Table 1: Disease Overview for the Elderly — Osteoporosis

Disease Category	Osteoporosis
Epidemiology	**Incidence:** 1,550,000 osteoporotic fractures per year (300,000 hip fractures, 700,000 vertebral fractures, 250,000 wrist fractures and 300,000 fractures at other sites) **Prevalence:** 10,000,000 (advanced); 25,000,000+ (total); 41,000,000 (estimated by 2015) **Mortality:** 24% fatality rate within one year of hip fracture
Total Cost of Illness	**Total cost:** More than $14 billion annually
Direct / Indirect Costs	**Direct costs (hospitals and nursing homes):** $14 billion in direct national expenditures (hospitals and nursing homes)
QoL / Functional Status	Primary domains impacting patients with osteoporosis include: pain, physical functioning; major QoL instruments include: OAQ, OQLQ, QUALEFFO, OPTQoL
Comments	**Sources:** NPS Pharmaceuticals, 2000; NIH ORBDNIH, 2000

NIH ORBD-NRC: National Institutes of Health Osteoporosis and Related Bone Diseases National Resource Center
OAQ: Osteoporosis Assessment Questionnaire
OPTQoL: Osteoporosis-Targeted Quality of Life survey Instrument
OQLQ: Osteoporosis Quality of Life Questionnaire
QoL: Quality of life
QUALEFFO: Quality of Life Questionnaire of the European Foundation for Osteoporosis

Table 2: Biotechnology Pipeline Products for the Elderly — Osteoporosis

Pipeline Product	Phase / Date Submitted	Company	Therapeutic Area	Class	Indication	Mechanism of Action	Route of Admin. / Dosing
ALX1-11	Phase III	NPS Pharmaceuticals	Musculoskeletal	Recombinant PTH	Treatment of osteoporosis	Trigger transient release of PTH to stimulate bone growth	Injection
OPG	Phase I / preclinical	Amgen	Musculoskeletal	Recombinant version of a naturally occurring protein	Treatment of osteoporosis	Protein is a clinical regulator of bone mass; inhibits bone destruction	Injection
PODDS calcitonin	Phase II	Emisphere Technologies / Novartis	Musculoskeletal	PODDS for salmon calcitonin	Treatment of osteoporosis	Salmon calcitonin, a synthetic version of a natural hormone that inhibits bone resorption, is delivered via PODDS	Oral
SomatoKine® (IGF-I/BP3)	Phase II	Insmed	Musculoskeletal	IGF-1	Treatment of osteoporosis	Stimulation of myocytes and fibroblasts	Injection

Pipeline Product	Impact on Morbidity	Impact on Costs	Impact on QoL (Patient / Caregiver)	Comments
ALX1-11	Significant increase in bone mineral density			Bourque, 1999; NPS Pharmaceuticals, 2000
OPG	In preclinical studies, OPG has demonstrated potential to inhibit bone destruction			*Immunotherapy Weekly,* 1999
PODDS calcitonin	Potential reduction in risk of spinal fractures and hip fracture risk		Potential pain relief from associated reduction in bone fractures	Emisphere, 2000
Somatokine (IGF-I/BP3)	Demonstrated ability to rebuild bone and muscle in osteoporotic patients in patients who underwent hip surgery			Paul, 1999; Shine, 1999

IGF-1: Insulin-like growth factor
OPG: Osteoprotegerin
PODDS: Proteinoid oral drug delivery system
PTH: Parathyroid hormone
SERM: Selective estrogen receptor modulator

G. Parkinson's Disease

Overview

Parkinson's disease (PD), a progressive neurodegenerative disease, affects an estimated half million Americans. Approximately 50,000 new cases are diagnosed each year, producing an annual societal cost ranging from $10 million to $25 million (PhRMA, 1999; PAN, 2000; Cummings, 1999). The true number of cases in the United States may actually be higher — potentially 1.5 million individuals (PhRMA, 2000) — because many individuals in the early stages of the disease assume that their symptoms are the result of normal aging and do not seek help from a physician (Parkinson's Action Network [PAN], 2000).

Most cases of PD begin after the age of 50, and there is an increasing age-related prevalence to at least age 80 years (Cummings, 1999). The average age of disease diagnosis is 60 years (Portyansky, "Parkinson's," 1999); however, unrecognized early symptoms of the disease may be present in as many as 10 percent of those over 60 years of age (Young, 1999). Symptoms of PD are seen in up to 15 percent of those between 65 and 74 years of age and almost 30 percent of those between the ages 75 and 84 years (Robinson, 1999). Epidemiologic studies conducted in the United States have found that PD is more prevalent in men than in women (approximate ratio of three to two) and that the prevalence of the disease is equal among whites and African Americans (Young, 1999).

The costs of PD to individuals, caregivers and society are substantial, especially considering the progressive nature of the disease and that patients will require treatment for a number of years. In a report by the PD Foundation, the total financial cost of PD was estimated to be $24,041 per patient in 1997. The direct costs of pharmaceuticals, surgery, physician visits and hospital and nursing home care accounted for $8,872 of the total annual cost. Indirect costs — such as disability payments and lost income due to forced early retirement — accounted for approximately two-thirds ($15,169) of the total annual cost of the disease (Parkinson's Disease Foundation [PDF], 1997).

Studies have also identified additional costs associated with PD. Levodopa is the current gold standard in treating PD. Ongoing care for patients with the disease generally requires visits to neurologists and various physical therapists and often treatment for depression. Typical early-stage annual medical cost per patient ranges from $2,000 to $7,000, with the cost for those with advanced disease running higher.

One of the many effects of PD is the tendency of patients to fall. It is estimated that 38 percent of all patients do fall, with 13 percent falling more than once a week. Treatment and hospitalization for these PD-related falls can cost $40,000 or more per patient. As the disease progresses, substantial disability (inability to maintain balance, walk, speak, move) requires assisted living and nursing home care, which can exceed $100,000 per patient annually (PAN, 2000).

The measurement of QoL in patients with PD is an important consideration in evaluating the effects of the disease and the potential of new treatments and drug therapies. Overall, patients with PD experience decreased QoL, mainly due to the following:

- Speech impairment — an estimated 60 to 90 percent of people with PD will develop some difficulty speaking.
- Dysphagia (swallowing problems) — at least half of PD patients develop swallowing problems (choking, food stuck in throat or congestion after eating).
- Intellectual changes — studies have indicated that over half of people with PD have mild intellectual changes and about 20 percent have more substantial cognitive impairment.
- Other disease symptoms that directly affect a patient's QoL include depression and other emotional disorders, restrictions in mobility, isolation, social embarrassment, constipation, weight loss, sleep disturbances and urinary tract infections (FCA, 1996).

Impact of Current Biotechnology Products

In the United States, the FDA has yet to approve a biotechnology drug indicated for use in treating PD; however, there are a number of biotech drugs in the pipeline.

The Promise of Future Biotechnology Products

NEUROCELL™-PD

NeuroCell-PD, Developed by Diacrin, Inc. and Genzyme Corporation, is a radical new treatment for PD that involves implanting fetal pig cells into the brain. It has already been tested on a small group of patients in the United States and was found to cure many of the symptoms associated with PD. The study involved 11 patients who received a low dose of pig cells and, on average, there was 20 percent improvement in symptoms. In recognition of the drug's potential to address an important unmet medical need, the FDA has designated NeuroCell-PD a fast-track product. The FDA has also granted orphan drug designation for NeuroCell-PD for advanced PD (*Daily Mail* [London], 2000; Saltus, 1999).[4]

NIL-A

NIL-A, from a series of FKBP neuroimmunophilins developed by Amgen Inc. and Guilford Pharmaceuticals Inc., represents a novel agent that has been shown to induce nerve growth and repair in several animal models of acute and chronic neurological disorders. This compound represents the first orally active small molecules that can cross the blood-brain barrier and promote repair and regrowth of damaged nerves as demonstrated in animal models. NIL-A will initially be developed for the treatment of PD (*PR Newswire,* 1997; *PR Newswire,* 1998). According to Dr. Joseph Steiner, Guilford's director of biology for the FKBP-neuroimmunophilin project:

> *"Previous laboratory and animal studies demonstrated potential applications for these compounds in the treatment of Parkinson's disease, Alzheimer's disease, multiple sclerosis, stroke and other neurodegenerative diseases."*

[4] Obtained from www.diacrin.com.

SPHERAMINE™

Sphermine, another novel agent being developed by Titan Pharmaceuticals, Inc. to treat PD, consists of cultured, dopamine-producing human retinal pigmented epithelial (hRPE) cells, designed to be implanted into patients' brains. PD results from the death of brain cells that produce dopamine, a key chemical messenger needed for smooth and coordinated movement. The hRPE cells are expected to produce dopamine in place of the patient's own neuron cells. Said Dr. Louis R. Bucalo, president and CEO of Titan (*Business Wire,* 1999):

> *"We are very pleased to begin this important initial clinical study of Spheramine. Unfortunately, most patients with Parkinson's disease eventually lose benefit from currently available standard therapies. We are hopeful that an agent such as Spheramine may help restore significant function that has been lost through disease progression. This initial study is the first step in assessing such potential benefit."*

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Table 1: Disease Overview for the Elderly — Parkinson's Disease

Disease Category	Parkinson's Disease
Epidemiology	**Incidence:** 50,000 (all ages) **Prevalence:** 500,000 – 1,500,000 (all ages)
Total Cost of Illness	**Total cost:** $10 billion – $25 billion dollars annually **Total cost per patient:** $24,041 per patient per year (1997)
Direct / Indirect Costs	**Direct costs:** $8,872 per patient per year (1997) **Indirect costs:** $15,169 per patient per year (1997)
QoL / Functional Status	Decrease in QoL due to speech impairments, dysphagia (swallowing problems), intellectual changes, depression and other emotional disorders, restrictions in mobility, isolation, social embarrassment, constipation, weight loss, sleep disturbances and urinary tract infections
Comments	**Source:** PhRMA, 1999

PhRMA: Pharmceutical Researchers and Manufacturers of America
QoL: Quality of life

Table 2: Biotechnology Pipeline Products for the Elderly — Parkinson's Disease

Pipeline Product	Phase / Date Submitted	Company	Therapeutic Area	Class	Indication	Mechanism of Action	Route of Admin. / Dosing
AAV Gene Therapy	Preclinical	Cell Genesys	Central nervous system	AAV gene therapy	Parkinson's disease	AAV vectors used to deliver the GDNF gene to a specific region of the brain affected with Parkinson's disease. GDNF prevents degeneration of nerve cells responsible for production of dopamine	Injection
CEP-1347	Phase I	Cephalon	Central nervous system	Signal transduction modulators	Parkinson's disease and Alzheimer's disease	Signals transduction modulators that may suppress or override neuronal survival mechanisms and thereby elicit neuronal death	Oral
GDNF	Phase I/II	Amgen	Central nervous system	Glial derived neurotrophic factor (GDNF)	Parkinson's disease	Reduces bradykinesia, rigidity, and postural instability from MPTP toxin and causes regeneration of nerves damaged by the toxin	Injection
GPI-1046	Phase I	Guilford / Amgen	Central nervous system	FKBP-neuroimmunophilin ligands	Parkinson's disease	Stimulates nerve regrowth, repair, and re-myelination. Specifically targets damaged nerve cells while leaving healthy cells alone	Oral
GPI-1216	Preclinical	Guilford / Amgen	Central nervous system	FKBP-neuroimmunophilin ligands	Parkinson's disease	Same as GPI-1046	Oral

Table 2: Biotechnology Pipeline Products for the Elderly — Parkinson's Disease (continued)

Pipeline Product	Phase / Date Submitted	Company	Therapeutic Area	Class	Indication	Mechanism of Action	Route of Admin. / Dosing
GPI-1234	Preclinical	Guilford / Amgen	Central nervous system	FKBP-neuroimmunophilin ligands	Neurological diseases	Same as GPI-1046	Oral
NeuroCell™-PD	Phase II/III	Diacrin / Genzyme	Central nervous system	Xenotransplantation (transplanting cells, not organs)	Parkinson's disease	Replaces function of neural cells damaged by disease. Transplanted cells become integrated into surrounding brain tissue and correct functional deficits	Injection
NIL-A (FKBP)	Phase I	Guilford / Amgen	Central nervous system	FKBP-neuroimmunophilin ligands	Parkinson's disease	Same as GPI-1046	Oral
NT-3	Phase I	Amgen / Regneron	Central nervous system	Neurotrophin-3; recombinant	Enteric neuropathies and Parkinson's disease		Injection
O-1369	Preclinical	Boston Life Sciences	Central nervous system		Parkinson's disease		Injection
Spheramine™	Phase I/II	Titan Pharmaceutical / Schering	Central nervous system	Cell-derived material	Parkinson's disease	Nonembryonic human retinal pigment epithelial cells, genetically modified to secrete dopamine, are attached to microcarriers that are injected into brain region lacking in dopamine	Injection
UniGraft Transplantation	Preclinical	Alexion Pharmaceutical	Central nervous system	Apogen T-cell therapy	Parkinson's disease	Immunoprotected porcine neurons transplanted into brain region lacking in dopamine. Restores dopamine production locally and selectively	Trans-plantation

Table 2: Biotechnology Pipeline Products for the Elderly — Parkinson's Disease (continued)

Pipeline Product	Impact on Morbidity and Mortality	Impact on Costs	Impact on QoL (Patient / Caregiver)	Comments
AAV Gene Therapy	Stimulates the production of dopamine; protects specific neurons from dying			Henderson, 1997
CEP-1347	CEP-1347 has been shown to prevent neuronal death *in vitro* and in several models of neuronal death *in vivo*			Cephalon, 1999
GDNF	Found to increase survival of dopamine neurons located in the brain			Cappiello, 1998
GPI-1046	Shown to induce nerve growth and repair in animal models			*PR Newswire*, 1997
GPI-1216	Same as GPI-1046			*PR Newswire*, 1997
GPI-1234	Same as GPI-1046			*PR Newswire*, 1997
NeuroCell™-PD	The results on a small group of patients in the U.S. was found to cure many of the symptoms associated with Parkinson's disease			Saltus, 1999; Diacrin, 2000
NIL-A (FKBP)	Same as GPI-1046			*PR Newswire,* 1998
NT-3				
O-1369				
Spheramine™	Expected to produce dopamine in place of the patient's own neuron cells			Portyansky, "Promising," 1999; *Biotech Business*, 1999; *R & D Focus Drug News*, 2000
UniGraft Transplantation				Alexion, 2000

AAV: Adeno-associated viral gene thearpy
GDNF: Glial derived neurotrophic factor

H. Stroke

Overview

Stroke is one of the major diseases affecting the elderly. According to the former U.S. Agency for Health Care Policy and Research (AHCPR), stroke is the leading cause of disability in seniors and the third leading cause of death. While stroke mortality has declined in recent years, the number of disabled stroke patients remains high: At any given time about 4 million people are living with some degree of neurological impairment due to stroke (AHA, 2000).

The cost of stroke-related treatment and disability is enormous. According to the American Heart Association, $51.3 billion is spent treating stroke victims annually, including direct and indirect costs (AHA, 2000).

In the 90 days immediately following a stroke, the cost of treatment can vary greatly: Although the average cost per patient for the first 90 days post-stroke is $15,000, about 10 percent of cases exceed $35,000. However, the lifetime cost for treating all types of stroke is much higher — about $103,576. Broken down by type of stroke, in 1990 the lifetime cost was:

- $228,030 for subarachnoid hemorrhage (SAH);
- $123,565 for intracerebral hemorrhage (ICH); and
- $90,981 for ischemic stroke (stroke that results from a lack of oxygenated blood to the brain) (Taylor, 1996).

Acute-care costs incurred in the two years following the first stroke accounted for 45 percent of total costs; long-term ambulatory care accounted for 35 percent; and nursing home care accounted for 17.5 percent.

QoL for patients is nearly always diminished following a stroke. Immediately following a stroke, one QoL study found "that the body change resulting from a stroke leads to both physical and psychological trauma, in which the psychological crisis can be very deep and best described as a personal catastrophe" (Backe, 1996).

Later, most patients cope with decreased levels of activity and reduced overall QoL, in many cases related to psychological problems such as depression and anxiety. Often caregivers also experience depression: dozens of studies have focused on the negative impacts of stroke on caregivers' psychological health (Low, 1999).

Impact of Current Biotechnology Products

In 1996, the FDA approved Genentech Inc.'s clot-dissolving agent Activase® (alteplase, recombinant), a genetically engineered version of the naturally occurring tissue plasminogen activator (t-PA), for the treatment of certain adult patients with acute ischemic stroke within three

hours of symptom onset. The therapy was the first product approved for the management of stroke. More than 1 million people have benefited from Activase®, according to Genentech.

Although contraindicated in many stroke patients (particularly those with hemorrhagic stroke), Activase has proved to be a powerful, cost-effective treatment for patients for whom it is indicated. Use of the drug has resulted in:

- **Improved functioning compared with placebo:** The FDA based its approval of Activase for stroke, in part, on data from a trial sponsored by the National Institute of Neurological Diseases & Stroke. The clinical trial showed an 11 percent absolute improvement to minimal or no disability using four stroke assessment scales, compared with placebo and a relative improvement of 34 percent in global recovery (*The Pink Sheet,* "Genentech Activase," 1996).

- **Cost-effective treatment:** Although expensive compared with other therapies, there is evidence that Activase is a cost-effective form of treatment. In a recent article appearing in *Science,* Columbia University's Herbert Pardes (1999) observed that:

> *"Using data from the NINDS rt-PA stroke trial, Fagan et al. found that hospital length of stay was shorter for treated patients and that more treated than untreated patients were discharged to home (rather than to institutional) care." Pardes noted that due to intracerebral hemorrhage that may be a side effect of rt-PA, hospital costs increased by $1.7 million per 1,000 patients, but "decreased rehabilitation and nursing home costs by $6.2 million — a net savings of $4.5 million per 1,000 treated stroke patients. Not only do costs decline but quality of life improves — 564 quality-adjusted life years were gained per 1,000 patients over their remaining life-span."*

The Promise of Future Biotechnology Products

While Activase represents one approach to treating stroke, there are many other products under study. In fact, in the next decade, there are likely to be a variety of stroke treatments for different stages of the process. One example might be neuroprotectants to shield nerve cells from damage due to lack of oxygenated blood during a stroke.

At present, there are at least 21 drugs in development for stroke, some of which are biotech drugs. These drugs employ a number of mechanisms. In 1999, some of them included:

- Centocor Inc.'s antiplatelet drug abciximab (ReoPro®) — thrombolytic ("clot buster");
- Cambridge NeuroScience Inc.'s aptiganel (CNS 1102) — ion channel blocker;
- Abbott Laboratories' recombinant pro-urokinase — thrombolytic; and
- Interneuron Pharmaceutical Inc.'s CerAxon® — (citocoline, cell membrane stabilizer).

The majority of drugs and techniques currently under research and development are being designed for the treatment of ischemic stroke. However, therapies are currently under evaluation to treat hemorrhagic stroke. Although hemorrhagic stroke accounts for less than one-third of all strokes, it represents a large proportion of fatal cases. Nearly half of hemorrhagic stroke patients do not survive the first month following the stroke. Current management of

hemorrhagic stroke relies only on supportive care and, where appropriate, surgical intervention. Biopharmaceutical initiatives toward the advancement of the treatment of this condition focus on agents that not only manage the consequential effects of the stroke, but that also treat or prevent dangerous stroke sequelae (*Stroke*, 2000).

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Table 1: Disease Overview for the Elderly — Stroke

Disease Category	Stroke
Epidemiology	**Incidence:** 500 to 800 per 100,000; 75% are new strokes; ranging from 14.4 to 27.9 per 1,000 aged 65+ **Prevalence:** 3 million; 1 million are severely impaired; 72% are aged 65+ **Mortality:** Third leading cause of death; 25.9 per 100,000 (1997); 88% of stroke deaths are aged 65+
Total Cost of Illness	**Total cost:** $51.3 billion (1999) **Per patient:** $103,576 per patient
Direct / Indirect Costs	**Total:** $30.6 billion (1999) **Hospital/nursing home care:** $25 billion **Physician:** $2.3 billion **Drugs:** $0.4 billion **Total per-patient cost:** $15,000 to $35,000 (in first 90 days of stroke) **Inpatient costs:** $12,151 (average LOS 27.1 days)
QoL / Functional Status	Leading cause of disability in the elderly; decreased mobility, ADLs, speaking; patients experience psychological problems (depression, anxiety); caregivers can suffer from depression
Comments	**Sources:** AHA, 2000

ADL: Activities of daily living
AHA: American Heart Association
LOS: Length of stay

Table 2: Current Biotechnology Products for the Elderly — Stroke

Product on Market	Relevant Indication(s)	Company	Approval Dates	Class	Mechanism of Action	Route of Admin.	Dosing
Activase® (alteplase)	AMI; pulmonary embolism; acute ischemic stroke	Genentech	November 1987; June 1990; June 1996	Recombinant tPA	Dissolves blood clots	IV	0.9 mg/kg infused over 60 minutes with 10% administered as IV bolus over 1 minute

Product on Market	Impact on Mortality and Morbidity	Impact on Costs	Impact on QoL (Patient / Caregiver)	Comments
Activase® (alteplase)	NINDS study found all-cause 90-day mortality was 17.3% for Activase and 20.5% for placebo; NINDS study showed 11% improvement to minimal or no disability on the NIH stroke scale compared with placebo and relative improvement of 34% in global recovery	Increased hospital costs by $1.7 million per 1,000 patients; decreased rehab/nursing home costs by $6.2 million per 1,000 patients; net savings of $4.5 million per 1,000 stroke patients treated; additional 564 QALYs compared with SOC		Weber, 1999

AMI: Acute myocardial infarction
IV: Intravenous
NIH: National Institutes of Health
NINDS: National Institute of Neurological Disorders and Stroke
QALYs: Quality-adjusted life years
SC: Subcutaneous
SOC: Standard of care
TPA: Tissue plasminogen activator

Table 3: Biotechnology Pipeline Products for the Elderly — Stroke

Pipeline Product	Phase / Date Submitted	Company	Therapeutic Area	Class	Indication	Mechanism of Action	Route of Admin. / Dosing
ReoPro® (abciximab)	Phase II	Centocor / Eli Lilly	Circulatory	GP IIb/IIIa inhibitor	Stroke	Inhibits platelet aggregation	IV
Corleukin® (recombinant NIF)	Phase II	Corvas / Pfizer	Circulatory	4-1-kDa glycoprotein; neuroprotective agent	Stroke	Blocks activation of neutrophilis, adhesion to blood vessel walls, migration into tissue	IA
Recombinant pro-urokinase (r-ProUK)	Phase III	Abbott	Circulator	Fibrinolytic recombinant protein	Stroke	Dissolves clots	IA

Pipeline Product	Impact on Morbidity and Mortality	Impact on Costs	Impact on QoL (Patient / Caregiver)	Comments
ReoPro® (abciximab)	Phase II trial: 35% of patients had minimal or no residual disability 3 mos. after first treatment vs. 20% of placebo patients		Phase II trial: 50% of patients had improvement in ADL vs. 40% on placebo	*Pharmaceutical Approvals Monthly*, "Centocor," 1999
Corleukin® (recombinant NIF)				*Biotechnology Newswatch,* 1997; *Biotechnology Newswatch,* 1994; *The Pink Sheet,* 1995
Recombinant pro-urokinase (r-ProUK)	Treatment with r-ProUK within 6 hours of onset of acute ischemic stroke significantly improved clinical outcome at 90 days; PROACT II: 40% of patients treated with r-ProUK had little or no neurological disability 90 days post treatment vs. 25% of heparin group			Furlan, 1999; *Medical Industry Today,* 1999; *Pharmaceutical Approvals Monthly*, "Abbott," 1999

GP IIb/IIIa: Glycoprotein IIb/IIIa inhibitor
IA: Intra-arterial
IV: Intravenous
NIF: Neutrophil inhibitin factor

V. GLOSSARY OF TERMS

Direct costs — The value of all goods, services and other resources that are consumed in the provision of an intervention or in dealing with the side effects or other current and future consequences linked to it.

Direct medical costs — The value of health-care resources, (e.g., tests, drugs, supplies, health-care personnel and medical facilities) consumed in the provision of an intervention or in dealing with the side effects or other current and future consequences linked to it.

Direct nonmedical costs — The value of nonmedical goods, services and other resources, such as child care or transportation, consumed in the provision of an intervention or in dealing with the side effects or other current and future consequences linked to it.

Domain — Generic element(s) of health status, also called health concepts, attributes or dimensions, generally used when discussing quality of life.

Epidemiology — The study of the distribution and determinants of disease frequency in human populations.

Effectiveness — The extent to which medical interventions achieve health improvements in real practice settings.

Efficacy — The extent to which medical interventions achieve health improvements under ideal (controlled) circumstances.

Functional status/ability — An individual's effective performance of, or ability to perform roles, tasks or activities (e.g., to work, play, maintain the house). Often functional status is divided into physical, emotional, mental and social domains, although finer distinctions are possible.

Impact on morbidity — Reduction in the number, frequency and/or duration of episodes of illness.

Impact on mortality/survival — Reduction in the number of deaths (either annually or as a percentage or proportion of patients or persons in the population, or a rate per patient or population) or an increase in survival time among patients.

Incidence — The number of new cases of a disease, relative to the population at risk for the disease.

Indirect costs — Any cost that is not directly attributed to treatment of a disease (e.g., lost work days as a result of illness). A term used in economics to refer to productivity gains or losses related to illness or death.

Prevalence — The total number of persons suffering from a disease at a specified point in time. *Lifetime prevalence* essentially means the percentage of the population that will experience the disease during his/her lifetime. The proportion of individuals in a population who have a disease or condition at a specific point in time.

Quality of life (QoL) — Physical, psychological and social domains of health, seen as distinct areas that are influenced by a person's experiences, beliefs, expectations and perceptions. Specifically, *Health-Related QoL* (HRQOL) refers to the impact of the health aspects of an individual's life on that person's QoL, or overall well-being. *Impact on QoL* assesses how QoL is positively or negatively affected by the disease and/or treatment.

Total cost of illness — Includes the "entire burden of illness" of a disease, either annual or lifetime, and either for the entire nation or per patient.